NEUROSCIENCES IN INDIA
Retrospect and Prospect

Edited by:

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PREFACE

The unique opportunity provided by three world congresses (neurosurgery, neurology and epilepsy) in India this year led the Neurological Society of India to attempt an analysis of the progress made by this country in the neurosciences. This volume is the outcome.

Our contributors have laboured hard to put together a comprehensive account. Questionnaires were sent out. The material received was evaluated, collated and linked. Each of the essays that emerged was edited and then reviewed painstakingly by several others of repute in the field. Reviewers often provided additional material. The suggestions made by peers having been incorporated, the essays were sent back to the authors for approval. The final versions were reviewed by Drs. B. Ramamurthi and P. N. Tandon.

Effort has been made to present all available material. Authors, reviewers and the editor are conscious that the essays are not complete but we hope that they reflect the status of neurosciences in India.

Drs. Kristian Kristiansen, Charles Drake and A. Earle Walker provided personal accounts at short notice. Dr. Jules Hardy and Dr. Lynne Quon-Mak (assistant editor, *Annals of the Royal College of Physicians and Surgeons of Canada*) readily permitted us to reprint Dr. Hardy's paper.

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Bombay, 15 August 1989 Sunil K. Pandya

Neurosciences In India: An Overview

P.N. Tandon

The birth of neurosciences in India dates back to our independence, when a number of scientists left for training abroad and returned to start nuclei of various neuroscience disciplines in different parts of the country. These pioneers struggled against all odds, gathered bright young people around them and started service, teaching, training and research. Some of these nuclei developed into full-fledged Institutes of Neurosciences with all modern facilities. Today such Centres exist in Bangalore, Calcutta, Delhi, Madras and Trivandrum and several others are in varying stages of development. In addition to these Institutes of Neurosciences, there has been a progressive increase in the number of both academic and service departments specially for clinical disciplines. Departments of basic neurosciences unfortunately could not be created at the same rate; the limited resources of necessity, had first to be allocated for provision of clinical services for the care of those suffering from neurological disorders. Nevertheless, there has been a progressive increase in numbers of those imbued with the spirit of enquiry who took up the path of quest for new knowledge. With India playing host to four major International Congresses in Neurosciences, it was decided to bring together at one place, the story of the birth and development of neurosciences in India over 4 decades.

The Neurological Society of India

Looking back one wonders not only at the foresight but also the "audacity" of the founder fathers of the Neurological Society of India. To start a Society with four members (proverbial "all Chiefs no Indians"), start a Journal, lay down rigid criteria for selection of its members and constitute a Society of neuroscientists and not just neurologists or neurosurgeons showed their perception of future developments. From its inception the Society played a much wider role than is usual for such societies. It has had many firsts to its credit. Even prior to starting postgraduate courses, the Society laid down guidelines for training and evaluation. It was the first Scientific Society in the country to start CME Programmes, and bring out regular publications; to provide financial support and encourage young trainees to participate in Society meetings and visit other Centres for short term training. On a continuing basis the Society formally enunciated the criteria for admission, period of training, curriculum, and methods of

evaluation for postgraduate training programmes. It is the only Society to have worked out future manpower needs, and lay down the minimum requirements for starting an academic department. Not only did it retain its multidisciplinary character but it extended its role to include Neurological Nurses and more recently Technicians. It is probably the only Society to host two major International Congresses and support two others in the same year.

Neurology India

Even before there were a dozen full members of the Society, its founding fathers, launched a Journal—Neurology (India) in 1953. B. Ramamurthi was its first Editor, successively followed by R.G. Ginde, Anil Desai, P.N. Tandon, A.K. Bagchi and S. Kalyanaraman. As a result of the efforts of its editors and active co-operation of the members of the Society, the Journal has become an important vehicle of dissemination of the contributions of the Indian neuroscientists to colleagues in the country and abroad. More recently, it has taken up the additional responsibility of abstracting a large number of international Journals for the benefit of many who do not have easy access to them. The papers published during the first 25 years of the Journal were abstracted and published as a monograph by M.C. Maheshwari and P.N. Tandon, since the earlier issues of the Journal were not available in most of our libraries. This has now been updated by M.C. Maheshwari to cover 35 years.

Interaction with National Scientific Organisations

Through its members the Society has aroused the interest of practically all science funding agencies and academies in the country. The Indian Council of Medical Research (ICMR) has, for over two decades, an advisory group for Neurosciences and has supported a number of national projects including those on Epilepsy, Subarachnoid haemorrhage, Head Injury, Stroke, Guillaine - Barre Syndrome and Epidemic Conjunctivitis. Besides supporting individual research projects, it promoted the creation of specialized units, for example a neuropathology unit at Bombay, a neurophysiology unit at Delhi, a psychopharmacology unit at Lucknow. As a part of its eighth five year plan, it proposes to develop a full-fledged institute of neurosciences.

The Department of Science and Technology (DST) has identified Neurosciences as one of its thurst areas. It has an independent Programme Advisory Committee (PAC) on Neurobiology to encourage and support research in this field, to peer review and monitor such projects, to initiate national facilities in identified priority areas and to organise summer/winter schools for manpower developments. It has supported national facilities for study of animal behaviour and for neural transplantation. More recently a fetal repository for study of

developmental neurobiology and a Magnetic Resonance Imaging Centre for Biomedical Research (in collaboration with the Department of Biotechnology). It has sponsored national courses in Basic Neurosciences on a continuing basis and liberally provided for series of publications of "Lectures in Neurobiology".

The National Biotechnology Board (since converted as a Department of Biotechnology) has been an enthusiastic champion of development of neurosciences in India and has supported several programmes in the field.

The Council of Scientific & Industrial Research (CSIR) not only has some of its laboratories (Central Drug Research Institute, Lucknow, Indian Institute of Chemical Biology, Calcutta and Indian Toxicology Research Centre, Lucknow) actively engaged in Neuroscience research, but has several extramural programmes to support research and development in neurosciences.

Likewise, ample support has been forthcoming from National Academy of Medical Sciences and Indian National Science Academy (INSA) for a variety of programmes, including symposia, seminars, workshops and publications. Neurosciences have been identified as an area for bilateral programmes between the INSA-USSR Academy of Sciences and INSA-Hungarian Academy of Sciences. This lead to the first joint Indo-Soviet Symposium on "Developmental Neurobiology and Neural Transplant", which was held at INSA in November 1988.

The National Informatics Centre has already accepted a proposal to create a data base of Indian contributions in neurosciences.

International Interaction

Indian neuroscientists cherish their interaction with colleagues from all over the world, through formal and informal linkages, exchange of visits, participation in and organising of regional and international congresses. The Neurological Society is the national federating body for the World Federation of Neurosurgical Societies, World Federation of Neurology, International Federation of Societies of Electroencephalography and Clinical Neurophysiology, and the International Society of Neuropathology. Likewise, the Society is a member of the Asian and Oceanian Association of Neurology and Asian and Australasian Association of Neurosurgery. Close cooperation existed between our Society and the Middle East Neurological Society. Members of the Society are actively involved with the International Society of Stereotactic Surgery, International Society of Pediatric Neurosurgery and International League against Epilepsy. From its very inception Indian neuroscientists have been members of International Brain Research Organisation (IBRO). IBRO organised a major Workshop and some years later a Symposium in India. Under its Visiting Scientists Scheme, some distinguished scientists have visited India and lectured in various parts of the country. Several young scientists have

benefited from its Visiting Fellowship Programmes. More recently other channels of such interaction on a continuing basis have evolved through the establishment of Academia Eurasiana Neurochirurgica and Europa-India Foundation. The first Indo-European Neurosurgery Symposium was recently held in Tubingen, Germany under the aegis of the latter. A number of our members have been and are office bearers of these bodies.

Even more important than these formal associations, we cherish our long lasting friendship with a large number of colleagues and interaction with Institutions all over the world. Not only have the Indian neuroscientists benefited a great deal by their training, partial or complete, in institutions abroad, but this has resulted in strong bonds of friendship both at personal and institutional levels. Special mention may be made of Montreal Neurological Institute, Montreal; National Hospital, Queens Square, London; Newcastle General Hospital, Newcastle; Ulleval Hospital, Oslo; among many others in UK, USA, Germany, Austria, Switzerland, Ireland and Australia.

Several major research projects including on Epilepsy, Cerebrovascular Diseases, Head Injury and Muscular Dystrophy have been carried out with the support and collaboration with International agencies and scientists.

A number of Indian neuroscientists have been elected to the academies and societies in UK, USA, Europe, Scandinavia. Some have been invited as Visiting Professors and exchange scientists.

On its own part Indian scientists have contributed to the development of neurological/neurosurgical services in particular and neurosciences in general, in the neighbouring countries. These include Nepal, Afganistan, Bhutan, Bangla Desh, Iraq, Iran, Libya, Saudi Arabia, Quwait, Hong Kong, Muscat and some other gulf countries.

Neuroscience education and training

Formal teaching and training programme leading to a postgraduate degree in Neurosurgery was started first at Christian Medical College, Vellore, to be soon followed by Madras. Neurology programme was likewise initiated there. New programmes were added, as more and more centres were established. The late Dr. Ginde's chapter in this volume provides a chronological history of the development of these programmes upto 1970. Today such courses are available at atleast 20 centres in different parts of the country. There are two different streams for neurosurgery - one for 2 to 3 years after specialisation in general surgery and the other a direct 5 years course following compulsory internship. Course in neurology is for 2-3 years, after postgraduation in internal medicine. These are in-service programmes in academic departments mostly on the lines of residency system. Besides, these University department based Courses,

training is now provided in some well developed non-university centres. There is a National Board of Examinations which conducts postgraduate examinations for those working in its accredited departments.

Besides Neurology and Neurosurgery, no postgraduate degree courses are available for other allied disciplines. Short term diploma course have been instituted for Neuropathology and Neuroanaesthesia at a few Centres. Doctoral programmes in basic neurosciences have also been initiated in few institutions but these are however, very few. A culture of post-doctoral fellowship has not yet taken roots and fullfledged departments of basic neurosciences are few and a comprehensive Neurobiology department or Course non-existent. Consequently Neurology and Neurosurgery have developed more rapidly than the allied neurosciences disciplines. Some newer disciplines like neuroepidemiology, neuroimmunology and neurogenetics lag behind still further. It is obvious that special efforts would be required to develop these disciplines, if we have to keep abreast of recent global developments.

Looking at the last four decades of development of neurosciences in India, it is obvious that despite tremendous odds, commendable progress has been made. Individuals, groups, departments and institutes have provided nuclei of excellence in all fields of neurosciences. Facilities for practically all modalities of neurological investigations and treatment exist in the country. There are a number of neurosurgical departments where 300 or more brain tumours are operated upon every year. Stereotactic surgery, microsurgery, the use of lasers and ultrasonic suction have become commonplace. Clinicians have delineated the pattern of neurological diseases as seen in our country, identified the variations, evolved appropriate diagnostic and therapeutic regimes. In some areas they have contributed to advancement of basic knowledge of global interest. These contributions have been documented in this volume through the combined efforts of a number of people, but most notably - Dr. Sunil Pandya, who must be singled out for special tributes. In his unassuming and self effacing manner he has persevered and persuaded the authors of various sections to provide the manuscripts, got these refereed and painstakingly edited these to provide this monumental book. I take this opportunity to record our gratitude to the pioneers of neurosciences in India, and to all those who helped its development. At the same time I plead with the younger generation to take up the torch and make it shine ever brighter. I may end with the few lines from Richard Frost which inspired Pandit Jawaharlal Nehru, the architect of modern India and the patron saint of Indian Science.

"The woods are lovely, dark and
deep, but I have promises to keep
and miles to go before I sleep
and miles to go before I sleep"

A struggle to conquer

Reflections of the founder President,
Neurological Society of India.

Jacob Chandy.

I am greatly honoured to be asked to contribute to this publication on the occasion of the Ninth International Congress of Neurological Surgery of the World Federation of Neurosurgical Societies in 1989. arious aspects of the development of neurosciences in India have been described elsewhere in this volume. I have been asked to give my personal retrospective views on this theme.

Before 1949 there were no organised departments of neurosurgery or neurology or of any branch of the neurosciences in India. In Great Britain, even though neurology had attained recognition, neurosurgery was only beginning to take shape. Even that country lacked well planned training programmes. I was fortunate to see and study neurology and neurosurgery in well established institutions in the United States and in Canada. My teachers, associates, well wishers and organizers of the Christian Medical College, Vellore had promoted within me a desire to develop the neurosciences in India. I am particularly grateful to Dr. Paul W. Harrison, Wilder Penfield and Theodore Rasmussen of Montreal Neurological Institute, Jonathan Rhodes of University of Pennsylvania and Dr. Robert G. Cochrane, Director and Principal of the Christian Medical College, Vellore for giving me much needed encouragement and guidance. They kindled in me this great ambition for a career in the neurological sciences and an urge to establish these specialities in my country. It became all the more meaningful and relevant when in 1947, while I was still under training, India became an independent nation.

When I came back to India after my schooling in neurology and neurosurgery, I found that all heads of surgical, medical and basic science departments considered neurosurgery, neurology and its ancillaries -neuroradiology, neuropathology, neurophysiology and neurochemistry irrelevant under our circumstances. When they did accept reality and saw us develop, they insisted that we serve under their guidance and supervision. It was a continuous struggle to get rid of this controlling yoke. The struggle continues and it is especially unfortunate that youngsters setting up new departments even today face the same trials that we did 40 years ago.

Every case of papilloedema was then diagnosed by physicians as syphilitic pseudo papillitis and every case of raised intracranial tension was said to be due to a gumma. The other possibility that was considered was tuberculous meningitis. To get these cases of raised intracranial tension referred for neuroradiological investigations and surgical therapy was an uphill struggle. I had to go to the general medical wards, hunt for such cases, investigate them personally, make a diagnosis and then operate upon them after getting permission from the reluctant admitting physicians. This was a Herculean task. Over the years there has been a tremendous change. Neurosurgically treatable diseases are now diagnosed and referred in good time. Many ancillary diagnostic facilities are now available. The patients themselves are aware of the need to seek early neurological consultation.

In 1950 a small band of four full time neuroscientists met in the city of Madras [two neurosurgeons (B. Ramamurthi and myself), one neurologist (Baldev Singh) and one clinical neurophysiologist (Dr. S.T. Narasimhan)] to discuss and to find ways and means to develop neurosciences in India. As a result of this effort, the Neurological Society was inaugurated in 1951 in Hyderabad along with the annual meeting of the Association of Physicians of India.

We had unanimously decided on four charter principles;-

1. All branches of the neurological sciences shall keep together as a united body as long as possible for their own development which have close linkage and so shall be supporting each other;

2. Full members of the Society shall be only full time career workers in any of the neurological science disciplines;

3. The Society shall always strive for excellence in their disciplines; and

4. Competence shall be the hallmark of the clinical sections of the neurological sciences.

Keeping in mind these basic objectives we had framed the constitution and bye-laws of the Society.

From the very beginning we had difficulty with the second principle i.e. only full time career workers shall be full members. I firmly believe that the Society was able to attain the present status because of the adherence to these basic principles. Crisis of identity was no exception and we had to face this problem several times during the last forty odd years.

Inclusion of research neuroscientists in association with clinical disciplines is fundamentally important for creating excellence. There should be research both in clinical and basic sciences and this principle was instituted at the Christian Medical College from the very beginning.

For a large country like ours we wanted many neurosurgeons and neurologists but keeping in mind our basic doctrine of competence as the sine qua non of every clinician we adopted the North American and Canadian method of inservice training programmes. I had no difficulty in implementing this method of training at the Christian Medical College, Vellore, but to make it acceptable at all the teaching institutions in India we had to get the approval of both the universities and the Medical Council of India. It must be realised that in the United States of America and Canada there are respected organisations, independent of both government and the universities, that regulate postgraduate training in all medical and surgical specialities. In India it is the Medical Council, which is virtually an arm of the Government, which regulates our training programmes.

The Vice Chancellor of the Madras University, Padmavibhushan Sir Lakshmanaswami Mudaliar was a very dynamic, progressive medical educator, who approved our suggestions with enthusiasm and instituted at the University of Madras courses leading to postgraduate degrees in the higher specialities in medicine. He also championed the concept of residency programmes in training. The Medical Council of India was also made to approve our pattern. It is note worthy that to maintain high standards, the University of Madras enacted a regulation insisting that each candidate appearing for the examination leading to the M. Ch. in neurosurgery performs an actual operation under the responsibility and supervision of the professor of neurosurgery at the institution. This pattern has, since been adopted at all the other neurosurgery centres in the country.

The first neurosurgical training centre in India was at the Christian Medical College, Vellore. The Madras Medical College followed soon after. Since then training centres in neurosurgery have been set up in most other states. Many have obtained the coveted Master's qualification in neurosurgery and have spread out to render excellent service to the public in various parts of India.

The story of the development of the Neurological Society of India and its scientific publication NEUROLOGY INDIA is narrated elsewhere in this volume.

The government of India and the various state governments have encouraged and sponsored the development of our speciality.

The Society became a member of the World Federation of Neurosurgical Societies (WFNS), World Federation of Neurology (WFN), International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) soon after it was formed and it is indeed a pleasure for me to see it host the 9th International Congress of Neurological Surgery and then, in close succession, the 14th World Congress of Neurology and 18th International Epilepsy Congress.

May I take this opportunity to felicitate the officers of the World Federation of Neurosurgical Societies, World Federation of Neurology and Epilepsy International and the members of the respective organising committees for their untiring efforts towards these meetings that also see the fulfilment of a long cherished dream?

The future of neurosciences in India

B. Ramamurthi

Introduction

Crystal gazing and trying to predict the future of any area of human activity is not always successful, as events have a peculiar way of suddenly taking a zig-zag or unexpected twist and the future turns out to be something that one never could have predicted. In the year 1973, while delivering a prestigious oration at the Annual Conference of the Association of Surgeons of India, I predicted many advances in neurosurgery, like rheoencephalography, implanted thermal and chemical devices etc. but could never even remotely predict the stupendous advance in diagnosis that took place when a CAT suddenly jumped in and made the entire process of neurological diagnosis simple. Nature seems to have this uncanny capacity of taking entirely unexpected turns as witnessed in evolution, economics, politics or scientific discoveries. My attempt at predicting the future of neurosciences in India may provoke a tolerant smile after a decade or two in those wondering at the naivete or the audacity of the attempt. Even so, the human spirit is indomitable and man's faith in his own future so firm that he will make every attempt at optimistic predictions. Thus arises this crystal gazing.

Progress bound with economics

The future of neurosciences in India is closely connected with the economic progress of the country. Over the past four decades, clinical neurosciences have shown good progress. A large number of neurological and neurosurgical centres have been set up in the country. This number is far from adequate as is the number of neurologists and neurosurgeons, 500 of whom serve a country with a population of 800 million. India needs a minimum of 1600 neurosurgeons and an equal number of neurologists to give minimal care for the entire population. Though this may sound perfect from the statistical point of view, realistic possibilities are different. The economic condition of our country is still not strong enough to support the necessary number of neurosurgical centres.

India has made phenomenal progress in the 40 years since independence, when one realises that even safety pins were imported into the country while under foreign domination. Unfortunately, all this economic progress

has been swallowed up by the ever increasing population which has doubled itself in these 40 years. This seems to be the basic reason for the slow expansion of clinical neuroscience services in the country. One has to concede that the state and the central governments are doing their best to help set up such services and there is an expansion of clinical neurosciences in the private sector.

Spelling out minimum needs

On an average it needs a minimum of one million rupees, (eighty thousand dollars) to set up a neurological practice and a minimum of 5 million rupees (400,000 dollars) to create a neurosurgical centre. These amounts are often beyond the capacity of individual young doctors. Many doctors prefer to join government services, where minimum facilities may be available. The attraction is more if private practice is also allowed. Such doctors seem to be quite satisfied to work with whatever meagre facilities are available and often are not in a condition to wrest from the authorities all that is needed. Hence it became necessary for an authoritative body like the Neurological Society of India to spell out in clear terms the essentials for a neurological or a neurosurgical centre, different norms being prescribed for teaching and non-teaching centres. These are only recommendatory but are often utilised by clinical neuroscientists to convince the administrators about the facilities needed to start a department.

Neurosciences not "super" but relevant to health care

In the framework of India's health policy, naturally, primary health care and prevention of disease have the highest priority and other areas of medicine come lower down the list. Emphasising the important role of neurology and neurosurgery in health care delivery in the areas of cerebrovascular diseases, strokes, epilepsy, head injuries and infections, is now helping in making the decision makers realise that these areas are also important and deserve consideration. Apart from this, there is the advantage of pressure from the public. As more and more people are educated and become affluent, they demand better levels of care in the speciality areas and pay for it. It is this public demand that helps the opening of newer centres, both in the public (state) and private sectors This makes one optimistic about the future.

Voluntary and charitable organisations

Here should be mentioned one more important sector, namely, the voluntary or the charitable institutions, who help to combine service to the poor in general wards and to the rich in the special wards of the same institution. This sector is contributing more and more to the evolution of the specialities, specially since the government extended exemption from import duties to these institutions, enabling them to equip themselves well.

Sophisticated technology and increasing costs

Cost containment has become a serious problem even for the rich countries in the west and in Japan. The problem is compounded in India. Neurologists and neurosurgeons in India have to develop a firm policy of priorities to limit expenses and enable the creation of more centres. The policy of keeping up with the Joneses and buying all the available sophisticated modern equipment increases the prestige of the institution, but does not contribute to the expansion of neurosurgical facilities in the country. There is yet another sorry consequence. Young neurosurgeons are led to believe that highly sophisticated and costly equipment is sine qua non for good neurosurgery. The public is also misled. Here arises the necessity for a dialogue with the policy makers to convince them of the minimum essential expenditure for setting up a neurological centre and drawing up guidelines.

Different levels of training - the practitioners and the academics ? Will this help expansion of services ?

Is it necessary to train every neurosurgeon to treat, to teach and do research? Does the country need a slightly different level of training to produce neurosurgeons who are competent in routine neurological diagnosis and neurosurgical treatment? Can these surgeons not be given cost efficient equipment, to enable them to offer neurosurgical services to the public in the many non-metropolitan areas of the country? Or should every neurosurgical centre be fully equipped and manned? If the latter is insisted upon, how many decades will it take India to double the presently available facilities? These are points for debate, not only in our speciality but in the general area of providing medical and surgical care for the vast and varied population of our country. In the next decade or two, will economic circumstances and the pressing need to provide more extensive neurosurgical services make us change the present pattern of training and follow the two tier system, that is now being followed in some socialistic countries who have managed to provide such services to large numbers of their population?

Individual competence and patient relationship

Advances in diagnostic technology have a natural tendency to minimise the importance of clinical examination in the minds of the trainee neurosurgeon. Will the future neurosurgeon be only a competent technician or will he continue to contribute to the advancement of knowledge on the nervous system? Clinical neurological examination following meticulous history taking has been the main strength of clinical neurology and neurosurgery. These require the neurosurgeon to have expert knowledge of the functioning of the nervous system and also give him the opportunity of close contact with the patient. This enables him to deal with the problem

of the patient in a holistic manner, and thus provide the patient not only good treatment but also care and counselling. "When cure came in by the door, care went out of the window" is a trite saying, but nevertheless relevant for the future, where more and more technological advancement including the advent of computers is likely to take place, with machines making the diagnosis and robots performing the operation. The importance of the future neurosurgeon continuing to be a friend and counsellor to the patient and his family, apart from providing technological competence, cannot be overemphasised.

Preserving intellectual creativity

Increasingly sophisticated technology and greater emphasis on the technological competence of the neurosurgeon is also likely to affect his intellectual creativity, unless conscious precautions are taken. Hitherto, each neurosurgical procedure has been conducted almost like a neurophysiological exercise, the surgeon gleaning knowledge from each patient. Over the years, neurosurgeons have been able to contribute to the pool of knowledge in neurosciences. This desirable objective should continue to motivate future neurosurgeons, thus preserving their role as neuroscientists and contributors to knowledge. The foundation for such a future must be laid down now by the present leaders of neurosurgery. We must preserve our great traditions of learning and research.

Special areas and successes

Advances in diagnostic instrumentation like CT Scanning and MRI combined with sophisticated operating techniques using the microscope, ultrasound and laser have enabled the neurosurgeon to tackle competently most of the nonmalignant tumours of the brain. With special surgical approaches and combined efforts with ENT and plastic surgeons, it is now possible to treat successfully tumours in the base of the brain and the skull. Mortality from nonmalignant tumours of the brain has been reduced to below one per cent.

Large vascular lesions like giant aneurysms, arteriovenous malformations and carotid-cavernous fistulae can now be treated with confidence both by surgical techniques and by interventional neuroradiology. Balloon techniques by themselves help to cure vascular lesions and are also helpful as preoperative aids.

Persisting challenges

While the picture appears rosy on some fronts, it is grim in the field of malignant lesions of the brain and in the treatment of head injuries.

In the **treatment of gliomas,** surgery, radiotherapy, and chemotherapy

have not improved the outlook and immunotherapy seems to hold little promise. Will the near future change the outlook for these patients or as it seems to be more likely, will some unexpected breakthrough offer an entirely new approach?

With **head injuries** beyond a certain level of severity, no type of therapy seems to improve the outcome. All the extra effort put into the treatment of such severely injured patients merely creates more patients in vegetative states. Such a point of no return is now well recognised. Neurosurgeons realise that there are only two ways of improving the results in head injuries: one is to get at the injured person to hospital at the **earliest possible moment and the other to make all out efforts to prevent head injuries.**

A review of road traffic and other accidents in India is depressing, the accident rates being one of the highest in the world. Most of these accidents are preventible, and little attempt is being made to prevent them, both on the roads and in industries. **Neurosurgeons have to play a vigorous role in creating powerful public awareness that will lead to prevention of accidents.**

Neural transplantation

This is literally and figuratively in the embryonic stage. While transplantation of other whole organs has become possible, transplantation of the brain or the spinal cord seems impossible today. With presently available microsurgical technology, neurosurgeons can suture any nerve or blood vessel successfully thus making an anatomical brain transplant possible - but functional transplantation remains a distant dream. The apparently unsurmountable barrier is the inability of the central nervous system to regenerate and make functional distal connections. Till we understand the basic mechanisms involved in the regeneration of the CNS brain transplantation will remain a dream. Neurosurgeons would be happy if they could make the spinal cord regenerate, thus helping thousands of paraplegics all over the world. Sustained efforts in this direction is the immediate need of the future.

At the practical level, it is seen that embryonic neural tissue can continue to live inside the CNS and also make structural and chemical connections. This is where transplantation stands today. In the next decade or two more success is likely to be achieved in this area. It is possible for Indian neurosurgeons to play an important role in this field for helping patients with degenerative and other diseases of the nervous system because of the Medical Termination of Pregnancy Act and the availability of foetuses. We look forwards to rapid advances in this field in India, both at the surgical level and at the level of basic sciences.

Epilepsy, movement disorders

In the general field of neurology, no disease has challenged our intellect or fascinated us with its myriad manifestations as epilepsy. We still do not fully understand why an epileptic discharge should occur in the first place, how it spreads to involve the rest of the brain and why an attack once it had started stops spontaneously. We do not yet know why all brains are not convulsing and what factors are responsible for the non-occurrence of seizures in normal brains or why the orderly spread of impulses occurs along specified tracts. The electrochemical basis of epileptic disorders is continuing to be unravelled providing some answers to the above questions but there is still a long way to go.

Pharmacotherapy has progressed, but has not kept pace with the advances in basic pathophysiology. There are many patients, in whom the disorder cannot be controlled with all the available medication. This provides an opportunity for the neurosurgeon to plan new surgical techniques that may alleviate the disease in uncontrolled epileptics. Excision of the irritable foci and ablation of the temporal lobe have been practiced for many years, with notable benefit. Stereo-EEG, Magnetic Resonance Imaging and Positron Emission Tomography have all been used to delineate accurately the offending tissue. Stereotactic techniques have also been used to make lesions in the brain to control focal, partial and generalised epilepsies. Each one of these procedures also provides an unique opportunity for the neurosurgeon to understand and elucidate the pathways of spread of the epileptic discharge.

The treatment of **movement disorders** has also provided a similar challenge. Advancing knowledge of the neuro-chemistry of motor conduction inside the central nervous system has provided a reliable pharmacological base for therapy with good results in some areas like the treatment of Parkinsonism. There are other movement disorders that do not respond to medical therapy. Stereotactic lesions in the thalamus and in the subthalamic regions have helped many such patients. Efforts by interested neurosurgeons in this field should continue in the future.

The prediction that stereotactic surgery has had its heyday and will in the future be used only for tumour biopsy will be proven wrong. The ability of the neurosurgeon to reach accurately any part of the brain he needs to will become more and more useful as our knowledge of the functional and chemical anatomy of the brain improves.

Functional disorders and stereotactic lesions

The usefulness of accurately placed stereotactic lesions in certain strategic areas in the frontal brain has been proved beyond doubt and over the past two decades a large number of patients with intractable psychiatric

disorders have been benefitted. The term psychosurgery has unfortunately run into rough weather and has been replaced by the term *functional neurosurgery*.

Uninformed criticism and prejudiced science fiction stories have created a fear in the minds of the public in some countries. Our experiences in India and that of a few centres in the west have convincingly shown the value of surgical procedures in selected psychiatric disorders.

Small lesions accurately placed in the orbitofrontal region, the cingulum and anterior thalamus have proved effective in medically intractable cases of depression, obsessive neurosis and severe anxiety neurosis. With such proved positive evidence available, neurosurgeons cannot deny such treatment to needy patients. Till effective psycho-pharmacological therapy becomes possible, functional neurosurgery has a definite place in the treatment of selected psychiatric patients.

Microneurosurgery

One of the most beneficient applications of technology in neurosurgery has been the introduction of the microscope. Many Indian centres use the operating microscope regularly. It must be made available at all centres. Talking about the increasing use of the operating microscope in neurosurgery, I would like to confess that almost three decades ago, in the year 1961, when I along with Gazi Yasargil, trained in microneurosurgery with Professor Donaghy in Vermont,I did not foresee its real importance in neurosurgery. On my return from Canada I did not pursue the idea or attempt to get a microscope for the department or set up a small microsurgical laboratory, thus missing an unique chance. (Instead, I got involved in developing stereotactic surgery, a field full of interest and excitement at that point of time. Stereotactic surgery had its heyday for two decades, and gradually grew less important. Microsurgery gradually gained importance and the microscope has now become an indispensable tool in day to day neurosurgery, widely expanding its horizon. Perhaps, if I had assessed the future properly and started the use of the microscope in India in those early days, microneurosurgery would have been widespread in our country today.)

To become an everyday tool, **the microscope should be available at a cheaper price.** With the falling value of the rupee and the customs duty imposed by the Government of India, operating microscopes have become costly, thus preventing their wide use. Good microscopes made in India are available and the indigenous industry must be encouraged both by the government and by the neurosurgeons, to produce better and cheaper microscopes which will have a good market both within India and abroad.

Apart from its use in the treatment of various lesions of the nervous system,

the microscope has provided an opportunity for dealing with small blood vessels. Removal of other obstruction from inside the lumen of small blood vessels is now possible and with the discovery of appropriate **brain protecting agents,** embolectomy from small cerebral vessels is likely to be more commonly practiced. Vascular anastomosis by microsurgical techniques has helped in the surgery of deep lesions. In the near future, some type of vascular glue may be discovered, which can attach blood vessel walls firmly, without the lumen being occluded. This will take away a great tedium from the techniques of operative microneurosurgery.

Other technical aids

The use of ultrasound to loosen up the tissue in tough tumours and make it soft enough to be sucked out has been of use in tumours of certain type of consistency. The use of laser in neurosurgery has at present only marginally improved prognosis. Further advances in laser technology which may make it more useful in operating on the delicate tissue of the brain are awaited.

Neurology

Medical neurological services have to expand to cover large areas of India. Large numbers of neurologists are needed for providing care for common neurological illnesses and must be available in smaller towns and cities, or at least in the district towns. These neurologists must identify themselves with the primary health care systems in the local regions and provide guidance in avoidance of risk factors amongst the local population. For the future well being of India and its citizens, one cannot over-emphasise the dictum that every speciality should take its message right down to the doorsteps of the citizen.

Apart from these **clinical neurologists,** it is essential to have a large number of **academic neurologists** who will teach, train and do research. In academic neurology, the era of nosological classification of diseases and enumeration of signs and symptoms is now past. The future neurologist, in the academic field, has to get himself interested in any one of the associated areas, to look for his challenges: viz. epidemiology, neuro-psychology, chemical anatomy of the brain pathways, higher levels of consciousness, molecular neurobiology, genetics etc. We already see a trend in this direction, which augurs well for the future.

Neuroepidemiology seems to be a field in which much more knowledge would be welcome. Lack of proper facilities and inexperience in the technology of epidemiology seem to be the main obstacles. The prevalence rate of many ordinary neurological illnesses in India are not known and it has not been possible for the Neurological Society of India to advise the governments or the councils of research in the country about priorities.

Some of the areas in which epidemiological information is urgently needed relate to the incidence, prevalence and distribution of strokes, subarachnoid haemorrhages, congenital neurological deficits and muscle diseases.

Genetics. Many future advances in understanding and preventing neurological illnesses depend on discoveries in genetics. Work on basic genetics is going on in a few centres: Bombay, Hyderabad and Benaras. Clinical neurogenetics is still an undeveloped field in India but is an important necessity in view of the emphasis on family planning in our country.

Possible areas of research in India

Some of the areas of immediate clinical interest, where further knowledge is required are indicated below.

Tuberculomas of the brain. In the early years of neurosurgery in India, surgery for tuberculomas constituted 15-25% of all intracranial surgery for space occupying lesions. The C.T.scan has changed the picture remarkably and one rarely operates on tuberculomas any more. The diagnosis is made from the CT scan and the patient is treated with antituberculosis drugs with complete resolution. There are some patients who do not respond to such therapy and in them the diagnosis has to be revised and another disease such as glioma has to be considered. One also encounters a small number of patients who, though harbouring tuberculomas, do not respond to antitubercular drugs. The reason for this is not clear. The immunological and the pharmacological significance of such non-response needs study and will result in better understanding of the response of the body in general and brain in particular to tuberculous infection.

Leprosy. Unfortunately infection with leprosy is widely prevalent in India despite the vigorous and widespread measures adopted by health authorities to contain and eradicate the disease. Antibiotic therapy now offers good hope for these patients. The mode of spread of the disease and the peculiar immune response of the body and the nervous system to infection with lepra bacillus are ill understood. While tuberculosis has a predeliction for the central nervous system, the lepra bacilli tend to lodge themselves in the skin and the peripheral nerves. This may be due the differences in the surface characteristics of the cells of the central and the peripheral nervous systems and also due the differences in the myelination process between these cells. This will be a fruitful area of study in the country.

Cysticercosis. This disease is unfortunately prevalent in the country. Prevention is mainly a public health problem. Progress has been made in the curative areas with the use of praziquantel and albendazole. An intriguing problem is the reappearance of cerebral cysticercosis after an apparent period of cure or quiescence. Why does this happen? Is this a reinfection or a reactivation of the disease. Research in this area is needed.

Moving away from infections, the areas where we need further information are the **vascular diseases of the brain.**

In spite of many assertions to the contrary, the incidence of **aneurysms** in Indians appears to be low. During the 38 years of neurosurgery in India, great progress has been made in the investigation and diagnosis of nervous diseases. It is strange that we do not see in any neurosurgical centre in the country even half the number of aneurysms that one sees in neurosurgical departments in the west or in Japan. Vigorous and sustained efforts must be made to establish the true incidence of aneurysms and other vascular lesions of the brain by a collaborative study by many centres in different parts of the country.

The incidence of **intracerebral haematomas** in Indian subjects and the effectiveness of surgical versus nonsurgical therapy need to be studied.

Once a brain bank is established, the specimens may be used to study the anatomy of the major cerebral blood vessels and publish detailed vascular maps to facilitate the evolution of better microsurgical techniques. A study of the cerebral vasculature in different age groups will also yield knowledge on the incidence of atherosclerosis and other diseases in different age groups.

The brain bank may also be utilised to study the mapping of the internal structures of the brain to provide neuroanatomic correlates for stereotactic surgery (*stereotactic atlas*).

Other areas in which Indian neurologists and neurosurgeons may effectively contribute are listed below:.

1. Study of *speech disturbances in bilinguals and multilinguals.* Opportunity for such studies are unique in India. Which language is first affected in dysphasics, the mother tongue or the learned language? Which language recovers first? Are there different centres for these languages in the brain? These and other such queries need answers.

2. *Epilepsy.* The use of **anticonvulsants in pregnancy** has been made controversial, creating the fear of teratogenesis. Such a fear in Indian families, against the social background in India, creates havoc in family and marital relations. Collaborative research in this area, aimed at supplementing the findings of earlier studies showing that such fears are unwarranted, will help.

3. *Spinal arachnoiditis.* Arachnoiditis is often encountered by neurosurgeons and commonly thought to be of tuberculous aetiology.

However one meets patients in whom there is no evidence of any obvious infective process. Such cases need to be studied to determine the aetiology of arachnoiditis.

4. *Experimental spinal cord regeneration.* On the same analogy as neural transplantation in the brain, it should be possible in our country to try foetal tissue transplantation in spinal cord injury in the humans. In patients with complete or incomplete spinal cord transections, one should certainly try to induce some regeneration in the spinal cord by foetal tissue transplant. The modalities have to be worked out carefully and accurate records kept so that unbiased information can be obtained.

5. *Operant conditioning and neurological disorders.* The usefulness of such procedures in improving higher neurological disorders like headaches, anxiety, tension, hypertension and epilepsy need to be determined by properly conceived experimental techniques.

6. *Nonvolitional biofeed back techniques* using auditory and visual impulses have been suggested in the treatment of the above disorders. A comprehensive enquiry into this claim is justified.

7. *The influence of geo and electromagnetic fields on the behaviour of humans and animals* has been known for some time. A fully established research team will be able to determine the influence of such fields on normal human beings and help in the utilisation of such fields in the treatment of neurological disorders.

8. *Neurophysiology of awareness.* This is a fruitful field of research as important as the neurophysiology of consciousness. For example it will be interesting to find out if the "I" (the ego sense) is situated in the temporal lobes as has been suggested from a study of temporal lobe epilepsies.

9. It is well known that certain diseases are more likely to affect certain type of individuals. This has been well known in Ayurveda (the Indian system of medicine) for many centuries. A critical examination of the correlates, such as the type of personality and body structure that may influence the occurrence and progress of neurological disorders like strokes, epilepsy, headaches in the background of Ayurvedic Postulates will certainly be worthwhile.

10. *Meditation, consciousness and superconsciousness.* The most important contribution of Hindu civilisation to the human race is the science of yoga. The ancient seers in India had by introspection and self-experience realised that the human mind is capable of much greater achievements than is believed to be possible by the general run of the people. The vast hidden powers of the mind can be utilised by a person to acquire mastery over the physical functions of the body and also enhance achievements of the

intellect. Certain well defined exercises have been prescribed to make these hidden powers manifest resulting in a happier life for oneself and for all humanity. Such excercises and practices change the functioning state of the body and mind. The accompanying physical changes like reduction of metabolism, blood pressure, pulse rate, body temperature, respiratory rate etc. have all been proved by many workers.

The prime need now is to look into the neural and brain correlates of these states, by all available methods of investigations. It is conceded that the present techniques are too crude and inadequate for noninvasive investigations of the various levels of yogic achievements but we should do all we can to learn more about the highest levels of brain function.

It is my definite view that the future of humanity will not be determined by its technological advances but by its ability to evolve from interpersonal relationships riddled with violence and hatred to a more altruistic and less selfish plane of existence. This alone can lead to joy and happiness. Indian neuroscientists are uniquely situated to show how better utilisation of the highest functions of the brain can make this a better planet to live in.

Basic Neurosciences

The present state in basic neurosciences in India and the plans for the future have been discussed by Professor P.N.Tandon, New Delhi, in a thought provoking working paper presented to the Programme Advisory Committee of the Department of Science and Technology. He observed, "A survey of neuroscience activity in the country reveals that in the various fields of neurosciences, neuro-anatomy, physiology, pharmacology and toxicology, neurogenetics, pathology and clinical neurological and behavioural sciences, nuclei and groups exist scattered all over the country. There is unmistakable evidence of some very good and a few outstanding units in each field, but in general the overall activity in this very important field is still limited. There is a real need for interdisciplinary, comprehensive and coordinated activity cutting across artificial barriers".

While great interest has been aroused all over the world in neurosciences, India has not so far witnessed a surge forwards in this field. One neuroscience institute in Beijing has more neuroscientists than in the whole of India.

The Indian Council of Medical Research, the Department of Science and Technology, the Council of Scientific and Industrial Research and the University Grants Commission - to name a few organisations- have a fairly liberal policy of encouraging research in the neurosciences and substantial research grants have been made available by them. It is upto those who are interested to make use of these opportunities and also encourage young persons to take up research.

Research areas in neurosciences relevant to India

Prakash Narain Tandon, Professor of Neurosurgery, All India Institute of Medical Sciences and a member of the Science Advisory Council to the Prime Minister, has identified and highlighted the thrust areas for future research in neurosciences, based on the available facilities and the special problems that face our society and country (*Reference*: Note on Neurosciences Research presented to the Science and Engineering Research Council of the Department of Science and Technology). The following excerpts from this document summarise the general consensus arrived at as a result of consultations, discussions and deliberations amongst a large number of neuroscientists in the country.

Developmental Neurobiology

The large resource of human foetuses and adult brains from autopsies available in the country should be exploited to study developmental neurobiology utilizing modern neuroanatomical, and neurochemical techniques, combining various newer labelling methods (antegrade and retrograde Golgi staining, double labelling, immunoflourescent and imunocytological investigations) along with quantitative morphometry and fluorescent and electron-microscopy on the one hand and evaluation of regional distribution of various neurotransmitters and neuropeptides on the other. This would provide valuable information on the development of normal human brain, its organization, biochemical correlates and connectivity. Since large areas of the human brain remain uncharted even today and modern techniques can provide quick and reliable information, it is important to obtain this basic information about the normal state to answer a large number of questions regarding pathological states:

(i) the effects of malnutrition,
(ii) understanding the basis of a number of ill-understood developmental defects,
(iii) quantitative study of changes associated with aging,
(iv) plasticity and regeneration of the nervous tissue both at the central and peripheral level.

To enable such studies to be carried out it will be necessary to develop facilities for:
a) foetal and adult brain banks,
b) quantitative morphometry,
c) modern labelling techniques, specially possibilities to raise monoclonal antibodies and various marker isotopes,
d) microanalytic methods to measure minute levels of eurotransmitters-/hormones/modulators etc.
e) techniques of tissue culture, monolayer, explant and organ culture,
f) high voltage electron microscopy.

Besides enhancing our knowledge of basic neurobiology such studies are directly relevant to the newly emerging area of neural transplant for treatment of human diseases.

Neurophysiology

A number of new techniques for neurophysiological studies have been developed recently. Thus, in addition to the classical macro and microelectrode studies, patch-clamp technique, studies of brain slices in vitro, quantitation of behavioural parameters using computerised facilities and telemetry are some of the areas, which need to be developed.

Neurochemistry

Recent developments in neurochemistry have opened up completely new vistas ranging from the molecular to the behavioural level to the normal and abnormal nervous system. The existing expertise in this field could be utilized and strengthened to permit research in the frontier areas: static and dynamic studies on the transmitters and receptors and their modification by drugs and pathological states.

Neuropharmacology

Pharmacodynamic and pharmacokinetic action of known drugs, development of newer drugs utilizing computer modelling techniques are two emerging areas. Investigations for developing reliable and cheaper monitoring kits for drug levels, for clinical use needs to be encouraged. tudies on selected drugs used in the **traditional Indian systems of medicine** for modifying CNS function need to be explored.

Neuroimmunology

Studies are needed both to delineate the role of central mechanisms in immune diseases and to evaluate the usefulness of centrally acting drugs to modify the same.

Neurogenetics

New techniques could be utilized to understand some of the basic neurobiological mechanisms/phenomenon e.g. neuronal organisation, connectivity and even behaviour.

Neuroendocrinology

This is a fast developing field still in its infancy in India. Facilities for modern neuroendocrinological investigations are available in only a few centres. These studies are of great importance to understand normal

growth and development, effect of undernutrition and malnutrition on mental development (classical examples: iodine deficiency and mental retardation).

Study of pathological states

A whole range of pathological states affecting the central and peripheral nervous system remain ill-understood. Some of these disorders, specific to India, are of greater interest to us. These are malnutrition, infective disorders (tuberculosis, leprosy, viral and parasitic), degenerative disorders (motor neuron disease, ataxias), and certain toxic substances (lathyrus sativus, cannabis, country liquor).

Another important area is that of neuro-oncology. With the availability of newer techniques like in-vitro and in-vivo cell kinetics tissue culture, use of tumour markers etc. it has now become possible to investigate brain tumours to get a better insight into their histogenesis, biological behaviour, response to chemotherapy etc.

Neurotoxicology

Neurotoxicology is of great concern in view of the increasing exposure of man to a variety of neurotoxins of pharmacological, environmental and industrial origin. Recent studies have provided a clue to the role of neurotoxins in the aetiopathogenesis of several neurodegenerative disorders such as Parkinsonism, motor neurone disease, dementia etc. The following areas of research are, therefore, identified.

Development of animal models

Animal models need to be developed for the testing of environmental toxins and industrial pollutants. Priority should be given to solvents (particularly hydrocarbons), heavy metals (lead and manganese), pesticides and polymers.

An integrated approach using biochemical, electrophysiological, behavioural and morphological methods has to be used for the development of animal models. Biochemical evaluation would involve study of receptor changes, glycolytic enzymes and marker enzymes for subcellular components. Electrophysiological studies of peripheral and central nervous system including electromyography, neuromuscular transmission, nerve conduction and evoked potentials are necessary to provide essential information of the functional status. Behavioural studies would involve motility monitoring, maze test for memory and tailflick test for pain sensation. Morphological studies of peripheral and central nervous system using histological, histochemical and ultrastructural methods, need to be carried out.

Study of mechanism of action of neurotoxins

It is important to delineate the precise site of action of neurotoxins. To achieve this objective, in vitro methods using brain slices, tissue-cultured cells and subcellular fractions have to be developed. These studies would be critical in devising, in vitro assays for rapid screening of potential neurotoxins, while in-vitro testing cannot completely replace in-vivo, saving valuable animals, time and expense.

Application to human studies

a) The information obtained from basic work has to be applied to the actual human situation. Well designed neuroepidemiological studies will provide the frame work for obtaining prevalence data and allow intervention. Such studies will have to be conducted in selected population at high risk of exposure.

b) Neurotoxicology data obtained from animal studies will be valuable in determining the maximum permissible levels of exposure. In the Indian context, the influence of nutritional status has to be given due consideration while formulating the guidelines. Studies have to be designed to assess the inter-relationship between the effect of toxin and nutritional factors.

Biological Psychiatry

Another area of behavioural science research which has become possible today is the field of structural, biochemical, functional and behavioural correlates of a variety of psychological or psychiatric disorders. With the availability of techniques for precisely delineating structural, biochemical and metabolic abnormalities in intact animals (including human), it is now possible to explore various higher mental functions and their disorders from a biological stand point.

Study of memory mechanisms and their neuroanatomical, biochemical, physiological and behavioural bases constitutes a vital area of neurolog-ical research.

Drug/substance Abuse

In view of the current global concern on this subject and the problems peculiar to India, urgent attention is needed in this field.

Drug abuse

Basic studies on drug abuse are need in certain areas of special relevance to India. Important problems should include:

1) Development of animal models to study abuse of substances such as

opium, Indian alcoholic liquors, cannabis etc. We need detailed studies as their response may differ from the more thoroughly studied pure compounds like morphine, heroine, cocaine etc.

2) The abuse potential of some new psychotropic drugs developed and introduced in India needs to be studied.

3) Morphine and opioid peptides have now been shown to have marked effects on the immune system. Their effects on the time course of tropical infection has not been investigated so far.

4) With drug rules and surveillance becoming more strict in western countries a new class of drugs of abuse have developed called the designer drugs. These are derivatives of drugs of abuse which are not legally banned and can thus escape the enforcement network. It is necessary to have assay procedures for such compounds at least at some centres in the country so that their abuse can be detected before it becomes uncontrollable.

Neuromodelling; neural implants and neural prosthesis

Active interaction is required between neuroscientists, mathematicians, electronics and computer specialists and experts in biomaterials to develop these exciting areas which promise better understanding of the functioning of the nervous system and help in developing implantable devices to replace lost function.

Centralized facilities

There is an urgent need for creating centralized or regional facilities, fully equipped with the latest technological advances like nuclear magnetic resonance imaging and spectroscopy, total body scanner, positron emission tomography, SPECT etc. These facilities are undoubtedly very costly but have opened up completely new vistas in the morphology, biochemistry, metabolism, circulation and even pharmacokinetics in the intact human brain. This would have been unimaginable only a few years ago. The investment will pay rich dividends not only in the exploration of the functions of the normal human brain, but also for the study of a large number of ill-understood diseases of the nervous system.

Another centralized facility identified was a Brain Bank which could act as a repository of specimens of brains, at all stages of development, at various ages and those afflicted with diseases. These could be made available to interested researchers. Since the legalisation of medical termination of pregnancy the country has a valuable resource of human foetuses which could be used for studying all aspects of developmental neurobiology. Possibilities of utilizing this for neural transplant work opens up a challenging area of frontline research. Centralized facilities are also

necessary for quantitative morphometric studies which would be required for a large number of morphological investigations of the normal and pathological brains.

Centralised facilities need to be created for procuring and raising special strains/species of genetic mutants required for basic neurobiology research.

Human resource development

It is obvious that there is a paucity of scientists working in the various fields of neurosciences. Such scientists work in isolation within disciplinary boundaries. Even these groups are not adequately exposed to modern developments in molecular biology, bio-technology, computer modelling etc. which are now integral parts of frontline research in neurosciences. It is important to create an awareness of these developments, attract younger scientists to neuroscience, provide for multidisciplinary interaction and bring together various groups to learn from each other and develop collaborative research programmes. For this purpose the following activities are recommended:

–Summer-winter schools conducted by reputed scientists.
–Seminars and symposia on emerging areas, if necessary, supported by international experts.
–Brainstorming sessions, especially in multidisciplinary areas.-Travelling symposia.
–Training abroad: Young scientists should be selected for training abroad in newly emerging areas not yet developed in India. Some examples are neuro-immunology, neurogenetics, computer modelling of CNS activity. On their return, they could set up this activity in the country.
–Strengthen and support units of neuroscience in institutions where groups producing work of high quality already exist. Such support should be on the pattern set by advanced centres support programme or COSIST programmes.

National information centre for neurosciences

There is a need to collect, collate and computerise information regarding current neuroscience activities in the country, procure literature and information at the international level, critically evaluate this data and make it available to neuroscientists in the country.

These numerous and well thought out suggestions of Professor Prakash Tandon are from The guidebook for the development of neurosciences in India. It is obvious that a large amount of input of manpower and materials are needed to make these programmes possible. As stated earlier, greater enthusiasm among the clinical and basic neuroscientists with improving economic situation would certainly make all these dreams come true.

Neurosciences in ancient India

Asoke Kumar Bagchi

Introduction

Neurosciences were based on metaphysical assumptions rather than anatomical findings in ancient India as dissection of the human cadaver was no permitted. Examination of disintegrating human corpses was the chief means of obtaining anatomical information. Dissection of animals like goat, cow, sheep, horse and very occasionally the monkey enriched the knowledge of those anatomists. The principal authors of Indian medical texts were Susruta, Charaka, Vagavata, Vela, Madhava and a few others. In the following treatise these texts have been analysed to obtain a glimpse of basic neurosciences in ancient India.

Ancient Indian medical scientists were uncertain whether *hridaya* (heart) or *mastishka* (brain) was the seat of consciousness.

Although descriptions of anatomy and physiology of the nervous system are available in ancient Indian texts, a casual observer will be at a loss to find specific mention of the anatomy of the brain, spinal cord, peripheral nerves and the autonomic nervous system. This is due to the variations in nomenclature used then and now. (Fig. 1 and 2).

That the language in the original *samhitas* (texts) is liable to varied interpretation is illustrated by the following. Although siras (head) was recognised to be a very important organ, the word *mastishka* (brain) occurs in only 2 places and *mastulunga* also meaning brain in 9 places in *Charaka* and *Susruta* Samhitas. and while recognizing the nature of the brain matter as 'the material inside the skull resembling clarified butter (*ghritam*)' no function is attributed to the *mastishka* and *mastulunga*. The functions of the brain have been attributed to the *hrdaya* (the heart). *Dhamani* is generally translated as an artery. In fact, it indicates a nerve while the term nadi which is generally translated as a nerve represents artery. In ayurvedic language any hollow channel, such as the umbilical cord, intestine was termed *nadi*. (CHARAKA NIDANA 5,16). This has led to confusion when ayurvedic literature is studied in terms of modern medical science. In *yoga* and *tantra sastras* however *nadi* means a nerve.

The anatomy of the brain is not described in ayurveda as such but the term *siras* (meaning head) has been used to denote brain. Charaka refers to (CHARAKA SAMHITA 17/5), that part of the body to which all the senses are said to belong and which is said to be the most important of all organs and calls it siras. *Susruta* is also of the opinion that the head is the most important organ of the body (SUSRUTA SAMHITA 3/18). There are elaborate descriptions of how such affections as *unmada* (insanity) (CHARAKA NIDANA 7/3), *apasmara* (epilepsy) (CHARAKA NIDANA 8/23) are produced but everywhere the terms *hrdaya* and *dhamani* are used. Everywhere in ayurveda, *hrdaya* is said to be the seat of mind, intelligence, consciousness, and sleep. *Bhela samhita* is the only treatise which mentions that the seat of mind lies between the head and the palate, thus referring to the brain.

Hrdaya - the brain and not the heart

In ayurveda, *hrdaya* indicates nothing but the brain. The places, where *hrdaya* has been used to mean brain in ayurveda may be divided into the following 8 groups:

1. *Hrdaya* - the place of *atma* and *cetana* (consciousness, both the term atma and cetana are synonymous).

2. *Hrdaya* - the place of mind, *citta* (*citta*-feeling and *ceta* knowledge, *citta* and *ceta* are synonymous).

3. *Hrdaya* - the site of *anubhuti* or perception.

4. *Hrdaya* - the *site* of *Jnyana* or intellect.

5. *Hrdaya* - the *site* of *smriti* or memory.

6. *Hrdaya* - the *site* of *Jivana* or life.

7. *Hrdaya* - the centre for *Nidra* or sleep.

8. *Hrdaya* - the main centre of the nervous system or *Snayu tantra kendra.*

Though the term *hrdaya* has been used more than hundred times in *Charaka* and *Susruta Samhitas,* there is no reference to the physiology of *hrdaya* especially in respect of its functions. In ayurveda there is only the mention of heart, brain, lungs, liver, spleen, kidneys but no clear description of anatomy and physiology of these organs is given.

The functions of *hrdaya* meaning the brain, which are mentioned in a few places would, today, be grouped as functions of the brain. For instance the

verse '*Arthe dasamahamoolya*' runs thus: (1) The body consisting of the six limbs; (2) knowledge; (3-7) the five senses and the five objects of the senses; (8) the soul as invested with attributes; (9) the mind and (10) the thoughts are all established in the *hrdaya* (Charaka Samhita 30/2(1)).In the passage describing the *atma,* the qualities of *atma* have been listed as 'desire, malice, happiness, sorrow, instinct, consciousness, apprehension, intellect, memory and vanity' (Charaka Sharira 1/19). The seat of all these qualities is in the brain and not in the heart. The above passage continues. If the *hrdaya* is injured unconsciousness follows, if it is destroyed, the limbs of the body are paralysed and death may take place. The *atma* itself is aware of all cognisable things by perception and is known by the name of 'holder' of the body which is placed in the *hrdaya.* The union of body, *indriyas* (spinal senses) mind and soul is called the holder and that is the essence of life. *Hrdaya* is termed great and covetable as it possesses, important qualities.

Some of the passage in ayurveda where the term *hrdaya* is used to mean the brain are quoted below:

1. The soul as invested with attributes, the mind and thoughts are all established in the *hrdaya.* (Charaka Samhita 30/2 -2)

2. The *hrdaya* is the seat of consciousness. (Charaka Sharira 7/7-4)

3. The *hrdaya* is the special seat of consciousness. The channels carrying the vital principle of the body are attached to it. (Susruta Sharira 4/31-5)

4. The *hrdaya* is said to be the primary seat of consciousness in animated beings. Sleep overcomes a man whenever the *hrdaya* is enveloped in the illusive effects of *tamas.* (Susruta Sharira 4/35-6)

5. The *foetus* is endowed with consciousness owing to the formation of the *hrdaya* as this is endowed with consciousness. (Susruta Sharira 3/14-7)

6. The *dosas,* of the persons whose minds are assailed by rajas (passion), *tamas* (darkness) and the rest becoming excited seize the *hrdaya* which is the foremost seat of the inner-self as also the seats of the senses and locate themselves there. (Charaka Nidana 8/2-9)

7. The *hrdaya* is seat of intellect and mind. (Susruta Sharira 3/18 -10)

8. The *hrdaya* is called the seat of knowledge of mind. It is the opinion of Kritavirya. (Susruta Sharira 3/18-11)

9. In a person of sick mind, the *dosas* vitiate the *hrdaya* which is the

abode of intelligence and overwhelm the channels that convey impressions from the senses to the mind, quickly stupefy the mind. (Charaka chikitsa 3/3-12, Madhava-Unmad Nidan-4.)

10. Wine produces intoxication by quickly agitating the mind as also its seat. The *hrdaya* is said to be the seat of the channels that regulate the passage of *rasa* and the other *dhatus* and also of the mind, the understanding, the senses and the soul and also of the *ojas* which is the foremost of the *dhatus.* (Charaka chikitsa 24/9-13)

11. Mind the reason of all sorts of intellect is situated in the *hrdaya*. Mind is only the cause of all actions. (Vela. Ch. 8 p.149-14)

12. Mind is situated between the skull and the palate. Mind, intellect and all senses exist in the *hrdaya.* (Bhela Samhita, Ch.25 p.204-15)

13. Mind along with the organs of senses originates from the *hrdaya* of living beings. (Kasyap Phakka Ch.6-16).

14. *Vayu,* being afflicted and the understanding being disturbed the dosas become aggravated and provoked, then reaching the *hrdaya* and obstructing the channels through which the mind operates, they beget insanity.or the derangement of the mind, understanding, knowledge memory, devotion, behaviour, acts and practices.(Charaka Nidana 7/3-17)

15. It is called *hrdaya* as the channels are attached to it and these are rooted to the *hrdaya* being the lotus of knowledge. (Bhela Samhita Sh.4-18)

16. Mind- the principal of 10 organs is situated in lotus of *hrdaya.* (Vedanta Verse 12-19)

17. By the influence of anxiety and grief *vayu* being vitiated occupies the *hrdaya* and destroying the memory, produces epilepsy. (Madhava Nidan, Apasmara 1-20)

18. While located there and stirred by the impulses of lust, wrath, fear, cupidity, headlessness, joy, grief and anxiety, they overwhelm the *hrdaya* and the seat of the senses. The result of this is that the person becomes subject to a fit of epilepsy. It is a temporary introgression into darkness,accompanied by hideous contentions owing to the drowning of memory, understanding and mind. (Charaka Nidana 8/2-3-21)

19. Of persons whose tranquillity has been disturbed by the *dosas* being excited in a large measure and who take bad and impure food and drink,

epilepsy sets in when their *satwa* is destroyed by *rajas* and *tamas,* when their hrdaya is overwhelmed by the *dosas* and when their minds are afflicted by anxiety, lust, fear, wrath, grief, care and the rest. (Charaka chikitsa 10/3-22)

20. Accumulated *dosas* afflict the *hrdaya* by means of the channels (that have their roots in the *hrdaya*). The persons thus afflicted are tortured by his wandering mind in consequences of which he loses consciousness. Charaka chikitsa 10/4-23)

21. When *vayu* is aggravated by disease and migrates upwards from its own site and reaches the *hrdaya* and affects it thus producing pain in the head and temples. When the aggravated *vayu* leaves the *hrdaya,* the patient gets relief and when affected again he becomes unconscious. (C.Siddhi, 9/9-10-24)

22. The head is divided by five joints called the *seemanta* and is the seat of insanity fear and mind. The destruction of this part causes death.(Susruta Sharira 6/77-25)

23. All the senses of perception the channels for the flow of senses and the life are seated in head. (Charaka Samhita 9/3-26)

24. When the *kapha* takes its seat firmly in the *hrdaya* and covers up the intelligence also seated in the *hrdaya* the condition called sleep is produced. (Charaka Samhita 9/12-27)

25. Entering the hrdaya, alcohol by its ten quantities destroys the ten qualities of the *ojas* and brings the mind into an abnormal condition. (Charaka chikitsa 24/10-28)

26. Wine courses upward being regulated by the nerves and ultimately reaches the *hrdaya* and thence the organs of sense perception and mind and brings on intoxication. (Susruta Samhita 45/193-29)

27. In the *hrdaya* are seated the ten *dhamanis* and (1) *prana* and (2) *udana vayus,* (3) mind, (4) intelligence and the five (6-10) *mahabhootas.* Just as the rays of the sun are being supported by the sun, similarly the sense of perception and channels of the senses and life are also being supported by the head. (Susruta Sharira 9/3-30)

Chakrapani in commenting on the 5 *mahabhootas* mentioned in this passage, says that the *bhootas mean the 5 objects of the 5 senses of perception. Thus (1) kshiti* i.e. carrier of touch, (2) *apabhota* i.e. carrier of taste, (3) *teja bhuta* i.e. carrier of form, (4) *vayu bhoota* i.e. carrier of senses, (5) *akasabhoota* i.e. carrier of sound. All these are carried by their respective *dhamanis* or nerves. Each has a separate *dhamani* to carry the

abovementioned sensible objects. In this connection, the verse of Charaka (Charaka Samhita 30/2) may be referred to which indicates the following. In *hrdaya* there exist ten objects and they are carried by ten *dhamanis* to *hrdaya*. The ten objects are (1) six limbs, (2) knowledge (3-7) the five objects of the senses (8) the *jivatma* or consciousness (9) mind with thought of object and (10) *oja*. Here six limbs of the body have been mentioned instead of *prana vayu, oja* and *udana vayu*. The remaining objects are all similar.

In apoplexy, *dosas* after being aggravated affect the *hrdaya* which is the abode of life and take away the action of speech, body and mind. It causes suspension of all the functions of life in the weakened living creature. The man thus affected with apoplexy remains like a log of wood, apparently dead. (Charaka Samhita 24/20-31) When the *vayu* afflicts the weakened *hrdaya* it agitates the mind of the living creature and darkens (or stupefies) his perception. (Charaka Samhita 24/13-32)

It is obvious that the seat of mind, sense organs and life as well as the soul intellect etc. is in the head and especially between the skull and the palate i.e. in the brain as mentioned by Vela. (Bhela Samhita p.149 204 -35) Besides the determination of the seat of mind, the location of *hrdaya* may be settled by the identification of the seat of the object of soul and mind.

The Identification of the Seat of Objects of the Soul and those of the Mind

According to Charaka, desire, aversion, happiness, sorrow efforts consciousness knowledge intellect, memory and ego are the objects of the soul. (Charaka Sharira 1/19-56) Some are of opinion that desire, aversion, happiness, sorrow and efforts are the qualities of soul.

He also said that, thinking, deciding, discussion, grasping the determination and anything perceived by the mind are the objects of the mind.(Charaka Sharira 6/8)

A study of the objects of soul and mind shows that desire, aversion, happiness, sorrow, care, consciousness apprehension, intellect, pride, thought, judgement, argument, contemplation and determination are received by soul and mind seated in the *hrdaya*. Now the question is that whether these objects are received by the brain or the heart. According to modern science all these are the subjects of the brain and none of them are of the heart.

Hrdaya the Seat of Origin of Dhamani - The Nerve

Susruta says when the dosas affect the external sense organs and the mind

carrying *dhamanis* the individual suffers from unconsciousness.(Susruta Samhita 46/2-37)

Charaka says there are ten *dhamanis* attached to the hrdaya. (Charaka Samhita 30/2-38)

Vela mentions - There are ten dhamanis in the upper *hrdaya.* (Bhela Samhita S.20 P.39)

As regards epilepsy Charaka says: 'Accumulated *dosas* (pathological conditions) afflict the *hrdaya* by means of the *dhamanis.*' The person thus afflicted is then tortured by his wandering mind, in consequence of which he loses consciousness. (Charaka chikitsa 10/4-40)

Charaka says regarding the cause of insanity 'of a person of weak mind, the dosas vitiate the *hrdaya* which is the abode of intelligence and overwhelm the *dhamanis* that convey impressions to the mind quickly and stupefy the mind'. (Charaka chikitsa 9/3-41)

The agitated *vayu* while coursing swiftly through the *dhamanis* (nerves) of the body, shakes it in quick succession and a disease is originated which is called *akshepaka* (spasms, convulsions, seizure). (Susruta Nidana 4/45-42)

The disease in which the extremely agitated *vayu* affects the nerves which spread either in the left or in the right side of the body whether in the upward, downward or lateral direction making them lax and vigourless and in which the joints of the other side of the body become useless and inoperative is called *Pakshaghata* (hemiplegia). (Susruta Nidana 1/53-43)

Consciousness and a normal condition of the organism return with the passing of the enraged *vayu* from the hrdaya, while on the other hand, the patient relapses into unconsciousness simultaneously with the involvement of the hrdaya with that enraged vayu. This disease is called *apatantrakah.* (Susruta Nidana 1/56-44)

The *vayu* being excited enters into the nerves of the head. From the excited *vayu* one gets a severe headache. (Charaka Samhita 17/8-45)

Affecting the *hrdaya* causes pain in the head and temporal region. The eyes become fixed. The patient becomes unconscious and makes a peculiar sound. When the aggravated *vayu* leaves the *hrdaya* the individual becomes conscious and again becomes unconscious when the *hrdaya* is again affected. This condition is also called apatantraka. (Charaka Samhita 19/10-46)

When the *kapha* seated firmly in the *hrdaya* affects the special senses of the *hrdaya* the individual suffers from the affection of *tandra* (narcolepsy). (Charaka Samhita 9/12-47)

The potency of a wine promoted by the bodily heat of man causes an upward movement through the *dhamanis* and ultimately reaches the *hrdaya* and thence through its own subtility and the expansiveness, permeates the entire organism and gradually attacks and overwhelms the organs of sense perception and fogs the mind from reasons and brings on intoxication. (Susruta Samhita 45/193-48)

The above mentioned verses which deal with apoplexy and insanity, indicate that the nervous system being vitiated produces those diseases, which are the diseases of the brain and not of the heart. In connection with the description of *dhamani,* elaborate discussion has proved definitely that *dhamani* indicates nerve in all respects. It shows that the term *hrdaya,* which has been mentioned in ayurveda in relation to *dhamani* indicates brain. Because no nerve originates from the heart but from the cerebrospinal and autonomic nervous system.

Conclusion

The preceeding passages which have been quoted from ayurvedic literature definitely prove that *hrdaya* and *dhamani* as used in these passages always to indicate the brain and the nerve respectively and never the muscular heart and the artery as generally believed.

Concepts of autonomic nervous system

Ancient Indian doctors definitely recognised the function of the autonomic nervous system. The functions of different forms of *vayu* viz., the functions of *prana vayu* in regulating the heart, lungs and intake of food the functions of *samana vayu* in regulating the process of digestion those of *apana vayu* in regulating the process of excretion and parturition and the functions of *vyana vayu* in regulating the vasomotor functions, are those of the autonomic nervous system.

In *tantra* sastra the autonomic nervous system has been described in *Sat Cakra Niroopana* as follows:

In the space outside the *meru* (spine) placed on the left and on the right are the two *shiras* (*nadis*) of the nature of moon and the sun the *ida* and the *pingala.* The *nadi* sushumna (spinal cord) is in the middle. The *ida nadi* on the left comes from the left of scrotum and is of the nature of the moon. On the right *pingala* comes from the right of scrotum and is of the nature of the sun. These two nadis go upward from the *muladhara* and reach the space between the eyebrows after passing through the *ajana*

cakra and make with the sushumna a plaited knot of three (*triveni*) and proceed to the nostrils, the ida to the left nostril and the *pingala* to the right one. During their journey ida, *pingala* and *sushumna* conjoin at the three *granthis (knots): brahma granthi* (situated in *manipoora cakra*) *vishnu granthi* (*anahata cakra*) and *rudra granthi* (*ajana cakra*). These three are also called *triveni*. As all these three meet together at *muladhara* this place is called *yukta* (united) *triveni* and as they separate themselves at ajna cakra, this place is called mukta (separated) *'triveni'*.

Concepts of central nervous system in tantra sastra

This is generally studied in terms of *sat cakra* this is however not the place for a detailed description of the *Cakras*. A brief review only is given below:

The sat *cakras* or six centres can be studied under three categories (1) the gross anatomical (2) philosophical and (3) anatomophilosophical categories revealed only to the expert yogis. The last category consists of conception of different centres appearing like lotuses having petals varying from two (*ajna cakra*) to 16 (*vishuddha*). The *sahasrara* which is outside the six *cakras,* possess one thousand petals. There is also mention of different colours of the petals which bear the different alphabets again in different colour. The pericarp is said to represent the regions earthy to etherial in which is seated the *veeja sakti* and other deities possessing different articles in their hands and also possessing different carrier animals. There are other attributes occupying the *cakras*. These are kala (*attribute*), *tativa* (*category*), *bhuvana* (region), *varna* (letter of the alphabet), *pada* (words) and *mantra*. All these subtle anatomical details are said to be revealed exclusively to the competent yogi, so we are not concerned with their description here. The first two categories i.e. gross anatomical and philosophical are of considerable interest to our present study.

Gross anatomy of satcakra

It may be said that at least 4 terms have been definitely identified in terms of modern anatomy. These are Sahasrara- the brain (2) *Susumna*- the spinal cord (3) and (4) *Ida* and *Pingala*- the two chains of the autonomic nervous system, running by the two sides of the spine, *ida* the left one and *Pingala* the right one. Now let us try to identify the other structures anatomically. There are six main centres (*Cakras*) inside the spinal cord, which again consists of two structures – *Chitrini* and *vajrini*. The centres located inside the spinal cord (*susumna*) and named (1) *mooladhara* (2) *svadhisthana* (3) *manipura* (4) *anahata* (5) *visuddha* and (6) *ajna*. There are many secondary centres along with the primary 6 centres (*satcakra*).

The *nadi sushumna,* whose substance is the threefold *gunas* is in the middle and represents the form of moon, sun and fire, the nadi *vajrini*

situated inside the *sushumna* (i.e. gray matter) representing the moon and the *nadi citrini* situated within the *nadi vajrini* (i.e. substantia gelatinosa centralis)representing the sun.

"Her (*susumna's*) body a string of blooming datura (dhustura) flowers, extends from the middle of the *kanda* (the bulb situated 2 fingers above the anus and two fingers below the penis apparently the conus medullaris of the spinal cord) to the head. The vajra inside her (*susumna*) extends shining from the penis to the head. (lst sloka).

Inside her (*vajrini*) is *citrini* who is lustrous and attainable in yogis. She (*citrini*) is subtle as a spider(s) thread and pierces all the lotuses which are placed within the back bone. Inside her (*citrini*) is the brahma *nadi* which extends from the orifice of the mouth of Hara to the place beyond where *Adideva* is (2) Here the orifice of mouth of *Hara* is the *mooladhara* and *Adideva* is the supreme *Bindu* in the pericap of the thousand petalled lotus i.e. the brain. The *Brahma nadi* thus represents the spinal canal, extending from the conus medullaris to the ventricles in the brain. From these two slokas we can definitely identify the following anatomical structures.

Sushumna the spinal cord, *Vajrini* the grey matter in the spinal cord, *Citrini* the grey mater surrounding the central canal (substantia gelatinosa centralis) and the *Brahma nadi* the spinal canal. Now with the six centres situated in different parts of the spinal cord. The verses 4 to 13 deal with the description of *Mooladhara cakra*.

1. *Mooladhara Cakra* (verses 4-13)

The *mooladhara* lotus (it is called *muladhara* because of its being at the root (moola) of the six centres is attached to the mouth of *sushumna* and is placed below the genitals and above the anus. (4) In this is the *cakra* and *prithivi* (Or *Indra*) (5) He (*Indra*) carries on his lap the child creator (i.e. creator as the image of a child). (6) In the pericap of the lotus there constantly shines the beautifully luminous and soft, lightening like *kamaroopa* (i.e. by which *kama* is caused to be felt). There is always and everywhere the *vayu* called *kandarpa,* who is the Lord of Beings (he is *Svayambhu* in his *linga* (form) (9) Over him shines the sleeping *kundalini* gently covering the mouth of *Brahmadwara* by her own. It is she who maintains all the beings of the world by means of inspiration (10.11) within it (*Svayambha linga* round which *kundalini* is coiled) reigns dominant Para, who is wonderfully skilled to create and is subtler than the subtlest. (12).

2 *Svadhisthana Cakra* (verses 14-18)

There is another lotus placed inside the *sushumna* (spinal cord) at the root

of the genitals (14) within it is the white shining watery, region of *Varuna (15).*

3. Manipoora Cakra (verses 19-21)

Above it, and at the root of the navel is the shining (*Manipoora*) lotus. Meditate there on the region of fire (19) His (fire) hands are placed in the attitude of granting boons and of dispelling fear. He is the destroyer of creation (20).

4. *Anahata Cakra* (verses 22-27)

Above that in the heart is the charming lotus (*anahata*) It is known by its name anahata and is like the celestial wishing tree (*Kalpataru*). It is the region of *vayu.* (2) He who mediates on this heart lotus becomes the lord of speech and able like *Isvara* to protect and destroy the worlds (26) His inspired speech flows like a stream of water.

5. *Visuddha Cakra* (verses 28-31)

In the throat is the lotus called *vishuddha* which is pure. In its pericap, there is the ethereal region (*akasa*) (28).

6. *Ajna Cakra* (verses 32-38)

The lotus named ajna is like the moon beautifully white (32). Within this lotus dwells the subtle mind (*manas*). (33) It is here that *Bhagavan* manifests himself in the fulness, of his might. This is the incomparable and delightful abode of Vishnu. The excellent yogi at the time of death joyfully places his vital breath (*prana*) here and enters that supreme eternal birthless, primeval *Deva* the *Purusha* (38).

7. *Sahasrata* (verses 40-49)

Above all these in the vacant space, wherein *Shankhini nadi* and below *visarga* (upper part of *Brahma randhra*) is the lotus of a thousand petals. This lotus has its head turned downwards (40). Within the *Sahasrara* is the full moon. Inside it (moon) the (*chandramandal*) is the triangle and inside this again, shines the Great void (41). Well concealed is that subtle *bindu,* which is known to all as *Paramashiva.* He is the *Brahman* and *Atma* of all beings. He is the sun which destroys the darkness of ignorance (*ajana*) and delusion (*moha*) (42). Here is the supreme sixteenth *kala (amakala)* of the moon. From here whose source is the *Brahman* flows copiously the stream of nectar and she is the receptacle of the stream of nectar (46). Inside this amakala is *nirvana kala* of the shape of the crescent moon. She grants knowledge (47). Within the *nirvana kala* shines the primordial *nirvana shakti.* She is the life of all beings. (48) Within her is the abode of *Shiva*

known by the name of *Nityananda.* This is the place of the knowledge of the *atma* or the place of liberation (49). A close study of the relevant portions of *Satcakra Niroopana* quoted above shows the following. The figures in brackets indicate the number of *sloka* quoted above.

1. The body of *Sushumna* is like a string of blooming datura flowers (1) This may be interpreted as the segmented appearance of the spinal cord, due to the presence of the nerve roots originating from it.

2. The spinal cord extends from the regions of the genitals to the head (1).
3. The spinal cord, as has already been identified, consists of grey matter (*vajrini*) inside which is substantia gelatinosa centralis (*citrini*) inside which is the spinal canal (*brahmanadi*) (2).

4. The *Mooladhara Cakra* situated at the conus medullaris, the bulb of the spinal cord at the sacral region is the centre for procreation. The *Kamaroopa kandarpa vayu* with coiled up *kulakundalini* all signify procreation (4-12). Mooladhar (*mooladhara* i.e. the chief supporter) is generally interpreted to mean the chief supporter of the other *cakras* but it may also mean the chief supporter of creation itself as it is the centre for procreation.

5. The *mooladhara* probably represents the sacral enlargement from which the parasympathetic fibres originate and supply the genitals, urinary tract and sigmoid. The Hindus attribute to *Mooladhara* the control of the genitals only leaving the urinary tract to the control of the *Svadhistan Cakra.*

6. The *mooladhara cakra* represents the seat of *Prthivi bhuta.*

7. The *svadhisthan cakra* represents the watery region of *varuna* (15). This is thus the seat of *Apabhuta.*

8. Anatomically, the *Svadhisthan* represents the first 3 lumbar segments of the spinal cord, the fibres from which along with those from the two sympathetic chains ida and pingala form the inferior mesenteric ganglion which supply the sympathetic fibres to the genitals, urinary tract and sigmoid colon, the same regions supplied by the *mooladhara.* Here *Svadhisthan* is predominantly the controller of the seat of *Varuna* or *apabhuta.*

9. Considering these in terms of ayurveda, we find that all these functions are being controlled by *apana vayu* in the function of defecation, micturition and parturition. *Mooladhara* and *Svadhisthan* cakras are the spinal centres corresponding to inferior mesenteric ganglion of the autonomic nervous system, the seat of *apana vayu.* We may now conclude in terms

of *Satcakra* that the function of parturition, ejaculations are controlled by the *mooladhara,* the seat of procreation, while micturition, urine formation etc. are in the jurisdiction of the *Svadhisthan cakra.*

10. The *manipoora cakra* at the root of the navel, is the region of fire (19) Apparently the digestive fire, on what is termed in *Bhagavat gita* as *Vaistanara.*

11. Anatomically, this represents the thoracic region of the cord, fibres from which in association with those from the sympathetic chains *ida* and *pingala* form the solar plexus which again supplies the whole of alimentary system including the liver and pancreas.

12. The *Manipoora cakra,* thus represents the thoracic portion of the cord which regulates digestion.

13. The hands of the Fire situated in the *Manipoora cakra* are placed in the attitude of granting boons and dispelling fear. He is the destroyer of creation (20) This is quite appropriate as the digestive fire (the digestive secretion) is the main agent which digests the food and that alone can keep the individual living. If this fire is vitiated, it leads to death. We may compare with this what Charaka has said about the digestive fire. The fire which exists in the body as *pitta,* being normal or abnormal progress good or evil. (Charaka Samhita 12/15)

14. From ayurvedic point of view the *Manipoora cakra* represents the spinal centre corresponding to the solar plexus of the autonomic nervous system the seat of *samana vayu.*

15. The *Anahata cakra* situated in the region of the heart is the region of *prana vayu* (22). This represents the centre for respiration and circulation. Thus controlling most vital functions of the body, *anahata cakra* acts like the celestial wishing tree (*kalpavrksha*) (23) and also like Iswara protecting and destroying the world (26). This is also the centre for maintaining the speech (26).

16. Anatomically, the *anahata cakra* represents the upper segments of the thoracic spine from which arise the fibres, which supply the sympathetic fibres to the heart, lungs and trachea, thus maintaining circulation, respiration and speech.

17. From ayurvedic point of view, it represents the spinal centre corresponding to the cardiac plexus the seat of portion of the *prana vayu* (circulation and respiration). This also correspond to the portion of *udana vayu* (speech).

18. The fifth *cakra* or *Visuddha cakra* is in the throat and is the etherial

region (28). Ether (*akasha*) is all pervading and so this centre controls over a wide range of our body from the head down to the lower abdomen. This represents the portions of the medulla oblongata which supply the parasympathetic fibres.

19. Anatomically, *Visuddha cakra* represents the region of the medulla from which parasympathetic fibres supply through the 7th and 9th nerves, the salivary glands. It appears thus, that the *mooladhara* and *visuddha cakras* represent the parasympathetic system while the other 3 cakras the sympathetic system.

20. From ayurvedic point of view this *cakra* represents the medullary centre corresponding to the autonomic nervous system, the seat of the parts of *prana vayu* and the *samana vayu*.

21. The *Ajna cakra,* the seat of mind (33) is situated between the eye brows. Further, as the *jnanendriyas* e.g. eye ear etc. are also situated in the head, similarly the head i.e. the brain is the seat of the mind.

22. Anatomically, this may be taken to the midbrain which along with the 3rd nerve and parasympathetic fibres to the muscles of the eye. This may be called the seat of special senses the gateway to the mind.

23. From ayurvedic point of view, the *Ajna cakra* represents the cerebral centre, the seat of portion of *prana vayu* regulating the special senses, the other portion of *prana vayu* regulating the mind being situated in the cerebrum, the *Sahasrara* of the *tantra shastra*.

24. *Sahasrara* above all these in the vacant space is the lotus of a thousand petals with its head turned downwards (40) Here the vacant space represents the space within the bony skull while the lotus of a thousand petals indicates the cerebrum. The base of the brain is irregular while the vertex is regular in contour, so it may be conceived as its head turned downwards. The numerous gyri appearing as the petals gives the name as "thousand petalled lotus".

25. The great void (41) is undoubtedly the ventricular cavity which is well concealed in that subtle *Bindu* which is the chief root of liberation (42).

26. Within *Sahasrara* is the full moon (*chandramandal*) (41) This area might be interpreted as the white matter of the brain.

According to Susruta, moon is the predisposing deity of the mind (Susruta Sharira 1/7). This full moon might be taken to mean the seat of mind also.

27. The cerebrum of *Shahasrara* is undoubtedly the most vital part of the

body, controlling alone all the functions of the body and is thus rightly called the abode of "the *Brahman* and the *Atma* of all beings. This is quite true as the cerebrum is the seat of consciousness, and intelligence.

28. It is not possible here to correlate the other structures (1) the sixteenth kala of the moon (*amakala*) (b) the *nirvana kala* mentioned to be present in shahasrara in modern *anatomy*. They might be taken to indicate the basal ganglion.

29. From *amakala* flows copiously the stream of nectar and she is the receptacle of the stream. (46) This stream of nectar undoubtedly means the cerebrospinal fluid in the great void the ventricles.

30. This is the place of the knowledge of the *atma* of the place of liberation (49) The cerebrum is undoubtedly that place.

Nervous system as found in other Indian literature

Casual descriptions of the nervous system are scattered throughout the Hindu literature, philosophical or otherwise,especially in various treatises detailed for different *yajnas* in which an animal is to be sacrificed. *Yajnasastra* is fairly vast and it is not within our scope of study. The same thing is also applicable to *malla vidya* (the science of wrestling) in which apart from other anatomical details, those of the nervous system are also mentioned.

In dictionaries, again we find that the root meaning of several terms are extremely appropriate. One example can be considered here: *Kaseruka* meaning the spinal column. This word is derived from 'Ka', meaning vayu; 'sheta' lies i.e. in which lies the vayu. Thus the spinal cord is the holder of vayu. And we have already shown that the nervous system of our body is the vayu apparatus.

Summary

In the text of the article the neurophysiological and neuroanatomical concepts of the ancient Indian medical scientists have been very briefly related. Even though they lacked the facilities of dissection and experimentation, their concepts were not much behind those of the present times. The difficulties in the exact interpretations of the ancient verses relating to neurosciences created confusions and ambiguity in later understandings. The principal texts of Susruta, Charaka, Vela (Bhela) and Madhava have been referred to in the treatise for proper comprehension.

In short the above treatise is a rather brief account of the basic neuroscientific concepts of the ancient Hindus who authored the voluminous texts of the ancient Indian medical sciences widely known as the Ayurveda, meaning the science of life.

Note: The numericals in parentheses indicate the respective suktakas.

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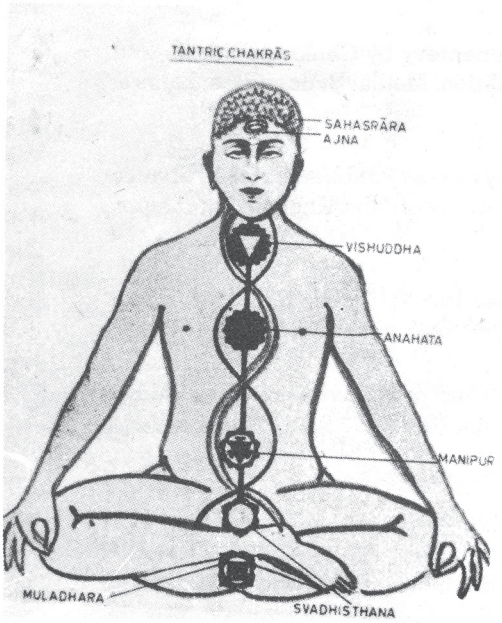

Fig. 1: Charaka.

Fig. 2: Susruta the surgeon in his youth.

Fig. 3: Sahasrara Chakra.

Fig. 4: Tantric Chakras.

A historical account on lathyriasis

K. K. Sinha

General Sleeman's clinical account of lathyrism in his book, **Rambles and recollections of an Indian official** published in 1884, is said to be the first of its kind in English. I recently came across two books by Dr. Francis Buchanan describing his experiences whilst travelling through Bihar in 1810-1812. He provides a clinical description of the disorder and even discusses its possible aetiology. This essay attempts to rectify an error in the history of lathyrism and pays tribute to Dr. Buchanan.

In 1807 Dr. Francis Buchanan was commissioned by the directors of the East India Company to undertake a statistical survey of Bengal. He had completed a survey of Mysore and had served earlier as the Superintendent of the Honourable Company's Botanic Gardens, Calcutta. His work in Mysore must have been very impressive to attract the attention of the East India Company's directors, who in a despatch to the Governor General in Council specially recommended Dr. Buchanan for this survey.

Among the many directions that the Governor General in Council issued on 11th September 1807, while appointing Buchanan for the purpose, were included "Your inquiries are to extend throughout the whole of the territories, subject at the immediate authority of the Presidency of Fort William ... Your inquiries should be particularly directed to the following subjects, which you are to examine with as much accuracy as local circumstances will admit ... II. The condition of the inhabitants, their number, the state of their food, clothing and the peculiar diseases to which they are liable, together, with the means that have been taken or may be proposed to remove them; the education of the youth; and the provision of resources for the indigent ..."

The area of 5330 square miles with which Buchanan was concerned in Bihar and Patna was part of the old 'Zila' (district) Bihar, consisting of the present Patna, Nalanda, Gaya and parts of Aurangabad districts of the present Bihar State. He surveyed them in 1811-12 and prepared his report for the East India Company. The elaborate tour diary maintained by Buchanan while conducting his survey in these districts was later edited by V.H. Jackson and published in the Journal of the Bihar and Orissa Research Society in 1922. (The manuscripts of his survey report are preserved in the India Office Library, London.)

Buchanan carried out the directions of the Governor General to the letter. Everyone who has studied his work is amazed at his capability and hard work. Succeeding state Gazetteers have been based on his reports. Buchanan's observations on diseases and problems related to health are especially praiseworthy in view of the short period and small staff allotted to him. Especially rivetting is his clinical description of spastic paraplegia resulting from lathyriasis and the prevalent theories of its probable aetiology "...There is a species of lameness called *Khungja* in the Sanskrit language and *Maghiya langra* in the vulgar dialect, as it is peculiarly prevalent in Magadha and in fact it is very common in Patna and its immediate vicinity, but I observed it nowhere else, although I am told it prevails in every part of both districts (Patna and Gaya). It attacks all ages and both sexes, and after continuing a year or two is considered incurable but some have recovered after having been affected for several months. It seems to consist of weakness and irregular motion of the muscles moving the knee, which are bent and moved with a tremulous irregular motion, somewhat as in the chorea, but not so violent. When the disease has lasted some time and has become confirmed, the legs suffer emaciation. It is not accompanied by fever, but in the commencement is often, though not always, attended with pain. It is attributed by some to eating *Khesari* (Lathyrus sativus) but this seems fanciful for although in Magadha this pulse no doubt enters largely into the diet of the poor, it does no less so in that of those in Matsaya (Dinajpur, currently in Bangla Desh) where the disease is as rare as in any other part of the world. By others it is attributed to sleeping on *Kodo* straw (a cereal grown in eastern India) an opinion which deserves more attention, for the grain of some fields of *Kodo* possesses narcotic exhalations very capable of affecting the health".

Lathyriasis continues to be a common neurologic disorder in Patna and Gaya. The toxic element in lathyrus sativus that leads to the damage of the corticospinal tracts in the mid dorsal spinal cord has now been isolated. It is of interest that continued use of lathyrus sativa as food was suspected to be the cause of this form of spastic paraparesis more than 175 years ago.

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Developmental neurobiology

Kalluri Subba Rao, Chinta R.K.Murthy

Developmental neurobiology, by definition, deals with the anatomy, physiology, biochemistry and pharmacology of the developing nervous system and the various factors which influence them. It is, at times, difficult to draw a line between studies on the developmental aspects from those on the ageing of the nervous system. This problem is especially evident in animals where the development of nervous system is postnatal and the process continues, albeit slowly, well into adulthood.

We describe in brief the work done in developmental neurobiology in various Indian laboratories.

P.K. Sarkar's group, at the cell biology laboratories of Indian Institute of Chemical Biology at Calcutta has worked on the elucidation of molecular and cellular basis of thyroid hormone (TH) action on brain development. It is well know that TH is required for normal growth and maturation of brain and this hormone promotes the formation of neuronal processes and synaptogenesis. Tubulin (a protein present in microtubules) was shown to be involved in these two process and the synthesis of this protein is induced by TH. These investigators have devised a method to isolate astrocytes (Chatterjee and Sarkar 1984) and have shown that glial cells contain more tubulin than neurons and that TH not only stimulates tubulin synthesis but also decreases its degradation (Chatterjee and Sarkar 1986, Chaudhary et al 1985). They have also shown that the astrocytic response to TH is seen in the first week of postnatal life in rats while the response of oligodendrocytes is seen during the second week (Sil and Sarkar 1987). These periods correspond with the two crucial phases of brain development, viz. synaptogenesis and myelinogenesis. According to these investigators, tubulin is formed in the glial cells and is transferred to the neurons. Currently these investigators are using monoclonal antibodies of the cell surface proteins to isolate different neuronal cell types (Chatterjee et al 1987) and cDNA probes to study the mechanism of action of this hormone at transcriptional level.

Lalitha and her colleagues at the Cancer Research Institute, Bombay have looked at the effect of high dose of hydrocortisone on the development of Purkinje cell arbor in rats. With daily administration of hydrocortisone

starting from the 10th postnatal day upto the 21st day there was tremendous granule cell deficit along with marked compression of Purkinje cell arbor where secondary and tertiary branches were vertically oriented. The basket cell axons were very prominent. These findings suggest that therapeutic use of glucocorticoids for fulminant infections during early neonatal life might have adverse effect on the cerebellar development which continues beyond birth in humans.

Anatomical aspects of the developing brain are being studied by the groups led by Bijlani, Gopinath and Wadhwa at the department of anatomy, All India Institute of Medical Sciences, New Delhi. These authors have shown abnormal cerebellar development in undernourished rats. The reduction in cerebellar surface area is associated with prolonged mitosis and proliferative activity in the external granular layer of this region in these animals. These were shown to be due to prolongation of SI phase and shortening of G2 phase of mitosis, with consequent delay in cell migration into the external granular layer of the cerebellum (Bijlani et al 1975, Deo et al 1975,1978,1979; Gopinath et al 1976). These workers have also examined the development of lateral geniculate nucleus, dorsal horn of spinal cord and cerebellar nuclei in the human brain (Damayanti et al 1983, Wadhwa and Bijlani 1983, Rizvi et al 1986, Bijlani et al 1987) and the innervation of human urinary bladder at different gestational ages. Employing histochemical techniques, electron microscopy and immunocytochemistry, they showed interesting aspects of cell proliferation, cell migration, cell death, axon elimination, dendritic growth, synaptogenesis and changes in the neurotransmitter localization and profiles in the above mentioned regions of the developing brain (Wadhwa et al 1985 a,b; 1986,1988 a,b; Mehra et al 1986; Mehra and Bijlani 1986; Wadhwa and Bijlani 1988, a,b).

G. Gopinath of the same department and her group are interested in the development and organization of the spinal cord in human embryos and foetuses, effects of malnutrition on the proliferation and maturation of cerebellum and damage to the developing brain by radiation (Gopinath et al 1976, 1981, 1987; Chowdhary et al 1982; Gopinath 1984). Recently, they have also been studying the long term behaviour of substantia nigra following neural transplantation (Mahapatra et al 1986, Gopinath et al 1987).

N.Z. Baquer and her group from Jawaharlal Nehru University of Delhi have described the metabolic changes in the developing brain. They observed an increase in the activities of glycolytic enzymes while those of enzymes involved in the synthesis of fatty acids declined under the same conditions (Zaheer et al 1968, Baquer et al 1968, 1973,1983; Hothersall et al 1983).

C.V. Ramakrishnan of Baroda and his group are well known for their

contributions on the influence of malnutrition on the biochemistry of the developing brain. They reported differential influences of malnutrition on the turnover of catecholamines and the density of receptors for these neurotransmitters in brain (Rajalakshmi et al 1974, Telang and Mandel 1983, Telang and Bhave 1983, Telang et al 1984). As undernutrition during development produces stress and as corticosteroids are involved in stress related phenomenon, these investigators have studied the corticosteroid mediated changes in cerebral metabolism. Since brain function is dependent upon membrane integrity, these investigators studied the effects of undernutrition on the composition of membrane lipids (Rajalakshmi et al 1974 a and b, Reddy and Ramakrishnan 1982, Uma and Ramakrishnan 1983 a,b). Presently, studies are being conducted by them on the influence of maternal alcohol consumption on brain metabolism.

In south India a group of workers led by T. Desiraju of the Department of Neurophysiology of National Institute of Mental Health and Neurosciences, Bangalore, has been studying the effects of malnutrition on the development of brain using anatomical, physiological and biochemical techniques. They have shown that dendritic growth and branching, though slower in undernourished rat pups, are greater than that seen in normal animals (Gundappa and Desiraju 1988). They have also shown that the learning abilities of the undernourished animals are greater than that of well fed age-matched animals (Mascarenhas et al 1986). They noted a spontaneous remission of certain anatomical and physiological parameters in the brain in the undernourished pups (Rajanna et al 1987). They also studied in detail the extent of prevention of occurrence of these aberrations by providing normal nutrition from the post-growth spurt (of brain) age and observed that it helped only to a limited extent. P.S. Sastry and his group at the department of biochemistry, Indian Institute of Science, Bangalore are working on the developmental alterations in the neurotransmitter receptors in human brain. (Ravikumar and Sastry 1985 a,b.) (For further details please see the article by P. S. Sastry in this volume.) T. Ramakrishna and his group at Calicut University are working on the electrical changes in the brain during maturation.

The group at Hyderabad led by one of the authors (K. Subba Rao) has studied changes in the nucleic acids, protein, lipids and activities of some enzymes in different regions of the normal human brain during development and in the brains of small-for-date babies (Subba Rao 1973, Sarma and Subba Rao 1974,1976; Subba Rao and Sarma 1976). Two phases were noted in the accumulation of various biochemical components, especially DNA and RNA, during the early development of human brain which may correspond to neuronal and glial cell proliferation schedules. The lag state between these two phases (around 22nd and 34th weeks of gestation) was markedly prolonged in the brains of fetuses from mothers of lower socioeconomic groups. Analysis of brains from small-for-date babies demonstrated no changes in the content of various biochemical components

per unit weight of brain while there was a reduction in these parameters when expressed for total brain. In the brains of children with Kwashiorkor there was no change in the number of cells but the cell size was reduced. A decrease in the proportion of long chain fatty acids and polyenoic fatty acids was seen in the brains of these children (Sarma et al 1983). The existence of a deoxyribonuclease with an acidic pH optimum was also reported in human foetal brain. The activity of this enzyme showed a positive correlation with cell replication (Subba Rao et al 1973). These studies were extended to an experimental model for small-for-date human brains. It was then learnt that there was a differential effect of undernutrition on the synthesis of various lipids (Subba Rao et al 1978). In their recent experiments on the rat brain, they have confirmed their earlier observations on the differential effects of early undernutrition. There was no influence of nutritional status on the activities of DNA metabolising enzymes, acid and alkaline DNases (Subba Rao and Subba Rao 1982). Further investigations on the DNA metabolism in developing and ageing brain are being carried out in this laboratory (Subba Rao and Subba Rao 1986; Subrahmanyam and Subba Rao 1988).

It will be noted that many Indian investigators have focused their attention on the effects of nutrition on brain development. Their findings will go a long way in helping to correct the tragic consequences of poverty so widespread here.

Lalitha and her colleagues at the Cancer Research Institute, Bombay have induced teratocarcinomas in mice by grafting 6 day old embryo under the kidney capsule. From these they have developed two transplantable tumour lines, one with a neural end point and the other pluripotential with a large neural component. They are engaged in isolation of neurotrophic factors from the neurogenic teratocarcinoma keeping in view that they may be useful for stimulation of axons in neurodegenerative diseases, during regeneration and maintain the neurones in neural transplants which usually start degenerating after several months.

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Neuroanatomy

Mahdi Hasan
(with technical assistance from Dhanraj Singh)

Historical account

The brain (*mastishka*)has been differentiated from head (*shiras*) in the Atharva Veda around the 2nd millenium BC. (Griffiths 1916) The science of medicine was very well developed in India of yore and the training of a physician was thorough and methodical. The teaching of anatomy was correlated with surgery and the physiological principles were emphasised during the teaching of internal medicine. There were no water-tight compartments between the different medical disciplines (Keswani 1974). Julius Jolly (1951), an authority on Indian culture during the early part of this century, commented 'Medicine can now be regarded as the oldest of Indian sciences and has been proved to be the science in which Indians specialized first.' Sushruta, the surgeon (circa 600 BC) and Charaka, the physician (circa 1st century AD) dominated the medical sciences in ancient India. In Sushruta Samhita it is clearly indicated that *unmada* (insanity) and *apsamara* (epilepsy) originate from shiras (head). Sushruta was also of the opinion that the 'head was the most important organ of the human body'.

Medical Heritage of India

Bhela, who is as old as Charaka, considered the brain to be the centre of mind, which he said is 'the highest of all senses and has its seat between the head and palate'(Keswani 1974).

Sushruta, the anatomist- surgeon credited with dissection of human cadavers in 600 BC, vividly described some cranial nerves connected with the specific sensory functions. He described two nerves coursing down behind the ears (*vidhura*) which, if cut, produced deafness. He also described a pair of nerves (*phana*) situated inside the two nostrils, which if cut, cause anosmia; a pair of nerves below the outer end of eyebrow, near the external corner of the eyeball (*apanga*) which, if cut, cause total blindness. The five special senses and sense perceptions, have been well-defined in the Samhitas. The five special senses mentioned are vision, hearing, smell, taste and touch (Keswani 1974). The Sushruta Samhita

states, 'Ten nerves maintain the functions of the body by carrying impulses of sound, touch, vision, smell, respiration, sighing, yawning, hunger, laughing, speech and crying.' On the other hand Charaka states, 'Memory is caused by the following eight impressions: coordination of mind practice, consciousness, concentration, repetition of sight, hearing or perception as tasting or smelling'. (Gulab Kunverba Ayurvedic Society 1949). The later tantric school considered cerebrum as the seat of the soul and the spinal cord as the centre for vital functions of the body. The whole of the nervous system, according to this school, is divided into various plexuses (*Chakras*), which extend from the root of the vertebral column upwards into the cranial cavity (Keswani 1974).

Some important research centres engaged in research in neuroanatomy in India

All India Institute of Medical Sciences, New Delhi.

A multidisciplinary approach to research in the neurosciences was fostered by R.K. Anand, L.W. Chacko, N.H.Keswani and Baldev Singh. Currently, Veena Bijlani and Gomathy Gopinath are conducting research in neuroanatomy at this institute.

The main thrust areas are as follows:

a) Developmental neurobiology in normal human and rodent.

b) Ontogeny of neurotransmitters and neuropeptides in different areas using immunofluorescence and immunoperoxidase techniques.

c) Morphometric studies on the developing brain in genetic mutants and under experimentally altered conditions.

d) Effects of undernutrition on developing brain.

e) Neuronal tracing techniques using horse radish peroxidase (HRP).
f) Pain pathways in developing human foetuses and monkeys

g) Neural transplantation.

Interdisciplinary Brain Research Centere, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh.

An Interdisciplinary Brain Research Centre was established in 1978 through the efforts of the author. Initially, the main thrust areas were neurotoxicology and neurogerontology. Both basic and applied research activities were undertaken at this centre to establish the correlation, if

any, between toxic changes in the brain as a result of chemical insults and heavy metals and physiological ageing. Heavy metals like thallium, zinc, cobalt, nickel and lead and pesticides like organophosphates and organochlorine derivatives were studied in depth. A new method for the histochemical demonstration of zinc was developed by Hasan (1977).

In the area of physiological ageing, the rate and intensity of accumulation of age pigment, lipofuscin, in the neurons and the normal and induced mechanisms of disposal of this pigment are being pursued.

Light microscopic observations using various neuroanatomical staining techniques, transmission and scanning electron microscopy are undertaken to study neuromorphological changes. Qualitative and quantitative histochemical techniques are utilized to study the mechanism of action of toxic substances and production and dissolution of lipofuscin. Physiological and behavioural studies are conducted simultaneously.

Department of anatomy, Christian Medical College, Vellore

Choroid plexus in experimental hydrocephalus is the target of research under the leadership of Mary Jacob. Morphometric analysis of the observations are also undertaken. Another area of research currently in progress is the experimental ischemic necrosis of various regions of the central nervous system.

Department of anatomy, Banaras Hindu University, Varanasi

Congenital defects induced by toxic chemicals are studied using histological and histochemical techniques. Some studies on normal development and neuroglia are also reported from here. Critical periods of development and the mechanism of action of teratogens are the main thrust areas of research. The centre was established by Shamer Singh and strengthened by G.C. Sen Sharma, Gajendra Singh and Jagdish Singh.

Department of anatomy, Postgraduate Institute of Basic Medical Sciences, Madras

Under the leadership of A. Krishnamurthy, studies on morphology and electrophysiology of the brain of the slender loris are carried out at this institute. The main areas under investigation are:

i) Morphology of different regions like cuneate nucleus, lateral geniculate body and cytoarchitectonic parcellation of the cortical areas using light microscopy.

ii) Electrophysiological mapping of the motor areas.

iii) Blood supply of various regions of the brain.

iv) Neural transplantation.

Department of anatomy, Grant Medical College and J.J. Hospital, Bombay

Investigations on the peripheral nerve with special reference to trauma and leprosy are carried out here under the leadership of Lata Mehta. Documentation of the early changes in the nerves affected by leprosy is the most significant achievement of this group.

Department of anatomy, King George's Medical College, Lucknow

Whereas R.C. Saxena and K.K. Bisaria have published a number of papers on cranial venous sinuses and on the cranial nerve relationships, D.R. Singh has worked on the effects of immobilization stress on the various regions of the brain using both light and transmission microscopic techniques. Scanning electron microscopy of the ventricular microscopic techniques. Scanning electron microscopy of the ventricular ependyma has been carried out by D.R.Singh in collaboration with M.Hasan (Aligarh) and V.R.Bajpai (CDRI, Lucknow).

Department of Anatomy, Government Medical College, Rohtak, Haryana

Morphometric reports on the anterior horn neurons and inferior olivary nuclei by Inderbir Singh and Usha Dhall are the significant contributions from this institution. Usha Dhall is currently engaged actively in immunohistochemical study of serotonin containing nerves in rabbit cerebral vessels.

Department of Anatomy, Medical College, Trivandrum, Kerala

Pandali had initiated investigations on the hypothalamo-hypophysial axis of reptiles and other vertebrates. Various staining techniques have been employed to identify the different cell types in the hypophysis during the early period. Currently the immunoperoxidase method is being used to localize the cells producing neurohormones in the hypothalamus and various hormones in the hypophysis cerebri.

Department of Neuropathology, National Institute of Mental Health and Neurosciences, Bangalore

Under the leadership of Sarala Das, investigations on genetic and biochemical correlations in human neuromuscular disorders, pathological and biochemical studies on ageing, dementia, epilepsy and mental retardation and ultrastructural studies on the biology of brain tumours are undertaken. Ultrastructural studies on human foetal and tumour vasculature to study the blood-brain barrier are carried out. Electron microscopic studies on synapses in human and amphibian models to understand neuronal plasticity are currently in progress.

Gross Neuroanatomy

Weight of the brain of Indian adults

Buchanan and Daly (1902) compiled a table of weights of the viscera of the 'natives' of Bengal and Bihar and noted that Rai Bela Ram Bahadur of Lahore Medical College had published the weights of the various organs of the natives of Punjab in 1894 in the Transactions of the First Indian Medical Congress. Based on the records of the Presidency Central Jail, Calcutta, where prisoners from Bengal and Bihar were kept, Maddox (1902) also published 2 tables on the organ weights in the 2 sexes. However, almost all the organs, the weights of which were noted by these workers,had been taken from subjects who had died from disease (Jit 1988). Modi (1920) gave the weight of the average adult male brain to be 49.5 oz. and that of a female as 44 oz. Later Modi (1936) reported the weights of the main organs in the subjects of Uttar Pradesh between the ages of 10 and 70 years.

Gjarpura and Jhala (1949,1950,1952) recorded the weight of several healthy organs. Their observations on the weight of the brain were, however, made on 46 adults. It was left to Jit (1988) to furnish reliable scientific data on the brain weight of 388 healthy adults (298 males and 90 females), aged 18 to 80 years, studied at autopsies for medicolegal reasons at the Postgraduate Institute of Medical Education and Research, Chandigarh from 1971-85. In each case the age, height, weight, sex and body surface area were recorded. The data was subjected to computerised statistical analysis. The average brain weight of a north Indian male is 1298 ± 102 (range 1,000 to 1530g) and that of a female 1195 ± 93g (range 945-1440g). Statistically, this difference is highly significant ($p<0.001$). Brain weight showed a positive correlation with body weight, height and body surface area and a negative correlation with age in both sexes. Thus a reported difference in weights of different races can be explained on the basis of difference in body weight and height. An increase was recorded in the mean values of the brain weight after the age of 30 years in both sexes.(Jit 1988) At the age of 60 years, the loss in brain weight (as compared with the average brain weight in the 3rd decade) was found to be 58g (4.4%) in men and 87.6g (7.2%) in women (Jit 1988).

The pattern of sulci and gyri in Indian brains

In 1911 Appleton reported the pattern of sulci and gyri of 2 Indian brains (one from Madras and the other from Andhra Pradesh). In 1920 the gross features of the brain of a patient from Goa were described by Cole. A detailed study of the patterns of cerebral sulci and gyri in residents of Uttar Pradesh (North India) was undertaken by Narayan (1947) who reported that the central sulcus cuts the superomedial margin in 75% of the hemispheres. In 5 out of 99 hemispheres it was in 2 parts. The precentral sulcus was single in 32 hemispheres, in 2 parts in 49, in 3 parts in 15 and

in 4 or more parts in 3 cerebral hemispheres. Most frequently it was found to anastomose with the superior frontal sulcus. In 1954 Jha supplemented this study by a more exhaustive investigation on 300 cerebral hemispheres obtained from North Indians. The ratio of brain weight to body weight was found to be 1:35.6 ± 1.5 in males and 1:35.4 ± 2.3 in females. Dioptographic tracings of the superolateral surface of the cerebral hemispheres were made and the length, width and depth of sulci measured directly but separately from the surfaces of the right and left hemispheres. The central and post central sulci were observed to be continuous in most hemispheres. The interparietal sulcus was usually shallower than the central sulcus. The terminal part of the lateral sulcus bifurcated in 146 hemispheres. The average length of sulci was detected to be greater on the left hemisphere except in the case of the inferior frontal sulcus which was larger on the right side.

Asymmetry in the length of human Sylvian fissure and depth of island of Reil

Sarfraz and Hasan (1985) have recently reported asymmetry between the two cerebral hemispheres. The left temporal lobe has been seen to be larger than the right in 65% of cases. According to Sarfraz and Hasan (1987) the mean length of Sylvian fissure was 5.9 cm on the left side (SE=0.12) and 5.3 cm on the right side (SE=0.18). ($p<0.01$). The mean depth of the island of Reil was 4 cm on the left and 3.4 cm on the right side ($p<0.001$).

The vertebral level of the termination of the spinal cord

Jit and Charnalia (1959) studied the level of termination of the spinal cord in 44 closely graded embryos and foetuses, 10 new-born infants and 80 adults from Punjab. The recession of spinal cord was rapid till the 120 mm C.R. stage when the termination reached the 5th lumbar vertebra. After this stage the recession was slower. At birth the termination was usually seen at the level of middle of 2nd lumbar vertebra. There remained an ascent of only half a vertebra before the adult level was reached. In 51.2% of adult specimens the spinal cord was found to terminate between the lower third of the lst and upper third of the 2nd lumbar vertebrae. In approximately half of these specimens the spinal cord terminated at the level of the disc between the lst and 2nd lumbar vertebrae. The range of termination of the spinal cord in adult varied between the lower third of the 12th thoracic vertebra and the disc between the 2nd and 3rd lumbar vertebrae. The level was not lower than the one described for adult whites. The cord terminated at a lower level in females. The range of variation in termination was the same in the two sexes. A statistical analysis of the findings indicated that there was a definite correlationship between the body length and the length of the spinal cord in both sexes, more so in females.

Arterial pattern at base of brain

Vare and Bansal (1970) investigated 175 human brains at Aurangabad

(Maharashtra) and reported many variations in the pattern of formation and branching of circle of Willis. The anterior cerebral arteries were unequal in size (11.4%), exhibited splitting in part of its course in 3.4%, had an anomalous origin (in 4 cases-2.3%- the left anterior cerebral artery arose as a branch of the right) or was present as a median anterior cerebral artery (1.7%). **Berry aneurysms** were detected in 6.9% of the specimens. The anterior communicating artery was duplicated in 10.3%, triplicated in 2.3%, string-like (diameter less than 1 mm) in 1% and absent on one side in 10.2%. The commonest variation of the posterior cerebral artery was its origin from the internal carotid artery. A right sided predominance of origin from the internal carotid artery was detected in 13.7% while it arose as a branch of the left internal carotid artery in 5.7%. **Aneurysms** were observed in 1.1%. The chief variations of the basilar artery related to the site of formation, size and the continuation as posterior cerebral artery. Most commonly it was formed at the lower border of pons but in 16% below this level and in 4.5% above this level. It was small in size in 5.7% and larger than the normal in 1.1%. It continued as the posterior cerebral artery on the right side in 5.7% and on the left side in 13.7% (thus exhibiting a left-sided predominance in continuation). **Aneurysm of the basilar artery** was detected in 2.3% individuals.

The arteries commonly showing attenuation of lumen to a diameter less than 1 mm were posterior communicating, proximal part of the anterior cerebral and anterior communicating artery. Duplications and triplications occurred in anterior communicating and anterior cerebral arteries. Anomalous origin of the posterior communicating artery (from the internal carotid) is much more frequent owing to the persistence of the developmental origin. The reason for it being more common on the right side was not explained by Vare and Bansal (1970). Prasad and Lal (1970) from Patna reported that variations occurred more commonly in the posterior cerebral-posterior communicating arteries. The posterior communicating artery was found to be absent in 6.5% (unilaterally or bilaterally) and it arose from the internal carotid in 8.7%. The posterior cerebral artery develops in the embryo as a branch of internal carotid artery. Later, its origin is transferred to the basilar artery. In some the earlier developmental characteristics persist. Investigations are under way on a very large collection of medico-legal postmortem brains at the Postgraduate Institute of Medical Education and Research, Chandigarh and there too anomalous patterns of the circle of Willis were found to be commoner than the incidence described in the standard textbooks.(Jit 1988b). Incidentally, as pointed out by Jit (1988b), the wisdom behind the naming of the circulus arteriosus after Willis has been questioned as the arterial pattern at the base of the brain was described by Casserius (1627) and Veslenguis (1651) much earlier than by Thomas Willis (1664), .

Anomalies of the posterior communicating artery and their clinical significance

Bisaria (1984) studied the posterior communicating artery (PCoA) in 126

adult cadavers and reported the following common anomalies: a fetal type of posterior cerebral artery in 31.7% ,macroaneurysmal dilation of the PCoA in 39.7%. One PCoA arose from the ophthalmic artery inside the optic canal and there were three PCoA's on one side in one case. Two posterior cerebral arteries of different origin o one side and junctional dilatations at both ends of one PCoA were also noted. Junctional dilatation at the commencement of the PCoA was seen in 6.3%.

The dilated area on the PCoA may leak or rupture to produce subarachnoid haemorrhage. The presence of anastomoses between these arteries (Fig.1,2) permits normal circulation when any one of them is blocked. Arteries- especially when they are ectatic- pressing on the oculomotor nerve may produce diplopia. Compression of the optic chiasm and tracts may cause visual defects (Bisaria 1984).

Venous drainage

Superficial Sylvian vein

A study of the termination of the superficial middle cerebral (Sylvian) vein in 140 specimens at the King George's Medical College, Lucknow by Bisaria (1985a) showed that in 80 brains (51.1%) the vein drained into both the sphenoparietal sinuses, in 9 (6.4%) into the sphenoparietal and cavernous sinuses, and in 19 (13.6%) into the sphenoparietal sinuses (Fig. 3) and middle meningeal veins. In 20 (14.3%) the vein drained into the cavernous sinus alone and in 8 (5.7%) it drained into the cavernous sinus (Fig.4) and middle meningeal veins. In one (0.71%) it drained into the vein in the foramen lacerum and sphenoparietal sinus, in one (0.71%) into the sphenoparietal sinus and the superior petrosal sinus, in one (0.71%) into the middle meningeal veins on either side, and **in another (0.71%) into the superior sagittal sinus, a finding which has not been reported in the past.** The presence of an uncal vein draining the medial surface of the temporal lobe was observed in 5.7%. **A part of the superficial middle cerebral vein and sphenoparietal sinus was seen to form a vein running a short course between the two layers of the lateral wall of the cavernous sinus.This has not reported previously in the literature.** This information should be of great value to neurosurgeons in the approach to the internal carotid artery through Parkinson's triangle (Bisaria 1985a).

Venous Sinuses.

The straight sinus is the one most liable to injury in tentorial surgery. Saxena et al (1974) examined the dura mater of the posterior cranial fossa in 86 adult cadavers after injecting India ink through the confluence of sinuses to visualise the extent, communications and tributaries of the straight sinus. In all 86 cadavers the straight sinus was present, double

in 9 and single in the remainder. The average length of the straight sinus was 50 mm with a minimum of 40 mm and maximum of 69 mm. The average breadth at the termination was 4 mm, with a minimum of 2 mm and a maximum of 5 mm. It communicated with the occipital sinus in 4, with the cavernous sinus through tentorial veins in 9, and with the right transverse sinus in 4. In 43 of 77 single sinuses, the straight sinus bifurcated and drained into the respective right and left transverse sinuses. Of 34 non-bifurcated straight sinuses, 6 terminated at the confluence of sinuses, l4 terminated in the right and l4 in the left transverse sinus. Of the 7 median double straight sinuses the superior terminated in the left transverse sinus in three. The two paramedian right and left paired straight sinuses terminated in the corresponding right and left transverse sinuses. The straight sinus received the tentorial veins in 3, the occipital sinus in 6, and the superior cerebellar veins in 2. Nine cadavers had double straight sinuses: in 7 the sinuses were median, in one it was superior and in the other inferior. In 2 both sinuses were paramedian,lying on either side of the midline. Following methylene blue injection through the confluence of sinuses, Saxena et al (1973) described double straight sinuses in 13.9% (6 out of 43 cadavers).

Torcular Herophili. Anatomic variations of venous sinuses in the region of the torcular Herophili seen after the removal of the cerebral hemispheres in 110 adult human cadavers were described by Bisaria (1985). The variations were of 3 types: Type l - where the sagittal sinus drains into one lateral sinus and the straight sinus into the other, without any connection between the two. Type 2 - where the superior sagittal sinus and the straight sinus fork and the forks from both sinuses join to form the lateral sinuses. Type 3 - where a confluence of sinuses exists, varying from the a common pool to a potential confluence, with pads, incomplete partitions, and complete partitions of dura matter. Rare findings, not previously reported consist of double straight sinuses draining into the transverse sinus; the superior sagittal sinus dividing into 3 channels with 2 transverse sinuses on one side; a transverse sinus originating from a tentorial vein and drainage of a tentorial vein into the confluence of sinuses (Bisaria 1985).

Occipital sinus. Das and Hasan (1970) classified morphological types of the occipital sinus as following: median occipital sinus (35%), double occipital sinus (22.5%), left occipital sinus (4%) and right occipital sinus (3%). This study was based on naked eye examination of the occipital bones and the dura matter of the posterior cranial fossa in 200 adult cadavers. Additionally, in 50 postmortem specimens, methylene blue was injected into the confluence of sinuses to visualize the extent and communications of the occipital sinuses. The length and breadth of the sinuses showed gross variation. The maximum length was 70 mm, the minimum l5 mm. The average length of more than 50% of the occipital sinuses was 35 mm. The maximum breadth was as much as 19 mm in one case, whereas the

minimum was 1 mm. In more than 50% of the specimens the breadth was 2 mm. The occipital sinus communicated with the confluence of sinuses in all cases, with the right transverse sinus in 8%, the superior sagittal sinus in 8%, the straight sinus in 6%, the right sigmoid sinus in 6% and the left sigmoid sinus in 3% of the cadavers examined. In summary, the occipital sinus was present in 64.5% of the 200 specimens examined by Das and Hasan (1970). In one of their specimens it communicated with all the sinuses situated in the posterior cranial fossa. Hasan and Das (1969) showed that the falx cerebelli may exhibit 2 or 3 distinct folds, instead of the commonly described median sickle shaped appearance. The occipital sinus is a potential source of difficulty in the surgical approaches to the posterior fossa.

Trilocular transverse venous sinus. Of 86 transverse sinuses in 43 cadavers examined by Beg et al (1974), 78 were unilocular, 39 on each side, 7 were bilocular, 3 on right side, 4 on left side and only 1 (the entire middle third on right side) was trilocular.

Grooves on the occipital lobe formed by dural venous sinuses. These were observed in 108 out of 110 brains (98.2%) by Bisaria (1984). In 21 brains (19.4%), the groove was unilateral. In 15 of these 21(71.4%) there was a well marked groove on the right occipital pole. In 87 out of 108 brains (80.6%) the grooves were bilateral. The groove on the occipital lobe was made by the tentorial ridge in only 2 of the cerebral hemispheres. In all the remaining specimens it was caused by the dural venous sinus (Fig.5,6).

Tentorial Notch

A metric study of the tentorial notch of 48 cadavers was undertaken by Das and Saxena (1975) at the King George's Medical College, Lucknow. The third cranial nerve was the only structure passing through the tentorial notch in 100% of cases. The midbrain passed through it in 43.8%, pons in 56.2%, basilar artery in 70.8%, superior cerebellar artery in 66.7%, posterior cerebral artery in 29.2%, trochlear nerve in 72.9%, cerebellar hemisphere 41.7% and vermis cerebelli in 35.4%. Statistical analyses of modes of frequency curves and cumulative frequency of measurements shows the range of anteroposterior distance (length) to be 42-60 mm, maximum transverse distance being 20-38 mm and elevation 16-32 mm.

Developmental defects of the tentorium cerebelli

Bisaria (1983) reported congenital defects of the tentorium cerebelli (Fig.7) in 16 out of 90 cadavers. Tentorial dural bands were seen in two,a hole in one, transverse ridges in eight and an aperture in five. In one specimen, the trochlear nerve made a spiral turn around the tentorial band before pursuing its forward course.

Relationship between the third cranial nerve and posterior clinoid process

The oculomotor nerve bears a variable relationship with the posterior clinoid process. It skirts the side of dorsum sellae in 53% of 50 cadavers examined by Joseph et al (1979). In 25% the posterior clinoid process was very sharp and pointed and in these cases the third nerve was nearer the attached and free margins of tentorium cerebelli. In 21% the nerve was midway between the posterior clinoid process and the crossing of free and attached margins of tentorium cerebelli. In 1% the third nerve crosses medial to the tip of the posterior clinoid process.

Meckel's cave-its dimensions and extent

After injecting a coloured solution of vinyl acetate in acetone, Halim and Abdi (1976) investigated the Meckel's cave in 47 adult embalmed cadavers by dissection. Its mouth, the trigeminal pore, was elliptical in shape and measured 7.7±1.16 mm transversely. The cave consisted of a proximal narrower portion, as wide as the trigeminal pore containing the roots of the trigeminal nerve and measured 3±0.75 mm in length. The distal portion of the cave was expanded, contained the trigeminal ganglion and measured 10.7 + 1.69 mm transversely. The extent of the cave along its roof (12.6±1.58 mm) as well as floor (12.3±1.50 mm) were almost equal, the difference being only a fraction of a millimeter.

Surface area of cerebral cortex by stereological procedures

Using Henning's formula, the surface area of the cerebral cortex was determined in one formalin fixed brain by Sayee and Bhargava (1972). It was estimated to be 1922.4 sq.mm. It was also observed that most of the sulci and gyri were without preferred orientation. In the coronal plane, a vertical preferred orientation was seen only in the upper portion. In the sagittal plane, horizontal and vertical preferred orientations alternate with each other.

Mapping of visual cortical areas by photic stimulation of retina

Pande mapped out the visual cortical area in 3 healthy dogs (1973) and in 3 monkeys (1972) by photic stimulation of retina after fixing the heads in a Horsley-Clark holder. The vision in both these animals is binocular and stereoscopic. Flashes of light were thrown on retina with a 200 watt bulb placed at a distance of 1 metre from the animal. Action potentials were recorded by electrodes touching the exposed brain surface, amplified by RC amplifier and observed on the screen of an oscilloscope. The visual cortex is present on all the 3 surfaces of the cerebral hemispheres of dogs and monkeys. Whereas in the dog the area was recorded as being largest on the superolateral surface and smallest on the inferior surface of the occipital lobe, in the monkey the larger visual cortical area was observed

on the medial surface of the occipital lobe (Pande 1972). In the latter, the area of the visual cortex, in sq.mm. was 858, 369 and 272 on the superolateral, inferior and medial surfaces respectively. The total area of the cerebral cortex was 7254 sq.mm, total visual area 1560 sq.mm and the ratio of the visual area to the area of cerebral cortex was 1 to 4.650.

Localization of nuclear groups in spinal cord and brainstem

Phrenic nucleus in the cervical spinal cord

The motor fibres of the phrenic nerve supplying the diaphragm arise in the cervical portion of the spinal cord from a group of lower motor neuron cell bodies termed the 'phrenic nucleus'. It might be presumed that the longitudinal extent of the phrenic nucleus would correspond with the segmental roots contributing to the formation of the phrenic nerve in the particular animal species investigated but many workers have reported to the contrary. In man the phrenic nerve arises from the ventral rami of the third, fourth and fifth cervical nerves. The human phrenic nucleus was located by Keswani and Hollinshead (1956) in the third to fifth or sixth segments. In the cat,it is located in the fifth and sixth cervical segments.(Keswani et al 1954) In the rhesus monkey. Bijlani and Keswani (1961) found it in the third, fourth and fifth segments. Ullah (1978), using the retrograde degeneration technique (chromatolysis after 2-4 weeks of right phrenicotomy) found the phrenic nucleus of the rabbit to extend from fourth to sixth cervical segments. Fusiform phrenic neurons occurred between ventromedial and ventrolateral column of cells in the cervical spinal cord forming a longitudinal uninterrupted column.

Spinal nucleus of the accessory nerve in the rabbit

Ullah and Salman (1986) removed a portion of the right spinal accessory nerve in the neck (before it supplied sternomastoid and trapezius muscles). Three to four weeks later, chromatolysis was studied by thionine staining. On the basis of retrograde degeneration, they found the spinal accessory nucleus (SNA) extending from the caudal fifth of the medulla oblongata to the cranial one-fourth of the sixth cervical segment. In the caudal part of the medulla, the nucleus (SNA) was located in the dorsal part of the detached ventral grey column. In the first cervical segment, the SNA was dorsolateral to the dorsomedial column and dorsal to the ventromedial column of the ventral grey. In the cranial part of the second cervical segment, the SNA shifted to the lateral margin of the ventral grey column. After this lateral shift, the SNA was located in the lateral part of the ventral grey column of the second, third and fourth cervical segments. In the fifth and cranial one-fourth of the sixth cervical segments, the SNA was not a well-defined column of cells but was represented by isolated cells scattered in the ventral part of the ventral grey column between the phrenic nucleus and the ventral border of the grey matter. The total number of

chromatolysed cells in the SNA of the right experimental side varied from 2723 to 3210 (Ullah and Salman 1986).

Localisation of the salivatory nucleiin the brainstem of monkey

Bijlani and Keswani (1970) studied the salivatory nuclei in the brain stem of the monkey. The neurons sending efferent fibres to the three salivary glands were located in discrete medial and lateral groups. The latter was in close relation to the vestibular group of nuclei.

Localization of the motor neurons of the median nerve

Chromatolysis in spinal cord segments was studied in the cat after sectioning its median nerve in the arm and at the wrist (Bajpai and Ullah 1977). After 22-28 days,the animal was perfused with 10% formol saline. The motor neurons contributing fibres to the median nerve were present in the 8th cervical and lst thoracic segment. They were present in column 5 (retrodorsolateral column of the ventral grey horn) at the 8th cervical and lst thoracic segments. The motor neurons of the median nerve supplying the short muscles of the hand were located dorsally and caudally in these segments (Bajpai and Ullah 1977).

Cerebellar nuclei

The morphology, size and cellular characteristics of the cerebellar nuclei were studied in 12 monkeys (Macaca mulatta) by dissection, reconstruction of serial sections and examination of paraffin sections stained by Kluver-Barrera's technique (Wadhwa et al 1977). Models of the nuclei were constructed from thermofoam sheets. The nucleus lateralis was seen to be in the form of a convoluted cord of grey matter with smooth contours and no evidence of gyri or sulci on its surface. Serial sections in the transverse plane showed undulations, some quite deep, in the lateral limb of nucleus lateralis. The nucleus interpositus anterior was seen to have a comma-shaped hook-like process directed rostroventrally. The nucleus medialis had an irregular prismoid shape. Microscopy confirmed the presence of four distinct nuclear masses separated by medullary sheets (Wadhwa et al 1977).

Anatomy of behavioural human brain by stereotaxy

On the basis of findings at surgery and after selective stereotaxic ablation to control the behaviour of restless, hyperkinetic and violent patients, a model of the brain controlling behaviour has been deduced by Balasubramaniam et al (1972). Amygdaloid nucleus, hypothalamus, the internal medullary lamina, the inferior orbital cortex and the periaqueductal grey were investigated and the effects of stimulation reported. A second series of structures (like the cingulate cortex, septum

and the dorsomedial nucleus) which reinforce behavioural reactions was also explored. Kanaka et al (1972) investigated the ventral tier of thalamic nuclei and the dorsomedial nucleus of thalamus. These nuclei have been the targets of neurosurgeons treating cerebral palsy. Demonstration of the individuality of nuclei between the oral and posterior groups has been accomplished and the importance of centromedian nucleus emphasized. The advent of stereotaxic surgery has stimulated a great deal of work and interest in the finer anatomy of the thalamic structures.

Developmental neurobiology

Studies on the sequential development and maturation of neurons of the spinal cord, cerebellum, hippocampus, lateral geniculate body and visual cortex have been carried out in the human and mammalian embryonic and foetal brains at the All India Institute of Medical Sciences, New Delhi during the past two decades. Rats were kept undernourished for varying periods during the immediate postnatal life and the effects on the developing cerebellum, peripheral nerves, skeletal muscles, dendritic branching, dendritic spines, cellular organelles, synapses, axonal and myelin thickness were noted. A certain amount of catch-up-growth was seen inspite of poor nutrition. The earlier rehabilitation was attempted,the more complete was recovery of the developing brain. Late rehabilitation slows down the catch-up-growth (Bijlani et al 1974, Bijlani 1975, Bijlani et al 1976, Bijlani et al 1979, Deo et al 1975, Deo et al 1979; Gopinath et al 1976). Bijlani et al (1980) used inbred mice (strain C3 HeB/Fej) to study the reduction in body and brain weight as a result of undernutrition. Animals were weighed daily after birth till they were killed and a complete growth record was maintained for each animal. Postnatal development of the cerebellar cortex was characterized by proliferation of cells of the external granular layer, migration of the granule cells across the molecular layer and simultaneous maturation of the Purkinje cells. At the same time there is elaboration of folia and fissures of the cerebellum. Observations on animals at the lst, 7th, 13th and 24th day postnatum showed that the size of the cerebellum and the degree of development of the cerebellar cortex were directly proportional to the weight of the animal for that age. The external granular layer normally declines in thickness in the second postnatal week due to migration of cells but persists for a longer time in animals with low weight. Mitotic figures were seen in litter mates with low weight until 22 days after birth whereas no mitotic figures could be detected in the external granular layer after the 15th to 16th postnatal day in litter mates with high weight.

Development and growth of human brain: Cerebellum

Hasan and Abdi (1988) followed the development of granule cells and Purkinje neurons in human foetuses of 100 mm, 150 mm and 200 mm C.R. length and noted that if birth date of a neuron was known it was possible

to predict where the cell will finally reside. The central problem in neurobiology is how the neurons find their place and make the right connections.

Development of the dorsal grey of spinal cord

Rizvi (1988) has traced the sequence of development of neurons and neuronal types in the dorsal gray of 51 fresh human embryos and foetuses of both sexes ranging from 8 to 24 weeks. She also studied the spinal cords from liveborn infants dying at 25, 26, 30 and 37 weeks, obtaining the specimens within 2 to 4 hours of death. There was no indication that the morphologic substrate for excitation and inhibition of 'encased neurons' (which are said to be inhibitory in function and perhaps concerned with the modulation of pain and analgesia) exists by 16-17 weeks of foetal life. In substantia gelatinosa inhibitory as well as excitatory contacts were present. These conclusions were based on a combination of cytoarchitectural and immunohistochemical studies. Immunocytochemical techniques also demonstrated the appearance of various types of synapses (which suggest the presence of neurotransmitters like substance P, enkephalin, GABA, serotonin and acetylcholine) at different stages of development. Presence of these synapses and neurotransmitters indicates that the morphological component for the relay of sensory input in the dorsal grey by primary afferent fibres exists even in the very early stages of development in man (Rizvi 1988). Lamination was identifiable at 13-14 weeks of gestation and the adult pattern was acquired by the 30th week (Rizvi et al 1988).

Cytoarchitectonic and ontogenetic study of the occipital lobe of a puppy

Sinha (1970) studied the occipital lobe of 3 mongrel puppies aged 18 hours, 15 days and 30 days. Increased laminar thickness, parity in number and size of cells in the laminae (except in the fifth and fourth layer respectively) vis-a-vis the human newborn of one month was noted. Cajal-Retzius cells were seen till 30 days. Ontogenetic study one month after birth showed dehision of neurons (seen in cohesion earlier) with extensive arborization of apical, basal dendrites and their collaterals. The thick interdendronic linkage between all cellular layers persisted for a fortnight and in the end it was predominantly replaced by extremely fine dendritic ramifications from cells of second layer to the 6th layers, in synaptic formation at random with small bipolar cells. Golgi-Cox and cresyl violet staining of 20-40 um serial sections were carried out.

Histogenesis of the human striate cortex

Light microscopic observations at 9,13-14, 16-17 weeks gestation showed that the thickness of the visual cortex increased with age. The cells in the cortical plate and subventricular zone were arranged in vertical columns

(Masood et al 1988). Bipolar and Cajal-Retzius neurons were identified in Golgi-Cox preparations at 14-15 weeks of gestation. In the cortical plate, the cells were arranged vertically. They were in the bipolar phase of development. The apical dendritic bouquets of these neurons were attached to the pia. The marginal zone was well developed with horizontally oriented large-sized Cajal-Retzius neurons (Farzana et al 1988).

GABAergic neurons during pre-and postnatal development in monkey striate cortex

Mehra et al (1988) carried out sequential studies on the same tissues using imcyt and in situ hybridization to identify: 1) sequence of appearance of transcription and translation products and (2) whether GABA and GAD exist in the same neurons. For in situ hybridization a 535 labelled riboprobe generated from a c-DNA clone for human GAD was used. Cortices of F 75, 125, 162 d, P1d, P3d, 20 week and adult animals were studied. Preliminary analysis showed GAD m-RNA and GABA to be present in the same neurons.

GABA immunoreactive neurons in the human lateral geniculate nucleus

Wadhwa et al (1988) performed a quantitative analysis of Nissl stained and gamma-aminobutyric acid (GABA) immunoreactive neurones in the lateral geniculate nucleus (LGN) of human fetuses ranging from 8 to 37 weeks of gestation. Total cell density in the LGN increases from 8 to 12 weeks of gestation with a subsequent, continuous decline upto 37 weeks. No GABA immunoreactive neurons were seen in the LGN of 8 and 12 week fetuses. At 15-16 weeks of gestation 1% of neurons are immunostained following incubation with rabbit anti-GABA serum, using a concentration of primary antibody of 1:1000 for 1.5 hour at room temperature. A peak rise is seen to occur at 17 weeks when 16% cells are GABA immunopositive. At 19 weeks there is an equally sharp decline in the percentage of GABA neurons to 4%. The magnocellular laminae begin to segregate at 22-23 weeks and at 26 weeks distinct laminae are present in the LGN of the monkey. The magnocellular regions have a higher density and percentage of GABA neurons at all gestational ages than do the parvocellular regions. Although the inhibitory GABA neurons are generated simultaneously with relay neurons, their cell bodies grow and elaborate dendritic trees later than the relay cells (Wadhwa et al 1988).

Developing lateral geniculate nucleus

Developing neurons in the human lateral geniculate nucleus

Dendritic growth and maturation of the lateral geniculate neurons has been analysed in human foetuses of gestational ages 15 to 32 weeks, premature infants of 32 and 37 weeks and a full term newborn aged 4 days. (Wadhwa

and Bijlani, 1988). Increasingly diversified forms of multipolar cells begin to appear at 17-18 weeks. From 23-24 weeks onwards the multipolar neurons acquire adult morphology. Further modelling of neurons with an increase in number of dendrites and dendritic branches occurs between 24 to 37 weeks of gestation (Wadhwa and Bijlani 1988). Cells of the magnocellular layers appear to be more mature than those in the parvocellular regions. The projection neurons appear in advance of the interneurons which are recognisable from 23-24 weeks onward (Wadhwa and Bijlani 1988).

Volumetric growth of prenatal human lateral geniculate nucleus

The volume of the lateral geniculate nucleus (LGN) has been studied in human foetuses of the age groups 17-18 weeks, 26-28 weeks and 34-35 weeks of intrauterine life (Khan et al 1988). Formalin fixed, paraffin embedded, 10 micrometre thick, thionin stained serial sections were used. The total volume of the nucleus was calculated using the point-counting method. The total volume of LGN increased from 15.78 cu mm at 17-18 weeks to 22.93 cu mm at 26-28 weeks. This further increased to 39.04 cu mm by 34-35 weeks - an increase in the total volume by about two and half times between 17-18 and 34-35 weeks. The volume of magnocellular laminae on the other hand increased from 8.17 cu mm at 26-28 weeks to 13.78 cu mm at 34-35 weeks, while the parvocellular laminae increased from 15.26 cu mm to 25.27 cu mm.

Ontogeny of alphafoetoprotein in human foetal brain

Antigenetically and electrophoretically foetal brain alphafoetoprotein (AFP) is similar to that found in human foetal serum. Like serum AFP it does not bind oestradiol. Ali et al (1981) studied the developmental profile of the proteins in foetal brain and found that it was distinct from that observed in foetal serum, amniotic fluid and maternal serum compartments. Peak levels of brain AFP were obtained in foetuses in the 20th week of gestation. These levels decreased rapidly and no AFP could be detected in foetal brains derived from the third trimester of pregnancy. The physiological role of human AFP in developing brain is, as yet, unclear (Ali et al 1981).

Amygdaloid complex in the newborn human foetus

Topography and morphology of amygdaloid complex and its exact location are of applied significance with reference to stereotaxic procedures like amygdalectomy. Kumar and Cooper (1975) undertook histological reconstruction using 12 micrometre sections stained with hematoxylin and eosin (H & E), Gomori, Bielshowsky, Porceau-methyl green and Mallory's PTAA. Serial reconstruction technique was employed to work out the location of amygdaloid complex in the newborn human foetus.

Teratology

Malformation of brain, liver and kidney induced by lithium in chicks (Singh 1988)

Fertile chick eggs were treated with 30-90 mg lithium carbonate per egg on days 4-6 of incubation and embryos were collected for study on day 20. Brain and liver were found to be reduced in size on gross examination. The cerebral cortex (light microscopic study) was thinner than in the controls and exhibited neuronal paucity. (Singh 1988).

Cell lineage in cerebellar ontogen

Datta (1988) experimenting with developing cerebellum noted that some neurons were more susceptible to noxious agents than others and proposed different lines of origin of cell types. Morphological evidence is lacking. Developing rats (on 4th postnatal day) were treated with cyclophosphamide. Subsequent histology showed some persisting regional cell clusters at the angles of pial invagination (12 day) and patchy loss of external granular layer. (16 day) Some Purkinje cells showed persistent growth retardation even on days 16 and 20. Cyclophosphamide destroyed a pool of developing cells then in the stage of synthesising DNA. The loss of some microneurons seems to have retarded the growth of Purkinje cells (Datta 1988).

Neurogenetics

Familial cerebellar degeneration

Grewal and Singh (1969) carried out a meticulous genetic study of a family suffering from familial cerebellar degeneration of the Marie-Kisenger-Brown variety. The family also had a high incidence of consanguinity in marriage. More than 25 members of this family were affected involving 6 successive generations. The trait behaves as an autosomal recessive one. Tissue culture and studies of the affected patients did not show any chromosomal abnormalities.

Familial anosmia

Singh and Grewal from New Delhi (1969) reported a family with total anosmia, premature baldness and episodes of vascular headache. The value of testing the ability to smell was emphasized. The pattern of transmission of this inherited disorder was discussed.

X-linked inheritance of mental retardation and muscle weakness

Kucheria (1976) demonstrated X-linked inheritance of mental retardation

and muscle weakness in a family followed up at All India Institute of Medical Sciences, New Delhi.

Sister chromatid exchange in epileptics on anticonvulsants

Recent reports have shown increased risk of congenital malformation among children born to epileptic women. Taneja et al (1988) cultured leucocytes from 24 epileptics (16 males and 8 females) in the age group of 18-45 years and analysed chromosomes. No increase in chromosomal aberrations was observed in epileptics. However, the frequency of sister chromatid exchange (SCE) was significantly increased in epileptics vis-a-vis normals ($p<0.005$). No correlation could be established between SCE and a specific anticonvulsant drug. Pedigree analysis showed a father and his month old daughter having epilepsy. In three other families one sib each was affected. Multifactorial inheritance was suggested. Increased SCEs in epileptics indicate increased somatic recombinations during DNA replication.

Dermatoglyphics in epilepsy

Heredity plays an important role in the genesis of epilepsy. Palmar dermatoglyphic patterns of 100 patients with idiopathic epilepsy were analysed by Bhardwaj et al (1988) using the Cottermann technique. Statistically significant differences in the pattern (higher incidence of whorls in the index finger, a lower a-b ridge count) were found in the epileptic patients as compared to the controls.. Dermatoglyphics may be used to screen first degree relatives of epileptic patients, to pick up high risk cases, and as an aid in genetic counselling.

Ultrastructure of granule cell organotypic culture

Aggerwal and Handelman (1981) explanted parasagittal sections of cerebellum from the new born mouse into Maximow chambers and incubated them at 35 degrees C for 3-4 weeks. At maturation, cultures were impregnated using a modified Golgi-Cox method or processed for electron microscopy. On the Golgi study, granules were found to be 5-8 um in size. Occasional bifurcating, T-shaped, axons were recognized. In semithin sections, the cells were found to be packed in clusters of 3-5. The dark basophilic nucleus was surrounded by a thin rim of cytoplasm. On electron microscopy, the nucleus contained large blocks of chromatin. Few granule cells were myelinated. The dendrites often contributed to a typical 'glomerulus' with a large bouton forming the central element. Typical parallel-fibre dendritic spine contacts were also present. In other areas of the neuropil several (3-10) dendritic spines appeared engulfed and were synaptically in contact with a terminal containing round vesicles. These configurations are not found in the intact animal. These results indicate that granule cell axons can undergo hypertrophic changes during development (Aggerwal and Handelman 1981).

Unique anomaly of brachial plexus

A single cord human brachial plexus

For the first time in India (and the second time in world literature [Pallie 1980]), a single cord brachial plexus was observed on the left side in a middle-aged male cadaver by Hasan and Narayan (1984). The solid constitution of the cord might be a result of retarded development of arteria axillaris profunda. In this case, the existing axillary artery appeared to be a compensatory development of the arteria axillaris superficialis (Pallie 1980).

Neuroanatomy of Drosophila

The anatomy of the nervous system of *Drosophila melanogaster* has been extensively investigated by Naresh Singh at T.I.F.R. Bombay (1988). This is described by him elsewhere in this volume.

Experimental hydrocephalus

The choroid plexus has been studied in experimental hydrocephalus by Dr. Mary Jacob of the Department of Anatomy, Christian Medical College, Vellore. Light and electron microscopy were supplemented with morphometric analysis of the observations. Since the choroid plexus is a primary site of the production of cerebrospinal fluid, its ultrastructure in cases of hydrocephalus is of considerable interest. Abnormalities were seen in choroidal cells, microvilli, mitochondria, Golgi apparatus and the shape of nuclei. Intercellular clefts were widened. The number of dark cells seen was greater than usual (Jacob and Abraham 1970).

It was only in the 1970s that attempts were made to define the ultrastructure of human choroid plexus. Jacob and Abraham (1973) studied under the electron microscope the choroid plexus obtained at surgery from the lateral ventricles of four children undergoing choroid plexectomy for congenital hydrocephalus. There were more electron opaque cells and polypoid microvilli. The changes were more marked in the specimens from children with hydrocephalus of 4 months or longer duration. Numerous dark staining mitochondria were seen though Golgi apparatus was unremarkable. Rough endoplasmic reticulum was abundant only in 2 of the 4 children.

Madhavi and Jacob (1988) carried out morphometric studies on the choroid plexus of 38 young guinea pigs,19 of which were rendered hydrocephalic by intracisternal injection of kaolin (125 mg/ml). The rest were used as controls. The volume and surface area of choroidal epithelium and interstitial tissue (blood vessels and connective tissue) were estimated from 2 micrometre thick sections. The mean volume and surface area of choroidal

epithelium of hydrocephalic guinea pigs showed a significant decrease as compared to that in controls, indicating decreased activity of the choroidal cells and in turn decreased secretion of CSF in hydrocephalus.

A rabbit model was developed by Gopinath et al (1977) at the All India Institute of Medical Sciences, New Delhi to study changes of the ependyma and neural tissue in hydrocephalus. Kaolin was injected into the cisterna magna of 10-day-old rabbits to produce aseptic meningitis. Kaolin obliterated the foramina of Luschka and Magendie. Intra-cardiac perfusion was carried out after varying periods (upto 38 days) and the walls of lateral and third ventricles and central canal of the cervical spinal cord were studied by light and electron microscopy. Progressive enlargement of ventricles was noted upto 20th day. The third ventricle and basal part of the lateral ventricle were the first to enlarge, followed by the dorsal region of the lateral ventricle and central canal of the spinal cord. The ependymal cells in the lateral ventricles were so flattened and stretched that clear spaces could be seen between the cells. Ultrastructurally the clear spaces appeared to be damaged cells in between normal ependymal cells. Widening of the gap junctions were noted with resultant communication between the cerebrospinal fluid and the fluid spaces in the subependymal region. Subsequently, Gopinath et al 1979) reported that changes in the ependyma and white matter were more marked than those in the grey matter. Deficits in dendritic spines and synapses were also seen in chronic hydrocephalus. Transependymal drainage of CSF into the periventricular tissue could be visualized (Gopinath et al 1979).

Scanning electron microscopy was used by Hasan et al (1980) for the first time in India to study changes in the surface ultrastructure of the ventricular ependyma of rabbits after inducing hydrocephalus by bilateral ligation of the jugular veins. Six control rabbits and six rabbits subjected to bilateral jugular vein ligation four to five days earlier were studied. Whereas in the control rabbits the mean CSF pressure was 27 mm H20, it rose to 71.5 mm H20 in experimental animals. The ependymal lining of the 4th and 3rd ventricles and the inferior horns of the lateral ventricles were examined after intracardiac perfusion-fixation, critical point drying using liquid C02 and gold-palladium coating in a Polaron E-5000 spluttering device. In the experimental rabbits, clusters of cilia emanating from ependyma were separated (Fig.10). This appeared secondary to ingrowth of cell processes covered with microvilli. Remarkable alterations were seen in the surface features of the dorsal and infundibular regions of the 3rd ventricle. While a marked reduction in ciliary density and appearance of pits was noticed in the former,an almost total replacement of globular excrescences (Fig.11) by pleomorphic microvilli was noted in the infundibular region. The morphological alterations that occurred in experimental animals suggested a modification from a surface capable of propelling CSF by ciliary movement to one capable of increased ependymoabsorption. Increased incidence of macrophage-like

supraependymal cells were noted in the experimental rabbits (Hasan et al 1980).

Singh et al (1986) noted the presence of macrophage-like supraependymal cells (resembling the epiplexus or Kolmer cells) over the choroid plexus (Fig.12) of the third ventricle in rhesus monkeys. Such cells exhibited pleomorphic shapes and had a star-shaped appearance or a triradiate soma (Fig.13).

Hypothalamic ependyma in the rhesus monkey during different stages of the menstrual cycle: A scanning electron microscopic study

The mammalian hypothalamus modulates pituitary functions for release of follicle stimulating hormone (FSH) and luteinising hormone (LH) via neurohormones in response to circulatory ovarian hormones during the menstrual cycle. It has been postulated that cyclic variation in the morphology of various cell types located in the hypothalamus influences the adenohypophysial secretions through specialized tanycytic cells in the ependyma. Bajpai et al (1986) obtained cyclicity in bilaterally ovariectomized adult rhesus monkeys by sequential administration of estradiol (E 2) and progesterone. In ovariectomized animals (E 2 levels 35 pg/ml) the surface morphology of the ependyma revealed polygonal non-ciliated (NC) cells, few supraependymal cells (SRC) and occasional cilia and miniblebs over the median eminence (ME). The apical surfaces of NCS exhibited short stubby microvilli (MV), and many intercellular pores. There was a striking increase both in number and size of microappendages after E2 peak (280 + 20 pg/ml) attainment by day 14 (Fig.14,15,16). Thus E2 peak (preovulatory surge) induced miniblebs and pitted microappendages which might act as physical transducers for CSF signals (bioactive substances) to modulate the hypothalamo-pituitary-ovarian axis (Rajpal et al 1986).

Scanning electron microscopy of supraependymal cells over circumventricular organs in the rhesus monkey brain

Singh et al (1986) observed a diverse array of varying populations of supraependymal neuronal perikarya (SEN) as well as axonal (neuritic) fibres over the ependymal surface in various parts of the 3rd and 4th ventricle (Fig.17,18). The ventricular ependyma of the area postrema (AP) was devoid of cilia. At the junction of the sparsely ciliated strip on the medial side of the AP with the densely ciliated vagal triangle, the SENs were arranged in a linear pattern (Singh et al 1986) (fig.19,20). In the most caudal portion of the floor of the 4th ventricle, pleomorphic SENS having numerous fine processes were seen perching over the ependymal surface. The SENs in the pineal recess were larger and generally possessed oval/spherical somas/bodies. Their somas were rough-surfaced. Stout

axonal processes with many collaterals emerged from them. The SENs also appeared to be neurosecretory. As many at 8-10 miniblebs and ruffled membranes characterised the surface of the neurosecretory SENs. Over the choroid plexus of the 3rd ventricle a number of typical epilexus (Kolmer) cells could be detected, but few of them resembled neuronal elements. (Fig.21,22) Close association of these SENs with the CSF is suggestive of their probable function as receptors to monitor ambient changes in the composition of some bioactive molecules present in the CSF. They may also act as connecting links between different regions of the cerebroventricular system to serve as an 'anatomical bridge'.

Neuroendocrine regulation of reproduction

The two endocrine functions of the central nervous system (CNS)- sensing endogenous levels of gonadal hormones and producing gonadotrophin releasing factors- are carried out by a group of neurosecretory neurons: the 'parvicellular neurosecretory neurons' lying in the circumscribed area, the hypophysiotropic area of the hypothalamus (Anand Kumar 1973). Circumscribed areas of ventricles of the brain are lined by specialized ependymal derivatives such as the subfornical organ, the sub-commissural organ, the pineal gland. They seem to be concerned with the integration of neural and endocrine functions, by either secreting into or sensing substances in CSF. The tanycytic ependyma, glandular cells in the floor of the III ventricle and the pineal gland have been ascribed this function.

The dependence of the size of the bulbous projections of the tanycytic ependyma on endogenous levels of gonadal hormones and the finding of oestrogen in the CSF within 15 minutes of injecting tritiated oestriadiol into ovariectomized monkeys (Anand Kumar and Thomas 1968) suggested that the role of the tanycytic ependyma may lie in the absorption or detection of gonadal hormones in the CSF and secreting substances at their terminals which affect gonadotrophin secretion in the adenohypophysis.(Knowles and Anand Kumar 1969) The tanycyte ependyma also responds to synthetic steroids affecting gonadotrophin secretion (Anand Kumar et al 1973).

Glandular cells in the floor of the III ventricle

Large glandular cells with coarse cytoplasmic inclusions occur amidst the ependymal cells lining the floor of the III ventricle in the region of the anterior tuber cinereum of the rhesus monkey (Anand Kumar 1973). Their processes probably end on blood vessels. Neurosecretory nerve terminals of the aminergic type have been found to make contacts with these glandular cells.(Anand Kumar 1968) The concept of the glandular cells in the rhesus monkey being concerned with the production of gonadotrophin releasing factors has also been supported by Anand et al (1957) who found that the electrical stimulation of the anterior tuber cinereum caused ovulation.

The pineal gland

The pineal gland is known to contain gonadotrophin inhibiting principles. Anand Kumar et al (1973) administered tritium labelled testosterone, progesteron and 17 alphahydroxy progesterone (or mestranol) to monkeys and showed that the pineal gland consistently accumulated the highest concentration of radioactivity (dpm/mg of tissue) in contrast to the other known target tissues such as the hypothalamus and reproductive organs.

The cerebrospinal fluid as a neural and hormonal pathway

A corollary to the concept of the circumventricular structures integrating neural and endocrine functions is that the CSF, in addition to its known supportive and nutritive functions, serves as a humoral pathway for transmitting chemical information to various regions of the brain. The possibility of CSF being a humoral pathway for oestrogen reaching tanycytic ependyma in the hypothalamus was explored by Anand Kumar and Thomas (1968). David and Anand Kumar (1973) showed that testosterone, progesterone, 17 alphahydroxyprogesterone, mestranol and norethynodrel also enter the CSF of monkeys injected with these compounds.

The habenular ependyma: a neuroendocrine component of the epithalamus in the rhesus monkey

Kumar and Anand Kumar (1975) showed that the ependyma lining the third ventricle in the region of the habenula of the rhesus monkey was structurally atypical and constituted one of the specialized ependymal derivatives lining the ventricles. There is also ultrastructural evidence to indicate that some of these habenular ependymal cells secrete into the CSF and that the function of these ependymal cells may be neurally regulated. A correlation between ependymosecretory activity and the neuroendocrine-status of the monkey could be established by Kumar and Anand Kumar 1975). They also noted that the ependymo-secretion occurred only in sexually immature, menstruating and gonadectomized monkeys.

Vagal afferents in area postrema: Elucidation of neural mechanism of vomiting

The area postrema, situated in the floor of the fourth ventricle, is the anatomical site of the chemoreceptor trigger zone (CTZ) for vomiting. According to Bhargava et al (1963), ablation of the CTZ completely protected against the action of intravenous salicylate but not of oral salicylate. There would thus seem to be sites of action of oral salicylates other than the CTZ. Interruption of vagal afferent pathways from the abdominal region protected nine of twelve animals from the emetic effects of oral salicylates (Bhargava et al 1963). Following lesioning of

supranodose in 10 cats, Hasan et al (1968) traced Marchi positive degenerating fibres to the area subpostrema, situated deep to area postrema. The degenerating fibres did not reach superficially upto the area postrema itself. The area subpostrema contains the special visceral sensory nucleus of vagus and the superficial ablation of area postrema (Bhargava et al 1963) could thus very well protect against the intravenous salicylate by not oral salicylates.

Thallium neurotoxicity

A notable feature of the study of hippocampal neurons following thallium intoxication was the proliferation of smooth endoplasmic reticulum and Golgi vesicles. Irregular electron-dense bodies and coated vesicles were frequently observed in these neurons (Hasan et al 1977 a). Hypothalamic neurons showed increased incidence of pigment granules and arcuate conformation of Golgi cisternae and vesicles. On the other hand, in the rat area postrema, (an area in the floor of the fourth ventricle outside the blood-brain barrier) remarkable changes were detected in the oligodendrocytes.

Frequently, large and small nuclear profiles of oligodendrocytes were observed in close proximity. They were not separated by a plasma membrane. Vacuolated electron-dense bodies were noticeable in their perikarya (Hasan et al 1977b). A small round profile, resembling a sequestrated part of a nucleus was also seen. Occasionally, an otherwise normal looking oligodendrocyte was found to exhibit a small uniformly dense body, separated by a membrane from the perikaryon. At times, large vacuolated single-membrane bound dense bodies were detected in the vicinity of the elongated and infolded nuclei of the oligodendrocytes (Hasan et al 1977b) (fig.23,24).

Thallium-induced alterations in the circumventricular areas of the rat brain

Electron microscopy by Hasan et al (1977) of brains of adult albino rats (150 + 20 g b.w.) after intraperitoneal administration of thallous acetate (5 mg/kg b.w.) over 7 days showed changes in the circumventricular organs which lack the blood brain barrier (area postrema, organum vasculosum of lamina terminalis and subfornical organ). Oligodendrocytosis, electron-dense bodies within these profiles, proliferation and increase in Golgi zones, onion-peel appearances in neuropil and multilamellated bodies in the vicinity of mitochondria were seen (Hasan et al 1977).

Age related changes in the concentration of trace elements in discrete regions of the rat CNS

Some divalent trace metals like Zn, Cu and Mn are biologically active,

whereas Pb, Cd and Al cause toxicity in the body. Neuronal ageing is a very complex phenomenon and many hypotheses have been put forward to explain the mechanism of ageing. The relation of trace metals to various enzyme systems and their role in carbohydrate, lipid and protein metabolism have been highlighted. Male rats (Charles Foster) were divided by Hasan et al (1988) into 3 groups:

Group I : 12 rats, 6 months old, 250 + 20 g.
Group II : 12 rats, 12 months old, 450+ 20 g.
Group III : 12 rats, 18 months old, 450+ 20 g.

Discrete regions of the CNS were dissected out and wet ashed in 3:1 concentration of nitric acid and perchloric acid. The metal analysis was done using DCP spectraspan (Beckman). The data was analyzed statistically using student's 't' test and ANOVA. Statistically significant increase in Zn levels was found correlated with increasing age. The maximum concentration of Zn occurred in the hypothalamus, followed-in order-by hippocampus, cerebellum, brainstem and spinal cord. Cu concentration was decreased in all regions of the CNS with the passage of time. The highest concentration of Mn was noted in the hypothalamus. Pb was maximum in hypothalamus and increased with age. Cd ions were concentrated in the spinal cord with lower levels being seen in the brain stem, hippocampus and hypothalamus. Aluminium was maximally increased with age in hypothalamus and hippocampus.

Age related changes in various regions of the brain: effects of drugs thereon

Neurons, the postmitotic cells of the nervous system, exhibit increasing accumulation of lipofuscin (the so-called 'age pigment') which has been correlated with ageing in mammals (Hasan and Glees 1972a; Hasan 1985). Lipofuscin is morphologically an irregular shaped membrane-bound inclusion consisting of an electron-dense structure. Lamellar figures have also been described as prominent components of lipofuscin by some investigators (Hasan and Glees 1972b; Singh 1982). Lipofuscin is closely associated with the cytoplasmic organelles, especially lysosomes and mitochondria (Hasan and Glees 1973b). The close relationship between pigment granules and mitochondria is striking. Frequently, osmiophilic bodies can be detected in mitochondrial profiles (Glees and Hasan 1976). With increasing age, mitochondria may undergo slow degeneration and auto-oxidation. In support of the concept of mitochondrial origin of lipofuscin is the evidence of a double membrane surrounding the pigment masses (Hasan and Glees 1972a; Glees and Gopinath 1973; Gopinath and Glees 1974). Observations of 'intra-mitochondrial dense bodies' by Hasan and Glees (1972b) supported by histochemical and biochemical studies have strengthened the view that the degenerating mitochondria are instrumental in the genesis of lipofuscin. The mode of dissolution and

removal of lipofuscin was studied ultrastructurally for the first time by Hasan et al (1974a, 1974b) in senile guinea pigs treated upto 56 days with hilfergin (dimethyl aminoethyl p-chloro-phenoxy-acetate hydrochloride 80 mg/kg b.w. im.). After 4 weeks of drug administration, the pigment masses were reduced. Particularly noteworthy was the incorporation of a few altered lipofuscin granules in the perikarya of reactive 'phagocytic' cells, rich in cytoplasmic organelles and exhibiting increased electron density. Occasionally these cells were observed close to capillaries and at times pigment granules were seen in the endothelium which was studied with numerous vacuoles (Hasan et al 1974b).

Hasan and Glees (1973a) have also shown remarkable diminution of axo-somatic synapses in the hippocampus of aged rats, dispersal of parallel cisternae of rough endoplasmic reticulum and fusion of oligodendroglial cells.

A new method for histochemical localization of zinc in the brain using 2-carboxy-2'-hydroxy-5'-sulfo-formazyl benzene perfusion staining (Hasan 1977)

Zinc is an essential element in animal nutrition. Deficiency or intoxication produces characteristic symptoms. The dithizone method commonly used for histochemical demonstration of zinc is not specific as it forms insoluble coloured inner complex salts with a number of heavy metals (Zn, Pb, Ag, Cu, Hg, Au, Cd). Zincon (2-carboxy-2'-hydroxy-5'-sulfoformazyl benzene) has been used for serum zinc determination and as an indicator for the spectrophotometric determination of zinc content of water. The zincon staining solution, which is deep red, forms a blue complex with zinc ions especially in alkaline solutions (pH 9-10). Cold knife or cold microtome sections are undoubtedly best for the demonstration of natural tissue zinc. The zinc complex is stable over a pH range of 8.5-10 (Hasan 1977). Atomic absorption spectrophotometric analysis of brain samples for zinc content has revealed that this method is highly sensitive and can be advantageously used to localize minute amounts of zinc in experimental animals rapidly and accurately (Hasan 1977).

Neurotoxicity of organophosphate pesticides

The use of organophosphate (OP) pesticides is increasing since they are less cumulative in the body than the organochlorine pesticides. Neurotoxic effects of OP are attributed primarily due to cholinesterase inhibition and consequent accumulation of acetylcholine. But accumulation of acetylcholine alone does not fully explain OP neurotoxicity (Hasan et al 1988). Alterations in regional brain monoamine levels have been correlated with behavioural changes in the rat (Ali et al 1981). Diminution of lipids in discrete areas of the rat CNS following OP metasystox intoxication occurred in concordance activity and lipid peroxidation (Islam et al 1983).

Another OP, DDVP caused dose related diminution of phospholipids (Tayyaba and Hasan 1980). Metasystox, a sulfur containing OP also induced alterations in the brain nucleic acid metabolism (Tayyaba et al 1981). Methyl parathion, on the other hand, caused dose-related increment of total lipids, phospholipids, cholesterol and lipid peroxidation but decreased gangliosides and glycogen (Hasan and Khan 1985, Khan and Hasan 1988). It also caused increment of Mg2 +ATPase and inhibition of succinic dehydrogenase activity in the brain (Tayyaba and Hasan 1985). Dimecron toxicosis reduced lipid levels and increased lipid peroxidation in various regions of the brain (Naqvi et al 1988). A remarkable dose-dependent change in lipid fractions and increment of lipid peroxidation was detected in the fish brain when exposed to DDUP in water (Wadhva and Hasan 1986). Matin (1988) has recently reported abnormal levels of dopamine in the corpus striatum, neurotoxic esterase in brain and GABA in certain regions of the brain associated with the motor dysfunction in chicken induced by delayed OP neurotoxicity.

Tri-ortho-cresyl phosphate per cutaneous application induced degeneration in the spinal cord and cerebellum of hen

Hasan and Glees (1971) painted 0.2 ml tri-ortho-cresyl phosphate (TOCP), a plasticiser lubricant and petrol additive, on the combs of 20 pullets with the help of a tuberculin syringe bringing the nozzle in direct contact with the skin. On an average, at the end of the first week of TOCP application, the hens exhibited stepping parade-like gait and were unable to climb up a ladder without losing balance. The extensors of the toes were predominantly involved. The hens were sacrificed after a marked degree of paralysis had developed (15th to 19th day). Swank-Davenport modification of Marchi technique, Glees Silver and Nissl methods were used for demonstrating the lesions. Well marked Marchi degeneration was visible in the ventromedial area of the spinal cord and in spinocerebellar tracts. The degenerating fibres could be followed into the cerebellar cortex and on occasions into the granule cell layer. The lesions in the lumbar spinal cord were restricted to the ventromedial area but in the upper cervical and medullary levels similar small lesions of the spinocerebellar tract and posterior column were detected. Mossy fibres of cerebellum were, on occasions, degenerated.

Thallium, nickel and cobalt administration increases lipid peroxidation in the various regions of the brain

Rats were given thallium (5 mg/kg),nickel and cobalt (2 mg/kg) intraperitoneally daily for 7 days (Hasan and Ali 1981). Thallium was most toxic, followed by nickel and cobalt. When studied after 7 days of treatment, the rate of lipid peroxidation was significantly increased in the cerebrum, cerebellum and brainstem of rats in all treatment groups. Thallium caused the maximum increase in the rate of lipid peroxidation in the cerebellum

while cobalt and nickel produced maximum changes in the brainstem. Electron microscopy revealed increase in the deposition of lipofuscin-like pigment in the cerebellar neurons after thallium intoxication. This correlated well with the increased rate of lipid peroxidation.

Trimethyltin administration causes diminution of total lipids, cholesterol-phospholipid ratio, free fatty acids and gangliosides in various brain regions

Hasan et al (1984) injected rats with 1.0 mg trimethyltin (TMT) intraperitoneally daily for 8 days. The administration of TMT diminished total lipid levels in all the regions of the brain. Phospholipids remained unaffected. The concentration of cholesterol was decreased in cerebrum and brain stem. C/P ratio showed decrement in these regions. Esterified fatty acids were remarkably depleted in various regions of the brain. Sulfhydryl radicals showed decreased levels only in the brain stem. Lipid peroxidation and lipase activity was elevated in the different regions of the brain. Electron microscopy showed remarkable accumulation of electron- dense pigment bodies in comparison with the control animals.

Experimental manganese encephalopathy

Chandra (1972) produced experimental manganese encephalopathy in rabbits by intratracheal innoculation of manganese dioxide (400 mg). After a period of 18 to 24 months manganese innoculated rabbits developed paralysis of the hind limbs. There was widespread neuronal loss and neuronal degeneration in cerebral cortex, caudate nucleus, putamen, substantia nigra and cerebellar cortex. This was associated with neuroglial proliferation. There was marked reduction in the activity of acid phosphatase and adenosine triphosphatase in the degenerated neurons in manganese innoculated animals as compared to controls. It has been suggested that manganese may possibly have an inhibitory effect on acid phosphatase and adenosine triphosphatase in affected neurons by disturbing the catabolism of enzyme protein or by destroying lysosomes and mitochondria.

Bilirubin Neurotoxicity

Bilirubin is known to be toxic to cells in vitro and in vivo. The vulnerability of the neonatal brain to bilirubin toxicity is attributed to the immaturity of the blood-brain barrier. To date, little information is available on the effect of bilirubin on areas lacking the blood-brain barrier: the circumventricular organs. Siddiqui et al (1988a,b) produced hyperbilirubinemia in 10 day old weaning rats by intraperitoneal injections of bilirubin (100 ug/g) followed by 6 injections of bilirubin (50 ug/g/hour/day) for 3 days. All animals were kept in the dark during these experiments. The serum bilirubin was monitored. They reported, for the first time,

degenerative changes in the pineal body and selective damage to the stroma of the choroid plexus with approximation of choroidal epithelium. The nuclei and cytoplasm of choroid plexus epithelium did not exhibit any changes. These findings indicate that bilirubin enters the choroidal stroma through fenestrated blood capillaries. Breakdown of blood-brain barrier leads to deposition of bilirubin in the brain. Bilirubin selectively damages stroma of choroid plexus affecting both fibroblasts and macrophages. The choroidal epithelium is not damaged due to tight junctions that disallow entry of bilirubin or due to high albumin content of epithelial cells.

Effects of electroconvulsive shock on the blood-brain barrier

Repeated electroconvulsive shock (ECS) causes an increase in the permeability of the blood-brain barrier (BBB) and allows entry into the brain of many plasma born solutes normally unable to cross this barrier. Increased leakage of horse-radish peroxidase into the perivascular regions of the diencephalon of rats after repeated ECS has been demonstrated by Awasthi et al (1980). The cataleptic activity was significantly increased in ECS - treated rats after i.p. administration of trifluperazine. This increase was not observed when the drug was given by intra-cerebro-ventricular route. The study suggests that the increased cataleptic effect induced by trifluperazine after electroconvulsions is due to increased permeability of the blood-brain barrier.

Effects of ultrasonic irradiation

Effects of ultrasound irradiation on developing neural tube in chick and rats

Ultrasound is being used for diagnostic, therapeutic, and research purposes for a number of years. It is known that ultrasonic waves stimulate hydrolysis, oxidative phosphorylation and glycolysis in tissues. Hasan (1975) exposed 36 albino rates to ultrasound (frequency 1-2 mega hertz, intensity 1-2 w/sq cm, duration 5-10 min.). Their brains were examined after 1-21 days for nerve fibre degeneration (Simonsen's modification of Fink - Heimer technique) and acid phosphatase activity (Gomori method). Degenerating fibres were clearly seen in subcortical white matter and the acid phosphatase activity was markedly increased in the experimental group of animals as compared with control. Although teratological effect of ultrasound has been disputed, species specific effects are reported with different frequencies of irradiation. Navagiri et al (1988) investigated the effect of ultrasonic irradiation in white leg-horn chick embryos at 72 hours incubation and the embryos were recovered on the 12th day. They observed a wide range of morphological developmental abnormalities. One embryo showed malformed post-umbilical region and so it was processed for histological study. The neural tube exhibited multiple lumina dorsal to the caudal vertebral centrum. Additional lumen was seen towards the ventral aspect of the centrum.

Glial changes in experimental ischemia in adult rat brain

Reports on changes in the brain following different kinds of anoxia/hypoxia are mostly confined to the description of neuronal changes. Their relationship to vascular changes have not been adequately described, especially with regard to the chronology of brain damage. Sen Sharma (1988) carried out an extensive study on the temporal and spatial neuroglial responses in the adult rat brain following ischemic anoxia produced by bilateral clamping of the common carotid arteries. The initial changes in the brain were characterized by reactive as well degenerative astrocytic alteration prior to neuronal damage and vascular endothelial changes. Microglial infiltration with transformation of red cells into gitter cells followed later along with neuronal degenerative changes, vascular endothelial swelling and capillary dilation. Degenerative changes in the oligodendroglia appeared last and were less pronounced.

Cellular and vascular changes in experimental cerebral ischaemia

The sequence of neuronal and vascular changes following cerebral ischemia remains unresolved inspite of the well adopted concept of 'no-reflow' phenomenon and irreversibility of neuronal damage. Experimental ischemia was produced in adult healthy albino rats by bilateral clamping of common carotid arteries for 5,10 and 15 minutes. Animals from each group were sacrificed on day 1,3,5,7 and 10. Neuroglial response was seen first. This was followed by neuronal damage and thereafter vascular change (Sen Sharma 1988).

Cerebral malaria: parasitic infiltration of glial and capillary endothelial cells

Mahdi et al (1988) obtained a virulent strain of Plasmodium Knowlesi from CDRI, Lucknow and innoculated 5 rhesus monkeys with it. A primary infection initiated by an intravenous innoculation of 10^6 parasitised erythrocytes resulted in a prepatent period of 7 days, followed by a rise of parasitaemia. Autopsy on 5 monkeys who died after 7-9 days revealed oedema and congestion of the external surfaces of the brain. Light microscopy of sections from various parts of the brain showed different stages of parasites inside the endothelial cells of the capillary and supporting glial cells of the cerebral cortex and medulla. The presence of these parasites within the cells is certainly a novel observation.

Effect of burn injury and dehydration on the supraoptic hypothalamic nucleus

The supraoptic nucleus (SON) neurones of the hypothalamus, besides being neurohormonal effectors,are known to be sensitive to dehydration. Nagar and Prakash (1988) inflicted burns under anaesthesia on the trunk of adult

Wistar rats by immersion in water at 100 degrees C for 15 seconds. The brains were removed 24 hours post-injury and processed for paraffin embedding. Serial sections (7 micrometre thick) were cut in coronal, horizontal and sagittal planes and stained with cresyl fast violet and Bergmann's chrome haematoxylin. Controls were studied simultaneously. In the experimental rats the size of the neurones increased significantly with an associated reduction in the intervening glial tissue. The nuclear and nucleolar diameters of the SON neurons revealed a statistically significant increase ($p < 0.05$). The cytoplasm exhibited depletion of neurosecretory granules. A number of cells showed two or more nucleoli. These changes are suggestive of increased neuronal activity (Nagar and Prakash 1988).

Correlation of fine structure with neurotransmitter levels in acute brain oedema

Dave and Dastur (1985) experimentally produced brain oedema in cats by freezing the cortical surface with dry ice for 90 seconds. The cold lesion usually measuring about 1 cm2 on the surface, was produced in test animals while control animals were subjected to similar anaesthesia and the tissue excised without applying cold or producing any injury. The electron microscopic changes detected by Dave and Dastur (1985) were mainly those of vasogenic oedema, varying from distention and rupture of cytoplasm of neurons and perivascular glial end-feet, opening of endothelial tight-junctions and disruption of the neuropil. A cytotoxic component of the oedema was the separation and punctate degeneration of the myelin of nerve fibres. These changes were not observed in brains of identically maintained control cats. The level of noradrenaline was significantly higher in swollen oedematous gyri compared to that in the control cats. The concentration of 5-hydroxytryptamine was not significantly different between the two, suggesting that nor-adrenaline content was a better indicator of the breakdown of the blood-brain barrier. These observations strengthen the contention that many excitatory neurotransmitters may induce brain oedema, while inhibitory compounds do not. The structural and the biochemical substrates of blood-brain barrier seem to be disturbed even in acute brain oedema.

Serotonin containing nerves in rabbit cerebral vessels

Serotonin (5-HT) has frequently been implicated in the pathogenesis of migraine. Dhall (1988) studied the regional variations in density and pattern of 5-HT containing nerves in cerebral vessels of 10 adult rabbits. The 5-HT containing nerves were demonstrated by an indirect immunohistochemical technique on whole-mount stretch preparations. These nerves were present in all the arteries. The nerve fibres formed a meshwork. Most of these nerves showed varicosities at regular intervals. A few non-varicose fibres were also present. In the basilar artery the fibres

were predominantly arranged longitudinally while in the internal carotid artery they were arranged circumferentially. Quantitative estimation showed that the density of nerve fibres was greater in the arteries of posterior part of circle of Willis than in the anterior part.

Effect of restraint stress on the various regions of the central nervous system (CNS)

Stress studies, by accelerating changes normally occurring in the organism with passage of time, provides additional insight into the otherwise slow and subtle alterations associated with physiological ageing. Restraint or immobilization has been used as a stressor because it simulates the state of restricted activity commonly observed in aged individuals. Restraint for a period of 24 hours resulted in pyknotic changes in cerebellar Purkinje neurons (Fig.25) of young albino rats (Singh et al 1981b).

Transmission electron microscopy showed an increased incidence of lipofuscin granules in the oligodendrocytes and neurons of cingulate cortex (Fig. 26,27) amygdaloid complex (Fig. 28), cerebellum (Fig. 29) and anterior hypothalamus of young (4-6 months old) albino rats (Hasan et al 1982,1985b; and Singh 1982).

Singh (1982) also reported a regional heterogeneity of the percent increase in the fluorescent pigment intensity (measured at 365 nm and 445 nm excitation and emission spectra) in different parts of the brain in albino rats immobilized for 24 hours. The increase was correlated directly with the extent of increased lipid peroxidation as a result of damage to polyunsaturated lipids of subcellular membranes.

Vulnerability of Schwann cells and nerve fibres in peripheral nerve injury

Mechanical, vascular and bacterial (single and combined) injuries were produced experimentally by Mehta and Rasouli (1988) in the mouse sciatic nerve. Electron microscopy was undertaken. Initial loss of non-myelinated fibres was seen in all. Loss of fibres and type of trauma showed correlation. Schwann cells were seen vulnerable to blood loss by forming different patterns of abnormal myelinations. Schwann cell-axon interaction was also disturbed. Anoxia along with bacterial injury (M. leprae) had greater destructive effect on the Schwann cell (Mehta and Rasouli 1988).

Histochemistry of myelin lipids and certain enzymes in normal and degenerating peripheral nerves.

In the normal and transected ulnar nerves of dogs, Tanksale (1966) found that myelin lipids remained unchanged upto 1 week. Increased activity of acid phosphatase in degenerating axons was detected. There was a

decrease of true cholinesterase activity during degeneration. This was attributed to the breakdown and removal of axons (Tanksale 1966).

Work currently in progress and work projected into future.

With recent advances in technology, it has become possible to investigate the finer mechanisms involved in the fields of developmental neurobiology, neural transplantation, immunohistochemical labelling of neurons and neuronal pathways, artificial intelligence and computer vision.

Trophic interactions between developing neurons modification of functional activity and critical periods of development are of greatest importance in man. At every stage of development there is interaction of the genome with the 'milieu interior' of the cell and interaction with neighbouring cells. Molecular regulation of neural morphogenesis, N-CAM (neural cell adhesion molecule), Ng-CAM (Neuron-glia CAM), the role of cytotactin in neural and secondary inductions are currently the focus of attention. Characteristics of brain messenger RNAs, the neuronal identifier sequence, and axonal pathfinding during development are now better understood. Hopefully, mechanisms of growth and guidance of axons from the cerebral cortex and mechanisms of neuron-glia interactions will be better understood in the near future. At present the development and maintenance of selective synaptic connections is not clearly known. Genetic programs direct the assembly and maintenance of neuronal circuitry in the developing brain, but cellular interactions, hormones, neurotransmitters, neuronal activity and many other influences determine final form. Mechanisms of brain plasticity will be unfolded by the application of newer molecular techniques (for example 'in situ' hybridization of brain mRNA). Experimentally successful neural transplantation using embryonic tissue is currently being exploited for a better understanding of developmental neurobiology and for replacement therapy in patients suffering from progressive and fatal neurological degenerative diseases. Encouraging results in primate models of Parkinsonism have already prompted trials in human beings. With advancing knowledge in molecular neurobiology donor tissue can be used for grafting by hybridization of neurons in culture.

Interesting insight into the surface morphology of the ventricular ependyma is now available, thanks to advances in scanning electron microscopy. Variegated supraependymal cells, some neuronal and others phagocytic elements have been identified and interesting connections between neuronal elements on the ventricular lining have been discovered. Furthermore, a number of circumventricular organs have been detected which lack blood-brain barrier and their functional significance is being explored. It is apparent that the ventricular ependyma is not only an organ but more a system comprising of many diverse organs with significant functions.

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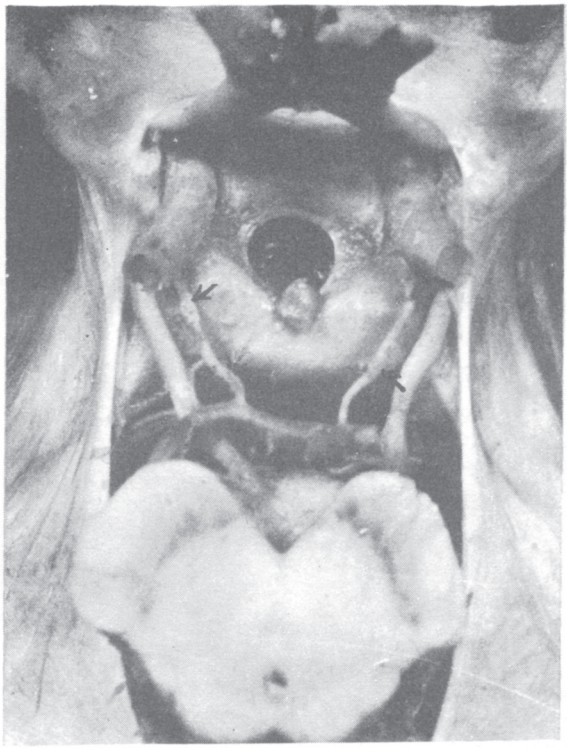


Fig.1 : Posterior communicating arteries arising from the posteromedial surface of internal carotid arteries.

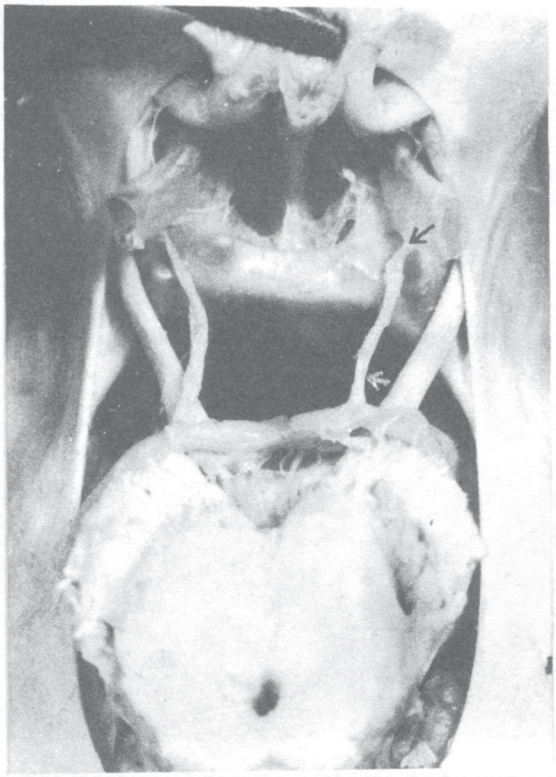


Fig.2 : A junctional dilatation and the neck of a funnel-shaped dilatation seen at the termination of the right posterior communicating artery.

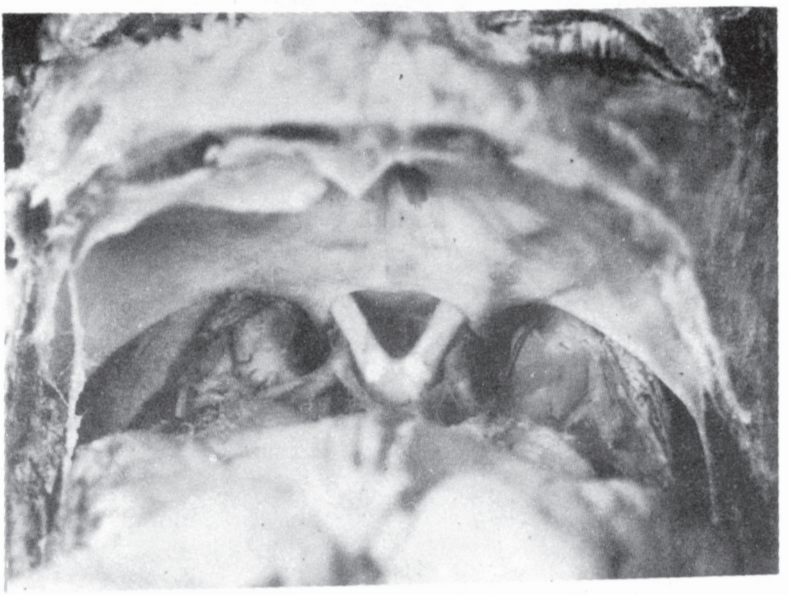


Fig.3 : The posterosuperior view of the region near the lesser wing of sphenoid bone. The superficial middle cerebral vein is entering the sphenoparietal sinus on either sides.

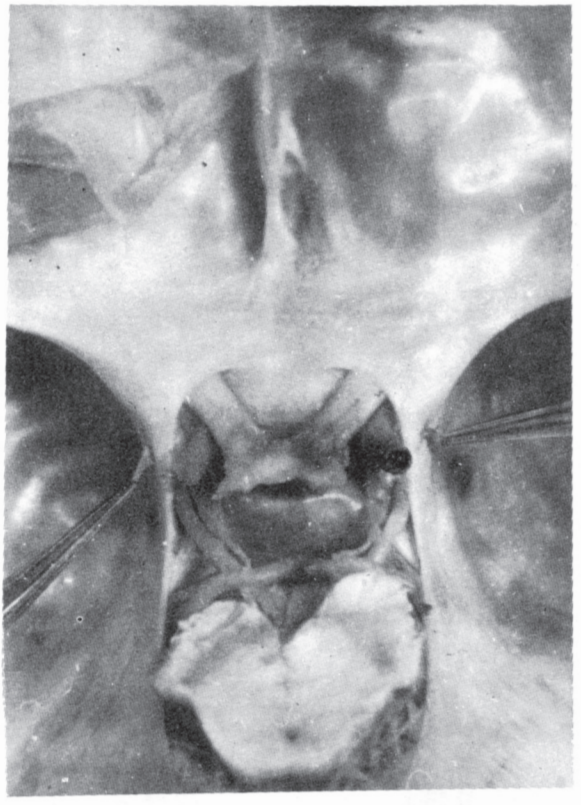
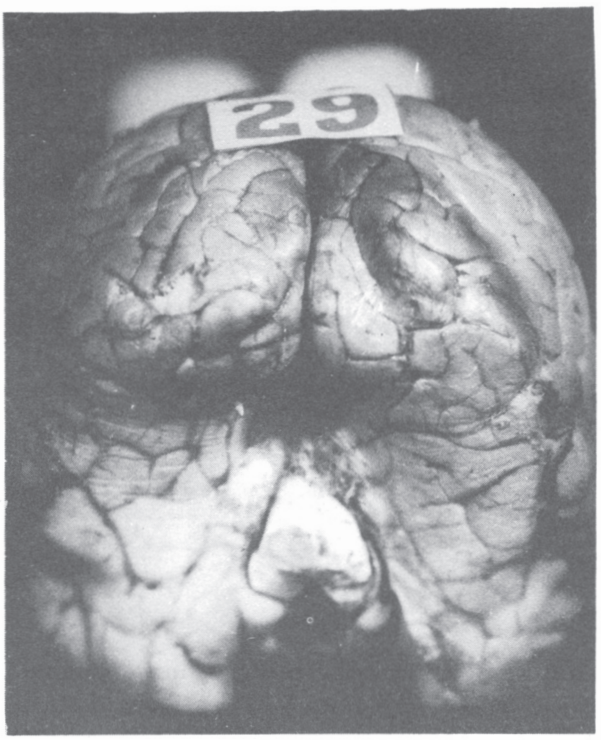


Fig.4 : Superior view of the middle cranial fossa; showing terminations of superficial middle cerebral veins in the anterior portions of the cavernous sinuses.



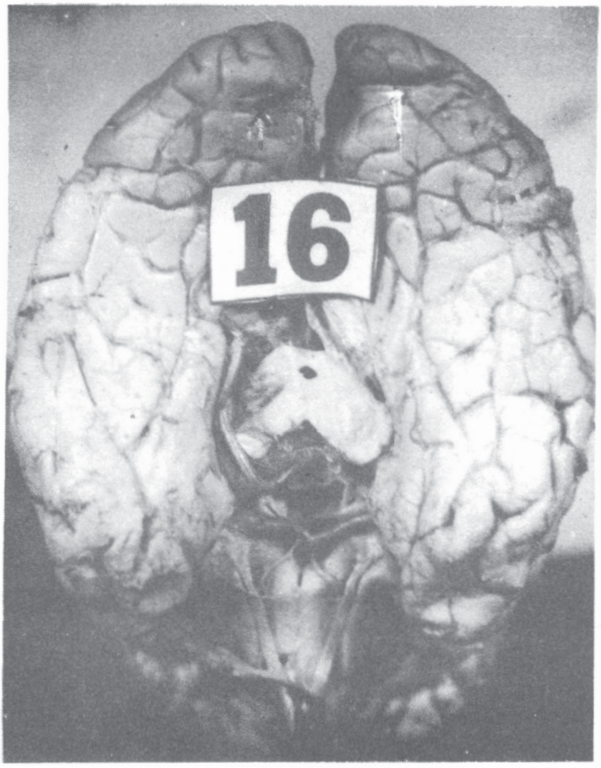
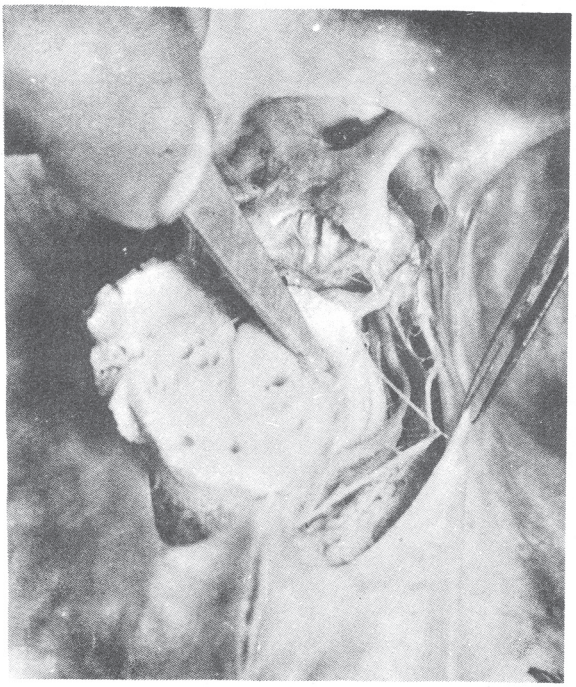


Fig.5 : An angular groove of considerable depth is seen on the right occipital lobe of brain visualised from the postero-inferior aspect.Fig.6 : Bilateral transverse grooves visualised on the inferior aspect of occipital lobes pointing upwards.



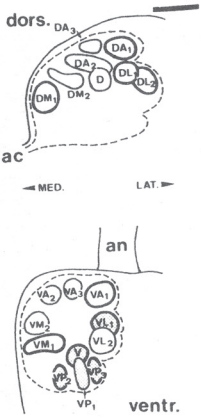


Fig.7 : A dissection of the tentorial notch showing a tentorial band across the notch.

Fig.8 : Right antennal lobes in *Drosophila* showing relative position, shape, and size of 19 glomeruli representing antennal projection areas. Ten heavily outlined glomeruli belong to major projection areas. Five stippled glomeruli receive exclusively ipsilateral input, the remaining receive bilateral projections, dors., ventr.=horizontal view of dorsal and ventral levels. A=anterior, ac=antennal commissure, an=antennal nerve, D=dorsal, L=lateral, M=medial, P=posterior, V=ventral; scale=25 um.

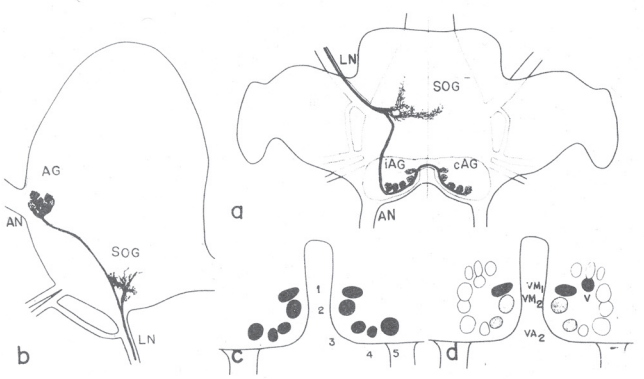


Fig.9 : Diagrams summarising sensory projection patterns from maxillary palp of *Drosophila*. (a)-(b) fibres project separately into posterior suboesophageal (SOG) and send distinct tract towards antennal lobe where they occupy 5 glomeruli bilaterally. Fibres projecting in posterior SOG show typical L-shaped branching pattern (arrow). (a) Horizontal view with posterior on top. (b) Sagittal view, dorsal on top, anterior toward left. (c)-(d) Horizontal views of ventral half of antennal lobes showing main projection patterns of sensilla basiconia from maxillary palp and antenna respectively. AG=antennal lobe; AN=antennal nerve; cAG=contralateral antennal lobe; iAG=ipsilateral antennal lobe; LN=labial nerve; SOG=suboesophageal ganglion. Scale=50 um.

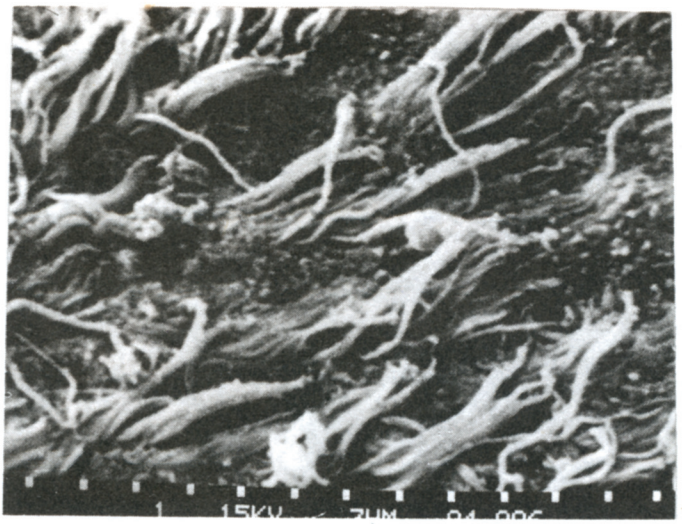


Fig.10 : Clumps of cilia emerging from the apical surfaces of ventricular ependymal cells.

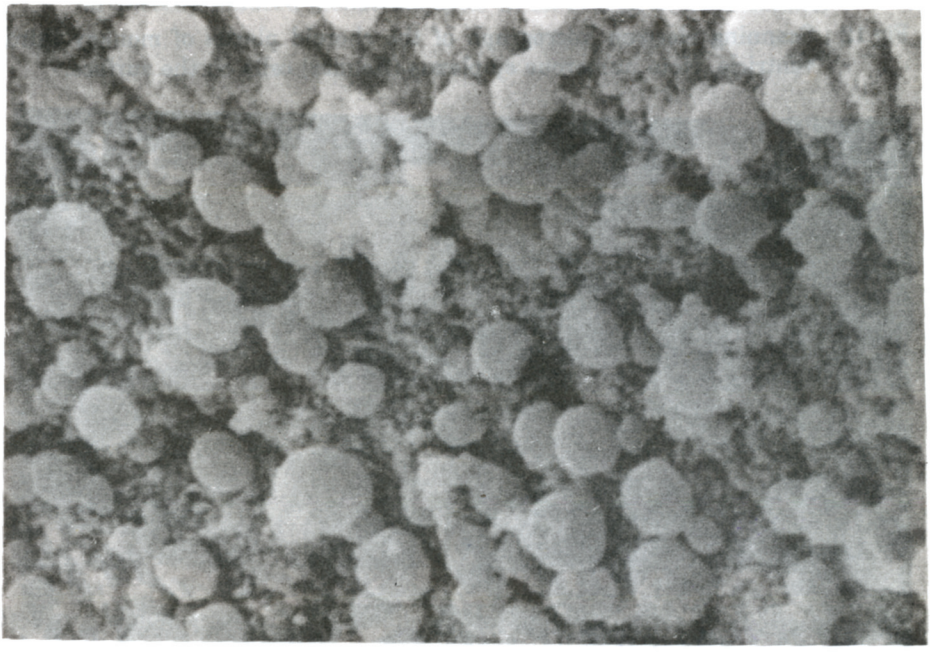


Fig.11 : Pleomorphic globular protrusions in the infundibular region of the third ventricle of rabbit.

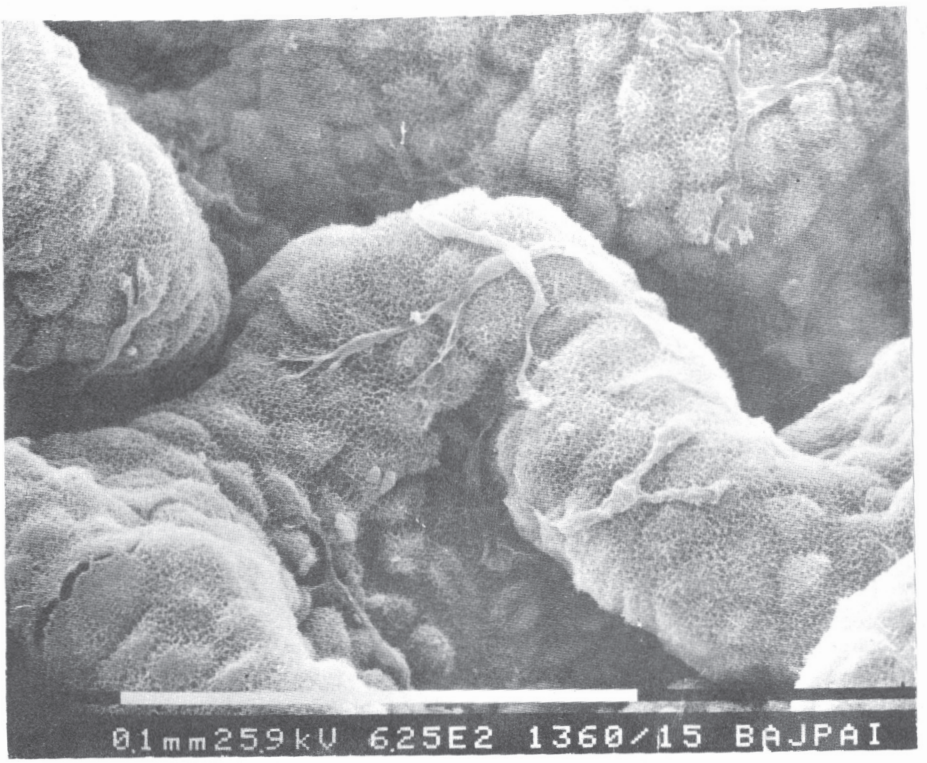


Fig.12 : Scanning electron micrograph of the choroid plexus of monkey third ventricle. Note numerous epiplexus (Kolmer) cells on the surface.

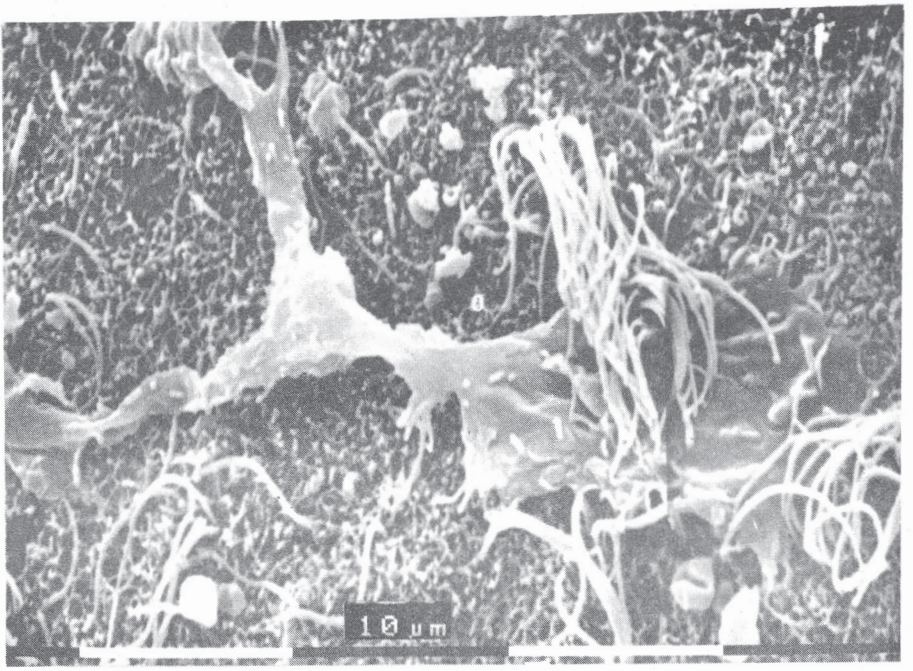


Fig.13 : A macrophage-like supraependymal cell with broad expansions near the termination of its processes. A ciliary tuft is adhered to one of the processes suggesting phagocytic activity of the cell.

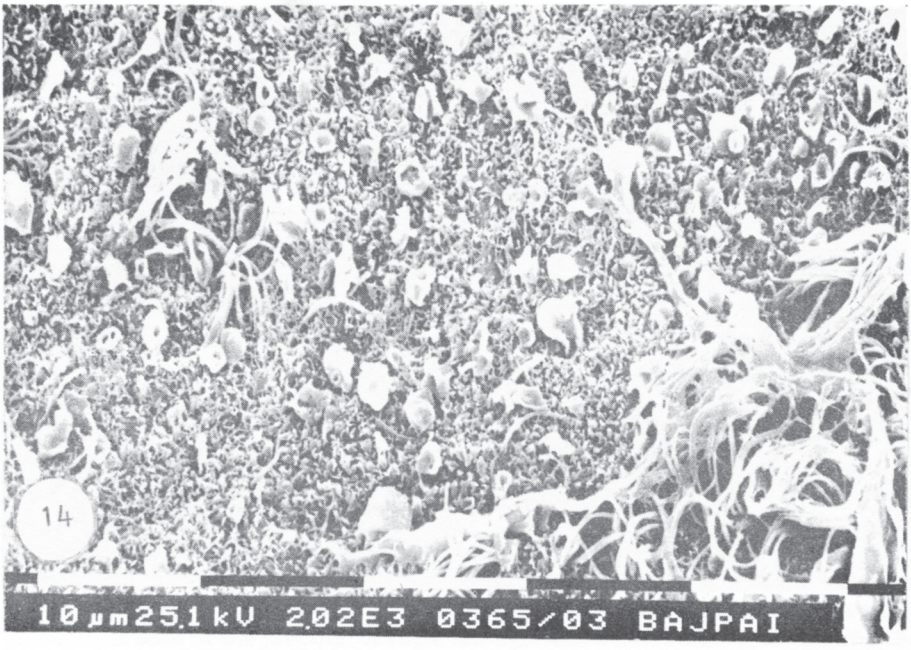
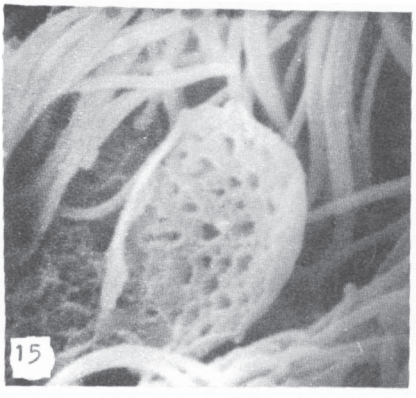


Fig.14 : Increased number of microappendages visualised over the hypothalamic ependyma of the monkey after the estrogen-peak attained at Day-14 of artificially induced menstrual cycle in an ovariectomized animal.



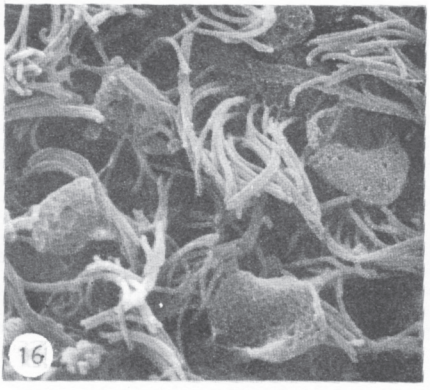


Fig.15 : A high magnification of a leaflet like ependymal microappendage showing numerous pinocytotic vesicles on its surface.

Fig.16 : Funnel-shaped microappendages are seen in the ventricular lumen of third ventricle in a rhesus monkey at day 14 of artificially induced menstrual cycle.

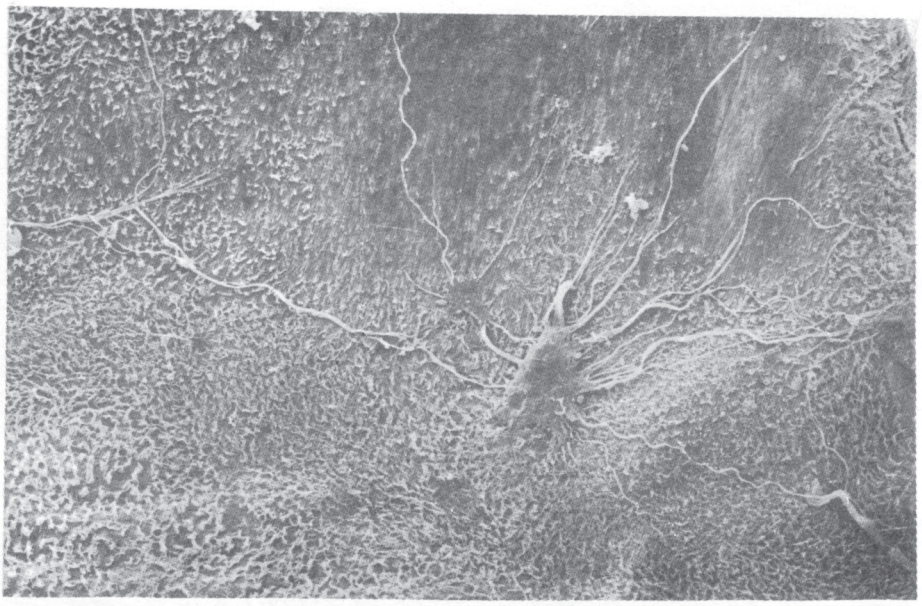


Fig.17 : A neuron-like supraependymal cell with many long fibre-processes extending over the ventricular ependyma of the dorsal portion of the lateral wall of the third ventricle of rhesus monkey.

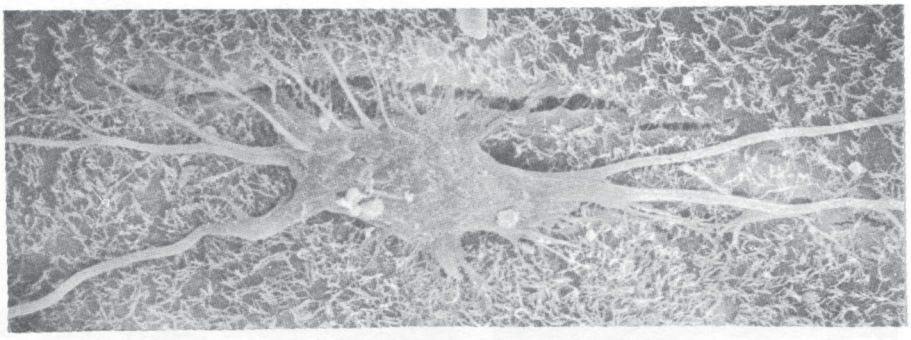


Fig.18 : A neuron-like supraependymal cell in the third ventricle of rhesus monkey.

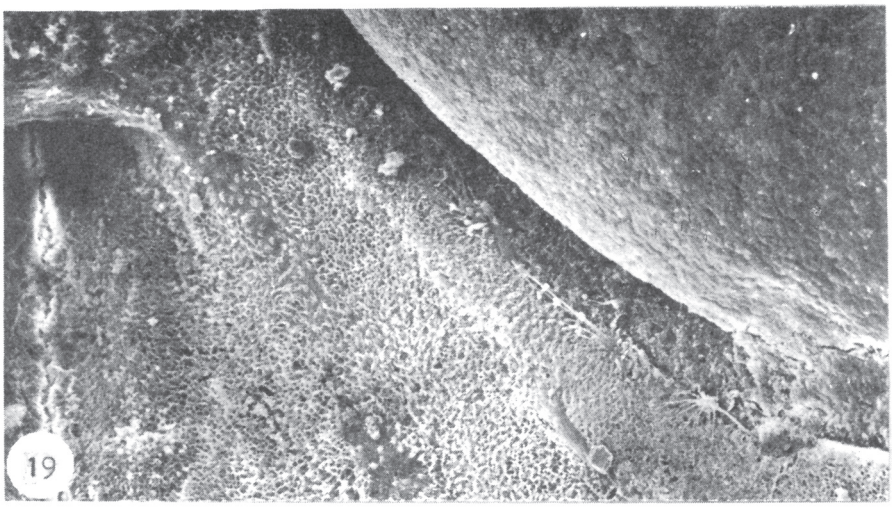


Fig.19 : A low scanning electron micrograph showing the floor of fourth ventricle of rhesus monkey. A row of supraependymal cells connecting each other is seen at the junction of vagal triangle and a narrow strip separating the area postrema (at the right upper corner) and the vagal triangle

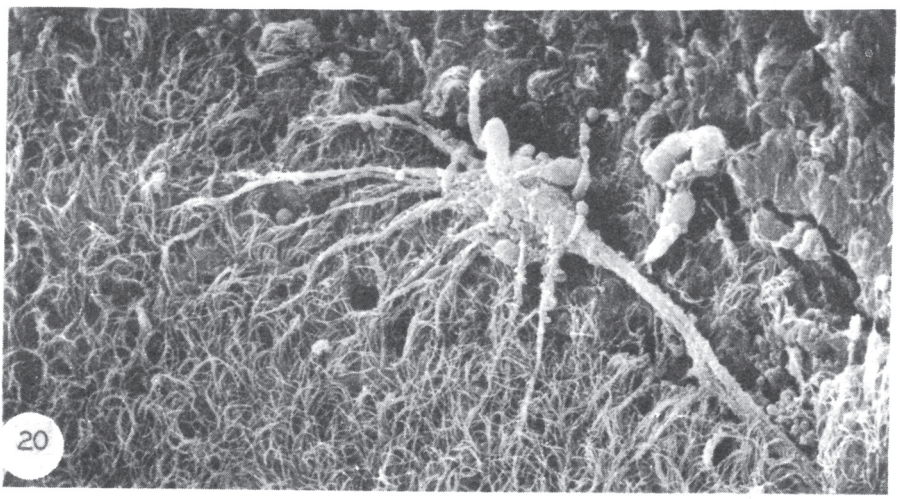


Fig.20 : A high magnification of a cell seen at the lower and of the row of supraependymal cells seen in the Fig.19.Fig.

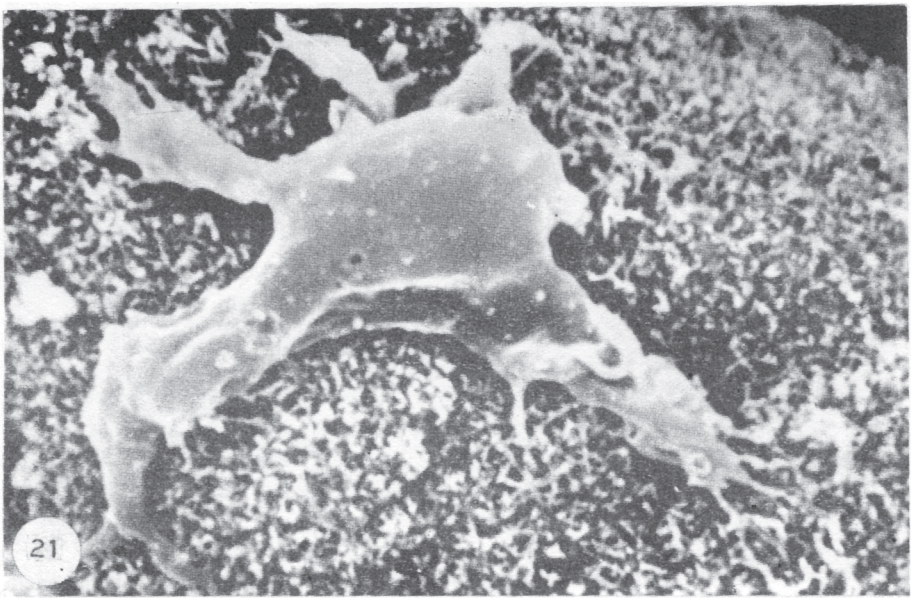


Fig.21 : A scanning electron micrograph of a histiocytic supraependymal (Kolmer) cell on the surface of rabbit choroid plexus.

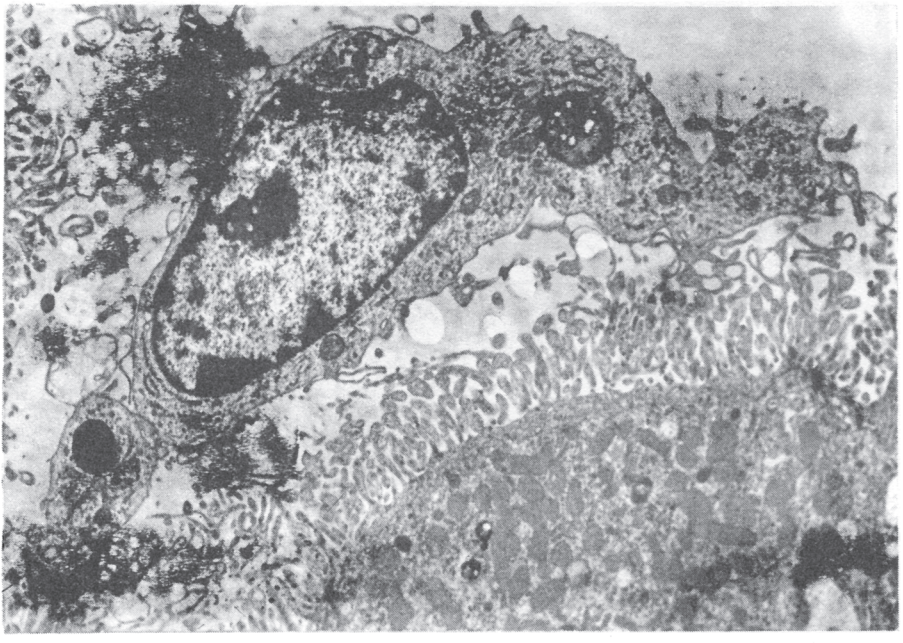


Fig.22 : A transmission electron micrograph of an epiplexus (Kolmer) cell on the choroid plexus is seen over the microvilli projecting from a nonciliated choroidal cell.

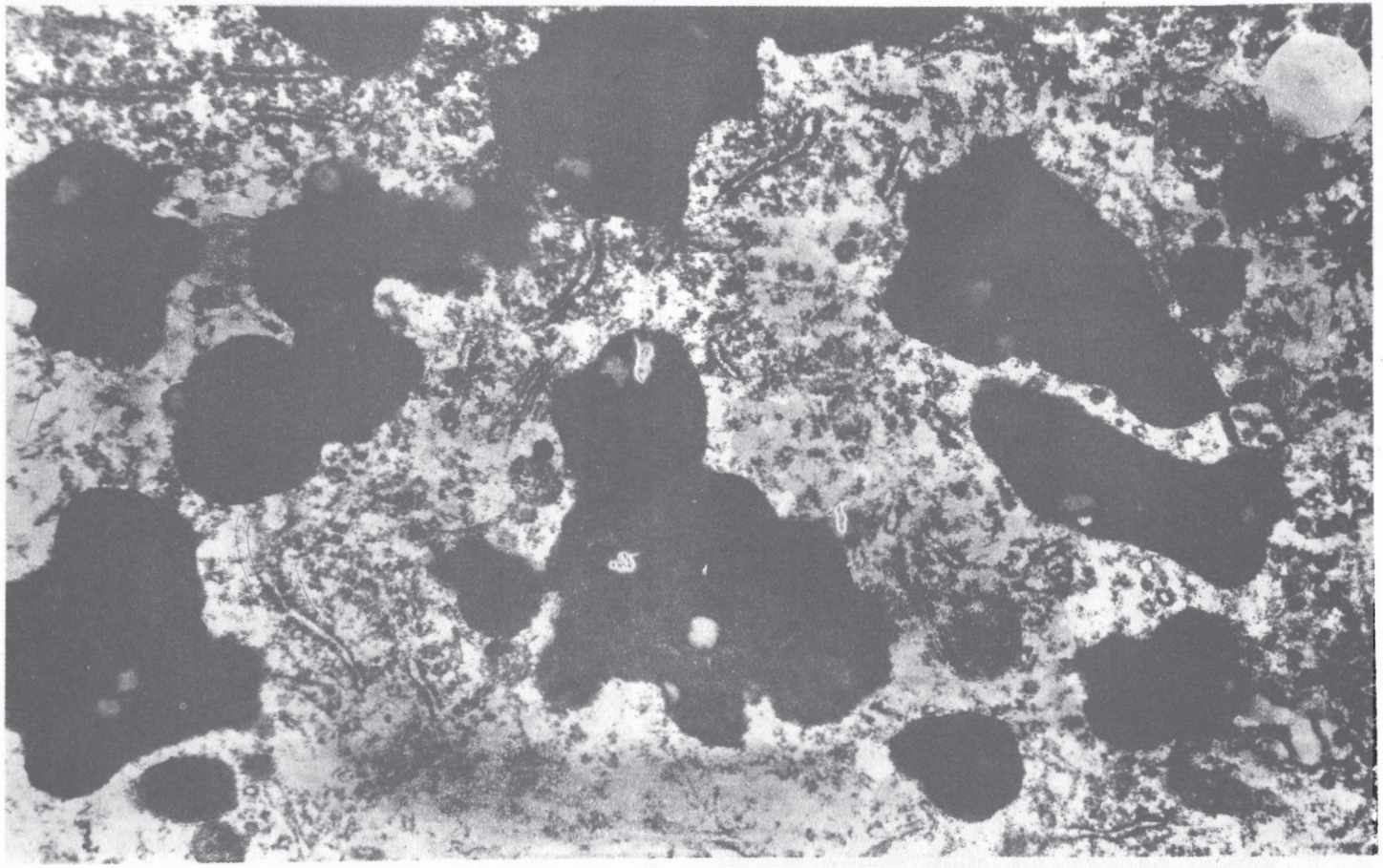


Fig.23 : A transmission electron micrograph showing various types of electrondense bodies (Lipofuscins) in a neuron of area postrema of rat intoxicated by thallium.

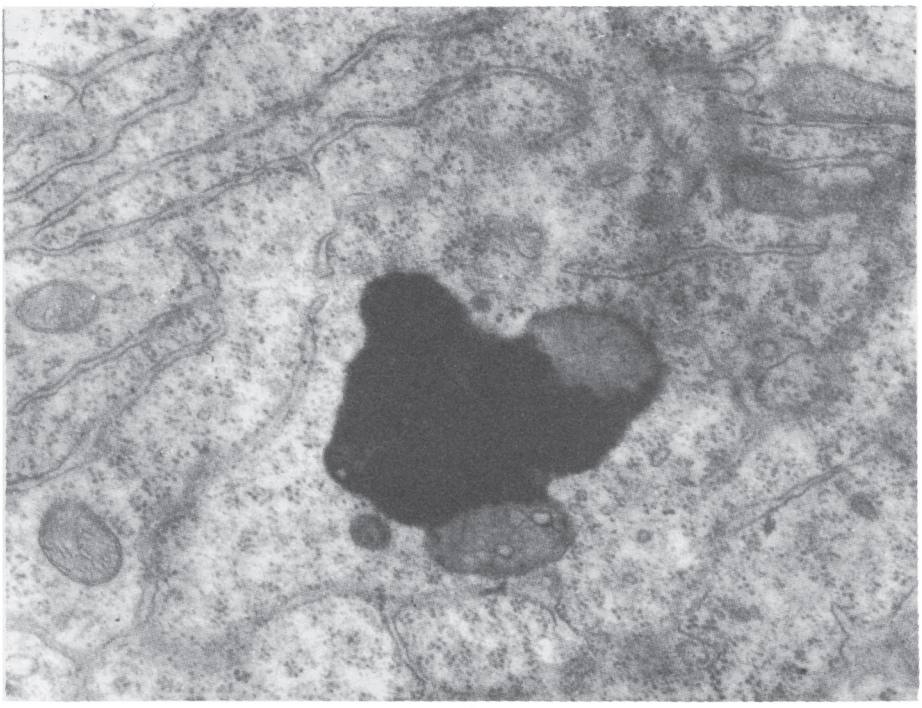


Fig.24 : A vacuolated single membrane-bound electrondense body (Lipofuscins) in an oligodendrogliacyte of rat after thallium toxicity.

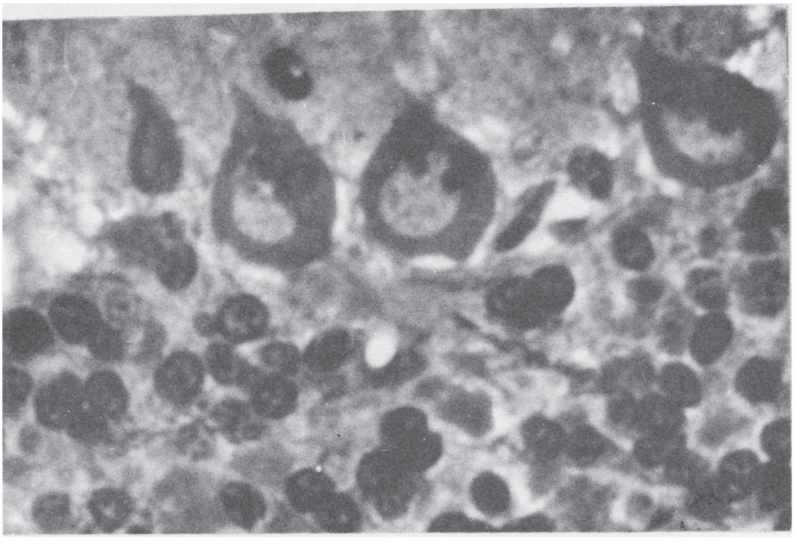
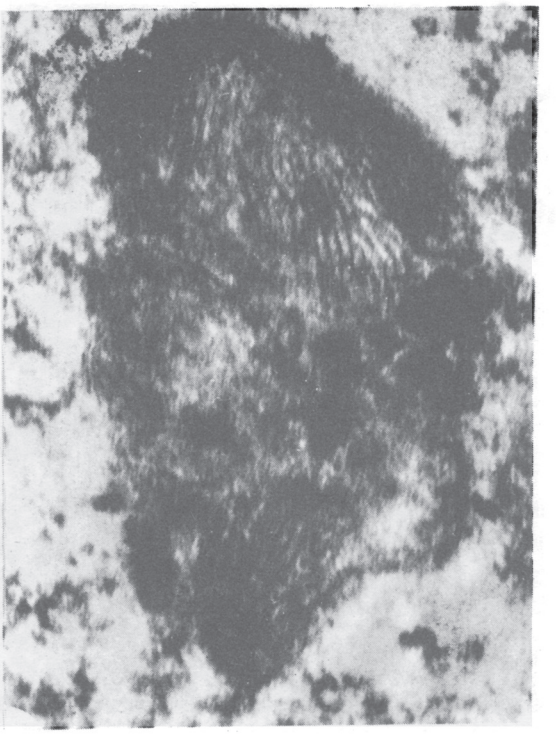


Fig.25 : A semithin section of cerebellum showing pyknotic Purkinje neurons in a restrained rat.



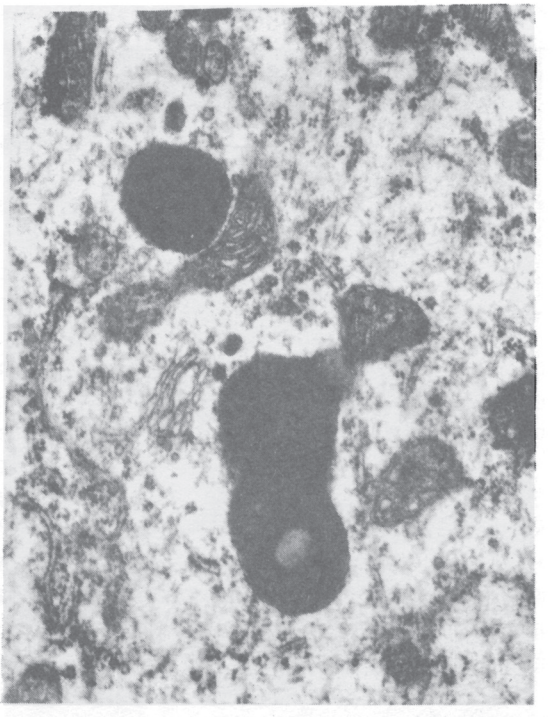


Fig.26 &Fig.27 : Lipofuscin granules in the cingulate cortical neurons of albino rat after 24 hours of immobilization.

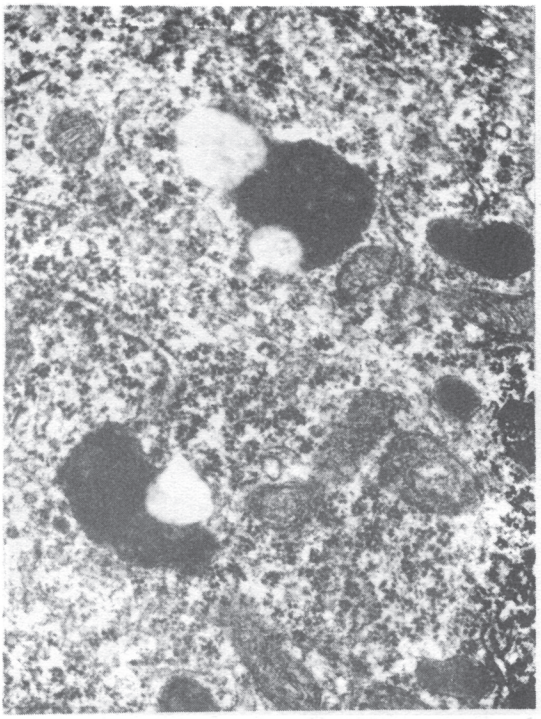


Fig.28 : Electronlucid vacuoles at the periphery of electrondense bodies (Lipofuscine) seen in the neurons of amygdaloid complex of immobilized rats.

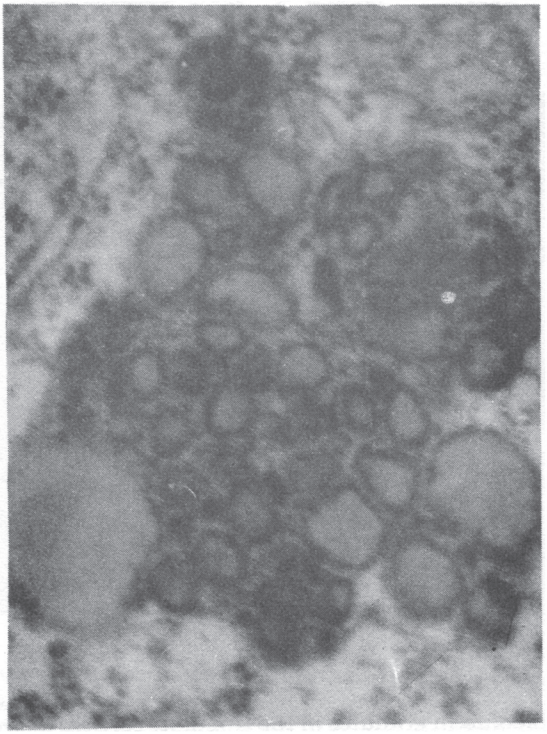


Fig.29 : An electrondense body (Lipofuscin pigment) in cerebellar Purkinge cells exhibiting a highly vacuolated appearance, in a rat immobilized for 24 hours.

Anatomy of the nervous system of *Drosophila*

R. Naresh Singh

Introduction

We perceive the world around us through the sensory organs such as eyes, ears, nose, tongue and skin. These sensory systems can be broadly classified into two categories (i) physical senses that detect energy, acceleration, pressure or field and (ii) chemical senses that interact with substances or molecules present in fluids such as air or water.

We became interested in the study of two of the chemical senses: olfactory and gustatory. These play important roles in the lives of animals and humans.

Drosophila melanogaster was selected for this study for several reasons. (i) Easy to propagate in the laboratory. (ii) Short generation time (about 10 days at 25°C). (iii) Large progeny size (about 200 eggs per female fly). (iv) Small number of chromosomes (4 chromosomes in each gamete). (v) Well studied genetics. (vi) Balancer strains are available for maintaining mutants. (vii) Genetic crossing over is rare or absent in male, although regularly present in the female. (viii) Cytological localization of genes is possible on salivary-gland chromosomes. (ix) Well developed behaviour amenable to quantification. (x) In a way *Drosophila* has two animals in one - larva and the adult fly.

We wished to determine the detailed structure and distribution of olfactory and gustatory organs of the fly, how these sensory organs project to the brain and the regions of the brain involved in processing olfactory or gustatory information. We have used light and electron microscopes. In light microscopy, Bodian reduced silver technique, Golgi impregnation, orthograde uptake of cobalt (II) or horseradish peroxidase were used for labelling neurons and analysing their projections. Whole mounts of the various organs stained with silver nitrate were used for mapping chemosensilla. Electron microscopy was used in transmission and scanning modes to analyse the internal and surface structures respectively.

This study, in conjunction with the electrophysiological, biochemical, immunological and gene-cloning studies being conducted by other workers

in our laboratory, is likely to lead to better understanding of the development, organization and function of the nervous system. In addition, behavioural mutants of *Drosophila* with altered perception of smell or taste are now available and the study of such mutants may add to the understanding of the nervous system and behaviour.

Material and Methods

Four to 5-day-old wild type male and female *Drosophila* melanogaster Canton S flies were used.

Observation on eating habits

Overnight food-starved, but water satiated, flies were transferred to a truncated bottle containing a spot of laboratory food a few mm wide for *Drosophila* on the wall. The mouth of the truncated bottle was closed with a transparent cellophane sheet and clamped with a rubber band. Flies were observed at meals under a dissection microscope.

Whole-mount preparations

The whole-mounts (of any appendage such as antenna, maxillary palp, leg or proboscis) were made after selectively staining the chemosensilla by immersing the entire fly for 2-3 days in 70% ethanol containing 0.1% silver nitrate. The appendage was removed, dehydrated, cleared and mounted in Permount.

Photographs were taken on a Zeiss RS III photomicroscope. The diagrams of silver-stained sensilla on the appendage were traced from photographic series made at different focal depths with the aid of a Zeiss DL 5.2 microfilm reader at final magnification of 1,740.

Golgi silver impregnations

The detached heads of flies were initially fixed with 2.5% glutaraldehyde solution in 0.1M sodium phosphate or 2.5% glutaraldehyde solution in 0.05M sodium cacodylate buffer at pH 7.4 for 4 hours. Specimens were washed 4 times with 2.5% potassium dichromate solution for a duration of 90 minutes. The washed specimens were processed with single or double cycle, by the Golgi Colonnier or by Golgi rapid methods (Strausfeld, 1980). Chromation was done at 37°C for 48 hours. A cut, over less than 5% of its surface, was made in the labellum, immediately before silver impregnation. The specimens were kept in 0.75% silver nitrate solution at 37°C for 48 hours in the dark. They were washed with water, dehydrated in a graded series of ethanol and embedded in Durcupan ACM (Fluka) through propylene oxide after orientation either in flat embedding forms or in inverted BEEM capsules. Polymerisation was done at 60°C for a

minimum of 20 hours. Fifteen um thick sections were cut either in sagittal or in frontal planes on a sliding microtome and mounted with Permount.

Photographs were taken on a Zeiss RS III photomicroscope. Diagrams of the silver impregnated fibres and the interneurons were reconstructed from photographic series at different focal depths with the aid of a Zeiss DL 5.2 microfilm reader at final magnification of 2,370.

Profiles of neurons were also traced on transparent cellophane sheets through a Zeiss RS III microscope fitted with an overhead Glarex projector at x 550. Volume of the fibre ending was determined by converting the actual fibre projection pattern into a nearest geometrical figure - either cone, cylinder, ellipsoid or a sphere and using the conventional volume formulae for these figures. The linear dimensions were determined either from photomicrographs or by direct measurement.

Orthograde uptake of cobalt (II)

Sensory projections from the selected regions of antenna or maxillary palp were examined by orthograde diffusion of cobaltous chloride (CoC12) in 3 different ways. (i) A glass micro-capillary filled with 5% aqueous solution of CoC12 was firmly capped on the small lesion made by fine scissors. (ii) For sensillum trichodeum, the hair-shaft was cut close to the base and a 2% solution of CoC12 in 70% ethanol was capped on it. (iii) In case of sensilla basiconica, a microcapillary filled with alcoholic CoCl2 was applied after making an injury with the capillary tip. After 2-4 hours of cobalt uptake, the flies were processed as described by Stocker et al (1983) and were subsequently silver-intensified according to Bacon and Altman (1977). Embedding was in Durcupan ACM (Fluka) following the schedule described by Nayak and Singh (1985). Twenty um-thick sections were cut on a sliding microtome either in sagittal, horizontal, or frontal planes and mounted under Permount and glass cover slip.

Uptake of neuronal marker horseradish peroxidase

Sensory projections of selected taste hair on the labellum were examined after the uptake of HRP (Sigma, type VI), dissolved in the following solutions: (i)0.1 M potassium chloride (A.R.), (ii) 0.1M sucrose (A.R.), (iii) 0.1M sodium chloride (A.R.), or (iv) distilled water. Solutions (i)-(iii) were prepared in glass-distilled water.

Immobilization of the fly and HRP uptake experiments were according to the schedules described by Naessel (1983) and the concentration of HRP in solutions was 2-3%. The tip of the sensillum was cut with a pair of iris scissors and the stub was inserted in a capillary filled with HRP solution of the appropriate composition. The flies were kept with the capillary stuck on them, overnight at 5°C in the dark. Subsequent dissection, fixation

and enzyme reactions were carried out according to Naessel (1983), followed by dehydration and embedding in Durcupan ACM (Fluka). Fifteen um thick serial sections were cut either in frontal or sagittal planes on a sliding microtome with a steel knife. Sections were mounted with Permount under coverslip.

Scanning electron microscopy

The detached heads of *D.-melanogaster* were air-dried and coated with about 20 nm-thick gold layer in vacuum. The thickness of the gold layer was measured on a glass slide with a step profiler. Specimens were examined in a JEOL JEM 100 S electron microscope fitted with ASID scanning system at 40 kV.

Transmission electron microscopy

The procedures followed were essentially similar to those described by Nayak and Singh (1983). To ascertain the location of silver grains whether they are inside or on the outside surface of the selectively stained sensillum, the specimens were fixed after staining with silver and processed as described earlier (Nayak and Singh 1983).

Results

Sensilla on the flagellum and the maxillary palp

Sensilla for the detection of odour in *Drosophila* are located mainly on the third antennal segment - flagellum and the maxillary palps. The distribution and morphology of sensilla on flagellum were studied with light and electron microscopy. Four types of hairs were identified. Three types of hairs innervated by dendrites are sensilla basiconica, sensilla coeloconica and sensilla trichodea (Fig.1). They occur amongst a large number of the fourth type of uninnervated hairs or spinules.

Sensilla basiconia and coeloconica can be easily identified by light microscopy on staining with 0.1% silver nitrate dissolved in 70% ethanol. The tip of sensilla basiconica and coeloconica appear dark-brown (Fig. 2a,b).

Most of the sensilla trichodea and spinules remain unstained. Patches of conspicuous thick sensilla basiconica were found with our silver staining technique (Venkatesh and Singh 1984). Thick sensilla basiconica had escaped detection in earlier studies by scanning electron microscopy (Hodgkin and Bryant 1978).

Thick sensilla basiconica are upto 3.5 um thick and 11 um long,

compared to slender sensilla basiconica which could be upto 1.5 um thick and 7 um long. About 1,200 pores are present on a thick sensillum basiconicum and about 300 pores on a slender sensillum basiconicum. Sensilla basiconica are innervated by either 2 or 4 sense cells (Fig. 1). Being single-walled, multiporous sensilla, with pore tubules and branched dendrites, the sensilla basiconica are similar to olfactory sensilla of other insects. It would be interesting to know by electrophysiology, whether thick and slender sensilla basiconica differ functionally.

Sensilla coeloconica are double-walled and have longitudinal channels near the tip. Dendrites do not branch in sensilla coeloconica or trichodea. Both are innervated by 1-3 neurons. No wall-pores were found by us on sensilla trichodea but Link and Stocker (unpublished results) have seen pores in the walls of sensilla trichodea by transmission electron microscopy. A tubular body, characteristic of a mechanosensory dendrite, (Thurm 1964, 1965), was absent from these sensilla on the flagellum.

Mindek (1968) had looked at the distribution of various sensilla on the flagellum. We decided to redetermine the distribution of sensilla using our silver staining technique (Venkatesh and Singh 1984). Some additional facts emerged: Populations of sensilla basiconica and sensilla trichodea occur in diametrically opposite, distinct regions on the flagellum - the former in the dorsomedial and the latter in the ventrolateral regions, whereas sensilla coeloconica are distributed on most of the anterior and posterior surfaces, including the cavity walls of the sacculus (Fig. 3).

Silver-stained whole-mount preparations of *Drosophila* mouthparts (Nayak and Singh 1983), also showed distinctly stained sensilla basiconica on the maxillary palps (Fig. 4a, b). In other insects such as crickets, cockroaches and locusts, the maxillary palps help to examine the ground or food particles and act as supporting or holding elements during feeding (Blaney and Chapman 1969 a,b, 1970; Blaney et al 1971; Burry and Moran 1973; Blaney 1974, 1977; Altner 1975; Klein and Muller 1978; Klein 1981).

Our controlled feeding experiments showed that *Drosophila* does not use the maxillary palps effectively during feeding. Unlike other insects, contact chemoreceptors or taste sensilla were conspicuously absent on the maxillary palps of *Drosophila*.

Three types of hairs were identified on the maxillary palp of *Drosophila*: (i) Single-walled, multiporous sensilla basiconica, which constitute 75% of the innervated hairs. (ii) Thick-walled non-porous sensilla trichodea, which make up the remaining 25% of the innervated hairs, and (iii) numerous spinules, which are un-innervated (Fig. 4a,b).

These sensilla basiconica uniformly contained 2 bipolar sense cells, whereas sensilla trichodea have a single dendrite with a tubular body at the base of each hair. A majority of the sensilla basiconica are located on the distal half of the dorsal surface, whereas sensilla trichodea are positioned on the tip and the entire ventrolateral ridge of the palp (Fig. 4a,b). Approximately 125 axons of the sense cells join to form a single maxillary nerve (Fig. 4c). The structure of sensilla basiconica and that of sensilla trichodea suggests that they are olfactory and mechanosensory respectively. However, confirmation of the functional roles asigned to these sensilla is needed either by electrophysiology or by some other method.

Unlike sensilla basiconica on the flagellum, which have either 2 or 4 sense cells (Venkatesh and Singh 1984); the sensilla basiconica on the maxillary palp are structurally a homogenous population having uniformly two neurons each. In addition, these sensilla occur as a well demarcated patch (Singh and Nayak 1985), which makes them quite suitable for micro-injections using cobalt (II), horseradish peroxidase, cytochrome c or similar substances.

Primary sensory projections from the sensilla on flagellum and maxillary palp

Cobalt fills from small defined regions of the flagellum and the arista show that the three types of sensilla on the flagellum and a fourth sensillum located in the arista project into 19 glomeruli of the antennal lobe. Five glomeruli V, VP1, VP2, VP3 and VL1 situated ventrally and close to the entrance of the antennal nerve receive exclusively ipsilateral inputs. The remaining glomeruli are innervated bilaterally resulting in a precise mirror-symmetry pattern when cobalt filling is done from one antenna (Fig.5).

Ten out of 19 glomeruli represent major projection areas. Aristal projections are strictly ipsilateral in glomeruli VP2 and VP3 whereas those from the other sensilla consist of an ipsilateral and a contralateral component. Sensilla basiconica mainly project to glomeruli V,VM1 and DM1, sensilla trichodea to VA1, DA1 and VL1 and sensilla coeloconica project to VL1, VM1 and DL2 (Stocker and Singh 1983; Stocker, Singh, Schorderet and Siddiqi 1983). Considering the projections from different points in an area bearing one type of sensillum, such as sensillum basiconicum, similar projections are produced. This suggests that projections observed reflect predominantly the type of sensillum rather than its location on the flagellum. This view was further confirmed while determining the primary sensory projections from the sensilla on the maxillary palp (Singh and Nayak 1985).

Golgi silver impregnations and cobalt fills show that the primary sensory fibres from sensilla trichodea and sensilla basiconica on the maxillary palp

project to the posterior suboesophageal ganglion (SOG), and the antennal lobe respectively (Fig. 6a,b).

A single fibre projects separately either in the SOG or in the antennal lobe. In the antennal lobes, the input received from sensilla basiconica is usually bilateral (Fig. 5a, c), and at least 5 glomeruli are innervated symmetrically on either side from the palp (Fig. 6c).

Three glomeruli in each of the antennal lobes seem to be innervated both by axons from the sensilla basiconica of the maxillary palps and antennae (Fig. 6c, d). Though glomeruli 1,2 and 3 in Fig. 6c; and VM1, VM2 and VA2 in Fig. 6d appear to be identical respectively, it is possible that they could be different as only stained glomeruli can be visualized in these preparations and not the unstained ones.

The sensilla basiconica located in a well-demarcated patch on the maxillary palp and those on the antenna project into antennal lobes. If similar type of sensilla located on two widely separated regions send axons in the same region of the brain, then the mode of primary sensory projections from a particular type of sensilla is predominantly dependent on the type of sensillum rather than its location on the body. It is possible that on achieving a higher experimental resolution one may observe a point-to-point correspondence in the location of sensilla and their primary projections in a narrow region within the central nervous system (Singh and Nayak 1985).

Gustatory sensilla on the tarsal segments and mouthparts of adult *Drosophila*

In *Drosophila* gustatory sensilla involved in feeding are mainly located on the external and internal mouthparts and on the tarsal segments of legs. Previous studies had shown that there are 2 types of bristles: those in which one or more dendrites extend through the length of the hair-shaft and those in which a single dendrite ends at the base. Many bristles on the tarsal segments are accompanied by a special trichome called a bract (Hannah-Alva 1958). Therefore, bristles can be divided into 2 types on the basis of their external appearance alone, bein either bractless or bracteate (Bryant 1978).

Sensilla on the tarsal segments of legs and on the external and internal mouthparts of adult *Drosophila* were studied by light and electron microscopy. Ethanolic silver nitrate stain distinguishes dendrite-containing bristles from other hairs on the tarsi. Stained bristles are bractless (Fig. 7a,b). Males have more silver-staining bristles than females on the first 4 tarsal segments of prothoracic legs (Fig. 8). Silver-staining bristles on tarsi have uniformly one mechanosensory and 4 chemosensory dendrites (Nayak and Singh 1983).

Among the taste bristles on the labellum many are 2-pronged (Falk et al. 1976). Both prongs were found to contain a pore at the tip by serial section transmission electron microscopy, but chemosensory dendrites enter only one of them. The taste bristles in the 2 medial rows on each half of the labellum are predominantly associated with 4 chemosensory and the peripheral bristles usually contain 2 chemosensory neurons each (Nayak and Singh 1983).

Five groups of paired sense organs were known to exist on the internal mouthparts (Stocker and Schorderet 1981). Amongst 9 sensilla present in the labral sense organ, electron microscopy shows that sensilla numbers 1-6 have one mechanosensory neuron each. Sensillum number 7 has 8 neurons with dendrites arranged in 3 groups: 2 triplets and a pair (Figs. 9,10a). The sensilla 8 and 9 have 2 neurons each. The ventral cibarial sense organ (VCSO) has 2 sensilla, one with 2 and the other with 4 neurons. Rows of hollow satellite bristles forming 2 sensory systems, dorsal and ventral to the VCSO have one mechanosensory neuron each (Nayak and Singh 1983). By virtue of the presence of a pore at distal end and morphology, the compound sensillum number 7 may be ascribed the role of a contact chemosensillum or a taste sensory organ.

The dorsal cibarial sense organ has 2 sensilla on either side of the midline, each containing 3 neurons.

The axon counts of all the prominent nerves of mouthparts at different levels were also determined (Fig. 10b). During the axon count of nerves, an external nerve loop connecting directly 2 regions of the brain the tritocerebrum and suboesophageal ganglion was found, which was named as 'Bypass' nerve (Fig. 10b), (Nayak and Singh 1983).

Primary sensory projections from the labellar sensilla to the brain of *Drosophila*

Golgi silver impregnation of sensory neurons arising from the labellar taste sensilla of *Drosophila* revealed 7 distinct types I-VII of primary (sensory) fibres projecting to the suboesophageal ganglion. Each fibre was classified on the bases of the neuropil volume occupied by its terminal arborisation, the shape of the neuropil region receiving the arborisations and the detailed morphology of the arborisations. The primary sensory fibre projections from the labella are confined to the SOG, where they project mainly to the anterior and central neuropil. No labellar sensory fibres project to posterior SOG. Of these 7 types of sensory fibres, three (types III, IV and VII) show ipsilateral projections, while others have both ipsilateral and contralateral branches (Fig. 11), (Nayak and Singh 1985).

Projections and functional implications of labellar neurons from individual sensilla of *Drosophila* as revealed by neuronal marker horseradish peroxidase (HRP)

We have identified the projections of the neurons present in a single labellar

taste-sensillum, using the neuronal marker HRP. Although the taste sensillum in question has five neurons, yet in a given experiment only one or at the most two neurons are labelled. The type of neuron labelled was found to be specific to the stimulant solute (sucrose, sodium chloride or potassium chloride) present in the HRP solution.

Irrespective of the stimulant present in HRP solution, Type-II fibres get labelled most of the time. However, type-IV fibres are labelled when attractants (0.1 M sucrose or $\leq$ 0.1 M sodium chloride) are used as stimulants in HRP solution and type-VI fibres are labelled when the stimulant is a repellant namely 0.1 M potassium chloride. HRP dissolved in distilled water alone, revealed type-I coiled fibres (Fig. 11). The present technique besides revealing projections of sensillar neurons to the brain at high resolution also allow us to infer their possible functions (Shanbhag and Singh 1988).

HRP enzyme-reaction carried out by using diamino-benzidine (DAB) in whole-brain tissue showed the presence of glomerular organization also in the taste-sensory region (Fig. 13) (Shanbhag and Singh 1988).

Interneurons

Four types of interneurons are possibly associated with taste perception. Type A interneurons are local interneurons with arborisations confined to the taste sensory neuropil of the SOG. The types B-D interneurons are interganglionic output neurons with axons projecting to various brain regions - SOG, calyces of the mushroom bodies, tritocerebrum and thoracic ganglia. These projections suggest that SOG, tritocerebrum, calyces of the mushroom bodies and thoracic ganglia are involved in processing the gustatory information (Fig. 12) (Nayak and Singh 1985).

Fine structure of the sensory organs of *Drosophila* larva

Larvae of *Drosophila* show distinct behavioural response to olfactory and gustatory stimuli, sometimes quite different from adults (Rodrigues 1980). These responses are primarily sensed by various types of sensory organs located on or inside the body of the larva. A knowledge of the fine structure of the larval sense organs is necessary for better understanding of the sensory physiology. Using the transmission electron microscope, we determined the fine structures of prominent external and internal sensilla of the larva, namely those on the antennal organ, maxillary organ, ventral organ, labial organ, dorsal pits, sensory cones on the 8th and 9th abdominal segments and sensory hairs on the body of larva. Several new sensilla were found. Prominent amongst them are two compound types of sensilla in the pharynx; one with 9 dendrites arranged in three groups of 4,3 and 2: the other with 6 dendrites grouped as 2 and 4 (Fig. 14) (Singh and Singh 1984). On the basis of their structure both these sensilla could be ascribed roles of contact chemoreception.

Discussion

The following are the highlights and main findings of our studies:

1. Extensive studies on two chemosensory systems related to the sense of smell (olfaction) and the perception of taste (gustation) in *Drosophila* were done.

2. Fine structure and composition of olfactory and other types of sensilla on antennae and maxillary palps were determined by electron microscopy. Distribution maps of various types of sensilla on the flagellum and maxillary palp were constructed. These maps are useful in carrying out electrophysiological studies with these sensilla.

3. Primary sensory projections to the brain from the sensilla on antenna and maxillary palp were determined. Sensory fibres from antenna project in at least 19 glomeruli of the antennal lobe. Projections from maxillary palp sensilla are found in 5 glomeruli. Three glomeruli seem to be common for projections from antenna and maxillary palp, indicating that sensilla basiconica located on two widely separated appendages, antenna and maxillary palp, project in the same areas of the brain.

4. Fine structure and composition of gustatory sensilla located on labial palps and tarsal segments of legs were determined by electron microscopy. In conjunction with silver staining and light microscopy the distribution maps of these sensilla were constructed.

5. In the two pronged taste bristles on the labellum, both prongs have a pore at the tip, but only one prong is innervated by dendrites. The other prong is an extension of the crescentic lumen.

6. Neuronal composition of sensilla located in the internal mouthparts of the fly was determined by electron microscopy. A new compound sensillum was found in the labral sense organ. This is a hairless sensillum with pore at the distal end. It has 8 dendrites arranged in 3 groups - 2 triplets and a pair. From its structure, it may be ascribed the role of a contact chemoreceptor.

7. An external nerve loop connecting directly two regions of the brain, the tritocerebrum and suboesophageal ganglion was found and named 'Bypass' nerve.

8. Golgi silver impregnation of sensory neurons arising from labellar taste sensilla revealed 7 distinct types of fibres projecting to the suboesophageal ganglion of the brain. Each fibre was classified on the bases of neuropil volume occupied by its terminal arborisation, the shape of neuropil region receiving the arborisations, and the detailed morphology of the arborisations.

9. Projections of neurons from individual taste-sensory organ on the labellum to the brain of *Drosophila* were delineated at high resolution by uptake of neuronal marker horseradish peroxidase. Possible functional roles of morphologically 4 distinct types of neurons could be inferred from these studies. The existence of glomerular organization was also found in the taste-sensory region of the brain.

10. Three types of interneurons possibly involved in processing gustatory information were found to interconnect the suboesophageal ganglion, the tritocerebrum, the calyces of the mushroom bodies and the thoracic ganglia. This suggests that at least these regions of the central nervous system are involved in the perception of taste.

11. A comprehensive study of the fine structure of various sensory organs located on the body of the *Drosophila* larva and those located in the pharynx was done. Several new sensilla were found. Prominent amongst them are a compound sensillum with 9 dendrites arranged in three groups of 4,3 and 2 dendrites and another sensillum with six dendrites arranged in two groups of 2 and 4.

Amongst the rich repertoire of chemosensilla of *Drosophila,* the mechanosensory neuron characterized by tubular body is present in taste sensilla but absent from smell sensilla. These sensory organs project to well-defined regions of the brain having glomerular or compartmentalized organization. How this information is projected further in the brain and processed is the subject of study.

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I thank Smt. Shubha Shanbhag and Smt. Kusum Singh for making photographic prints and helpful suggestions; and Smt. Girija Vijayan and Ms. Manju Roy for word processing the manuscript.

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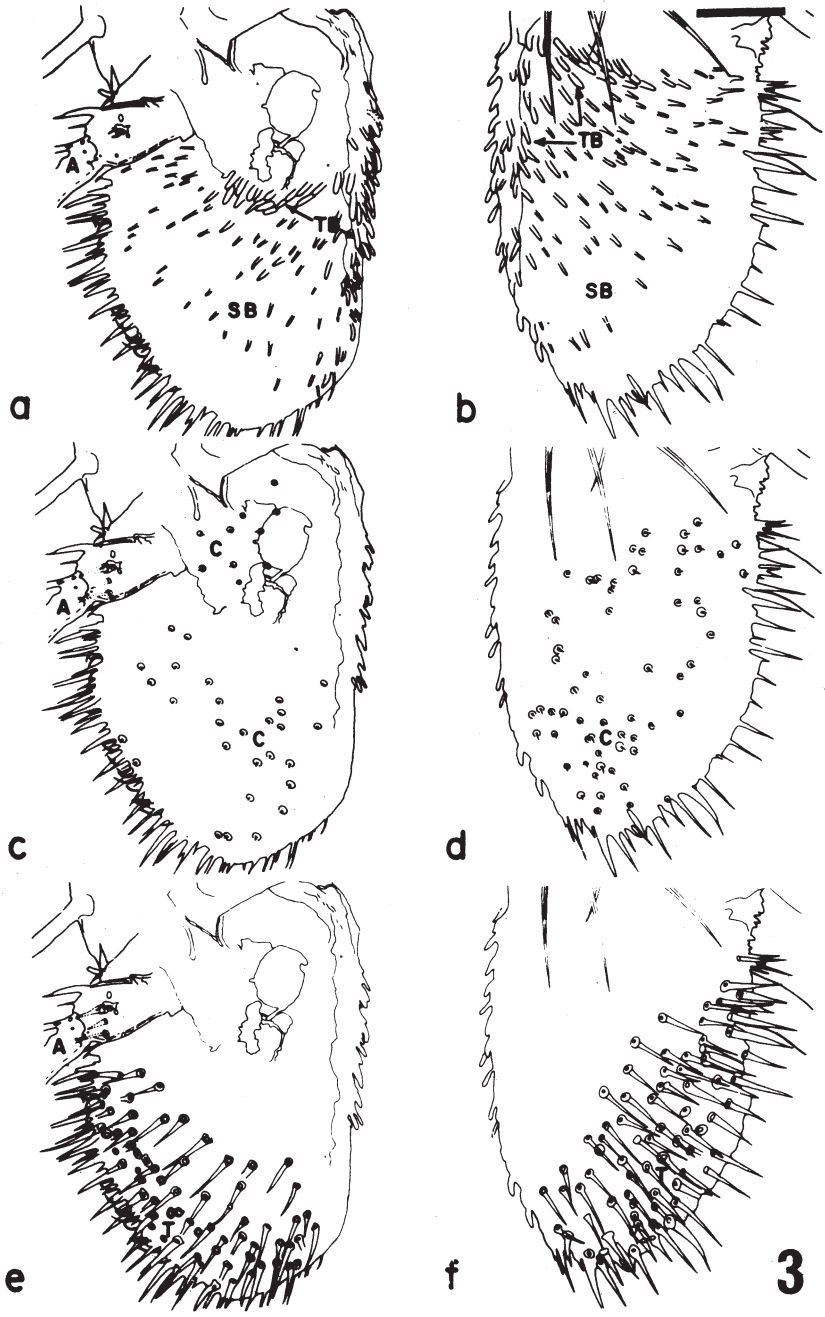

Figure 3 : Diagrams showing distribution of (a) sensilla basiconica on posterior surface, (b) sensilla basiconica on anterior surface, (c) sensilla coeloconica on posterior surface, (d) sensilla coeloconica on anterior surface, (e) sensilla trichodea on posterior surface, (f) sensilla trichodea on anterior surface. A = arista, C = sensilla coeloconica, SB = slender sensilla basiconica, T = sensilla trichodea, TB = thick sensilla basiconica. Scale = 25 um.

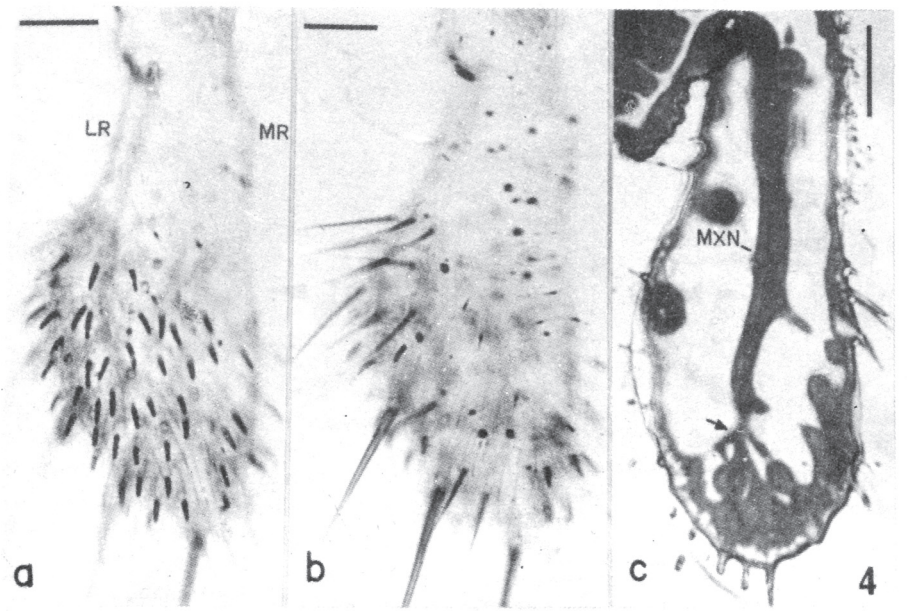

Figure 4 : Photomicrograph of ethanolic silver nitrate-stained whole-mount preparations of *Drosophila* maxillary palp. (a) Dorsal surface, showing darkly stained sensilla basiconica. (b) Ventral surface shows unstained sensilla trichodea mainly on ventrolateral region and very few silver stained sensilla basiconica. Note variation in hair-sizes of sensilla trichodea. (c) Photomicrograph of a 2-um-thick longitudinal section of maxillary palp stained with a mixture of methylene blue and toluidine blue according to Singh (1980). Sensory cells extend axons that converge near tip of the palp (arrow) to form a single maxillary nerve (MXN). LR = lateral ridge, MR = medial ridge, MXN = maxillary nerve. Scale = 25 um. (Singh and Nayak 1985).

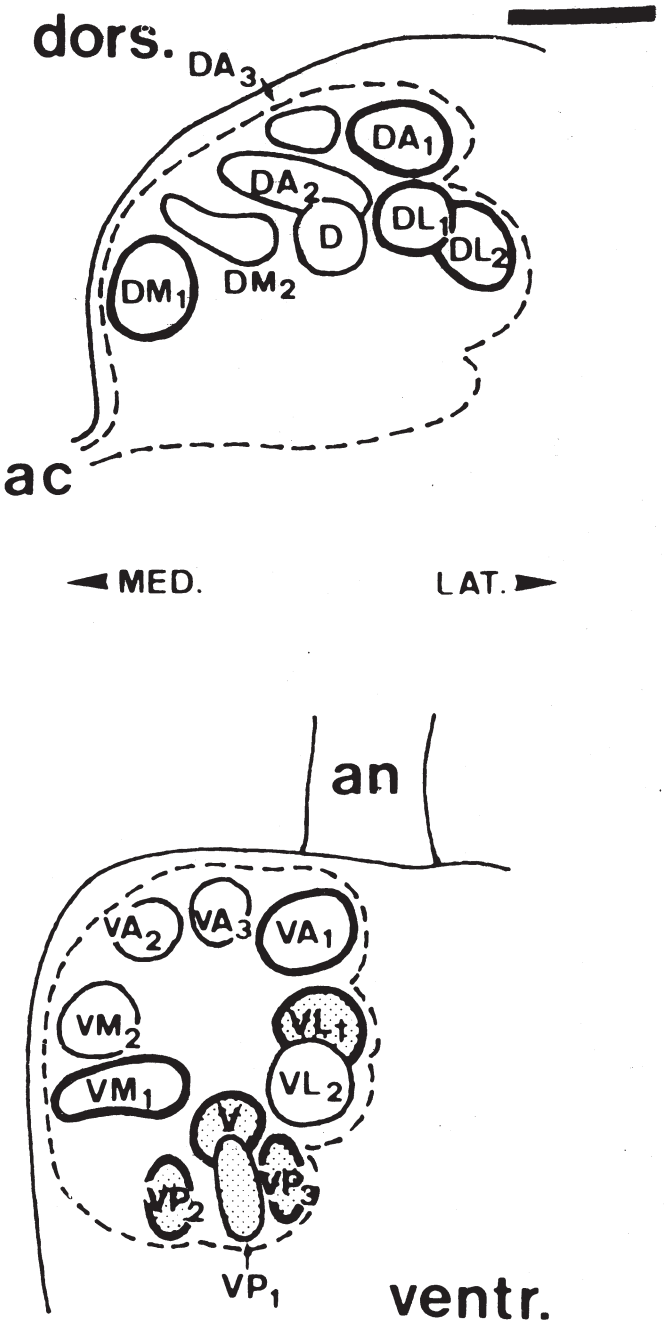

Figure 5 : Diagrams of right antennal lobes in Drosophila showing relative position, shape, and size of 19 glomeruli representing antennal projection areas. Ten heavily outlined glomeruli belong to major projection areas. Five stippled glomeruli receive exclusively ipsilateral input, the remaining receive bilateral projections. dors., ventr. = horizontal view of dorsal and ventral levels. A = anterior, ac = antennal commisure, an = antennal nerve, D = dorsal, L = lateral, M = medial, P = posterior, V = ventral. Scale = 25 um. (Stocker and Singh 1983; Stocker, Singh, Schorderet and Siddiqi 1983).

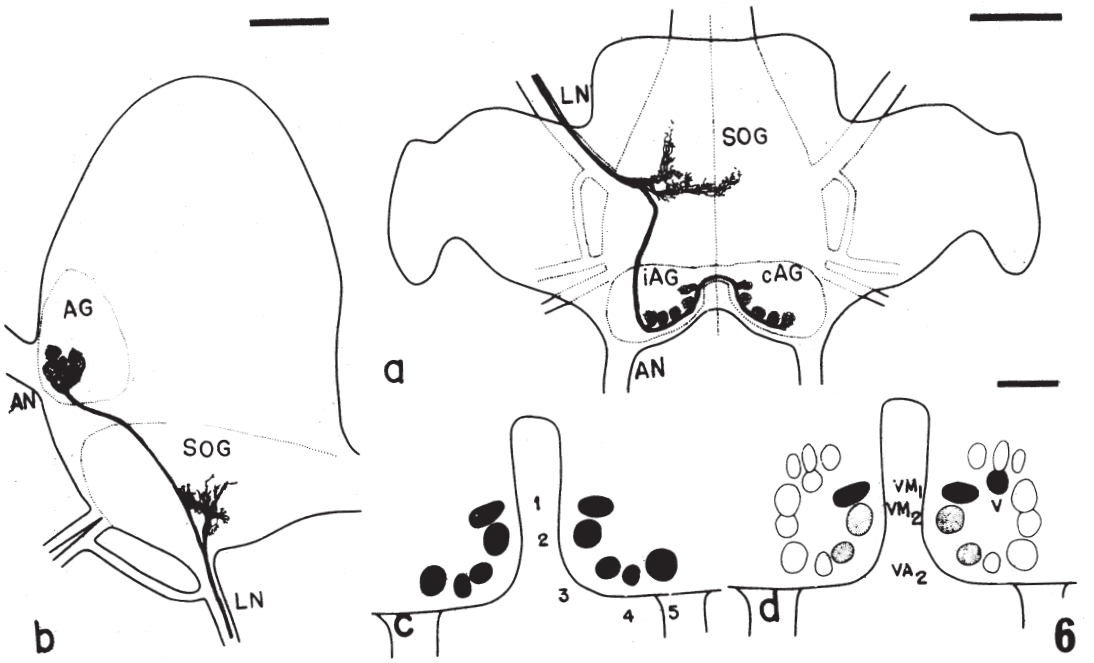

Figure 6 : Diagrams summarising sensory projection patterns from maxillary palp of *Drosophila*. (a)-(b) Fibres project separately into posterior suboesophageal ganglion (SOG) and send distinct tract towards antennal lobe where they occupy 5 glomeruli bilaterally. Fibres projecting in posterior SOG show typical L-shaped branching pattern (arrow). (a) Horizontal view with posterior on top. (b) Sagittal view, dorsal on top, anterior toward left. (c)-(d) Horizontal views of ventral half of antennal lobes showing main projection patterns of sensilla basiconica from maxillary palp and antenna respectively. Antennal projections are from Stocker, Singh, Schorderet and Siddiqi (1983). Glomeruli 1,2 and 3 having projections from maxillary palp sensilla basiconica correspond to glomeruli VM_1, VM_2, and VA_2 of Stocker, Singh, Schorderet and Siddiqi (1983). AG = antennal lobe, cAG = contralateral antennal lobe, iAG = ipsilateral antennal lobe, LN = labial nerve, SOG = suboesophageal ganglion. Scale = 50 um.

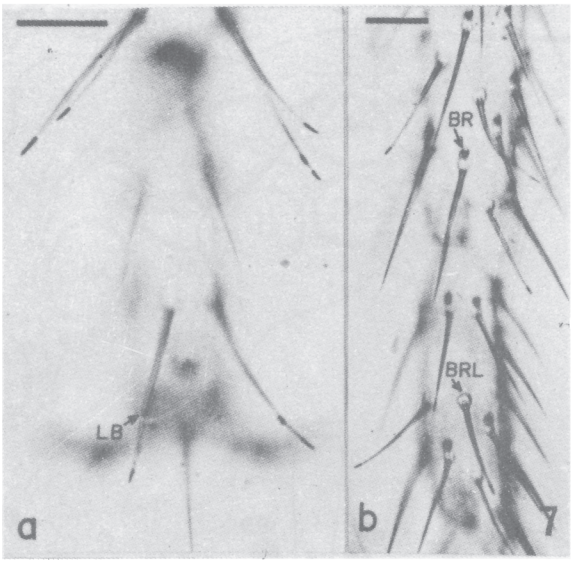

Figure 7 : (a) Distal tips of large bristles LB on 4th and 5th tarsi of prothoracic leg of *Drosophila* stained with ethanolic silver nitrate solution. (b) Most hairs on tarsihave bract BR, that are unstained. Only bractless hairs BRL, stain with ethanolic silver nitrate solution. BR = bracteate bristle, BRL = bractless bristle, LB = long bristle. Scale = 20 um. (Nayak and Singh 1983).

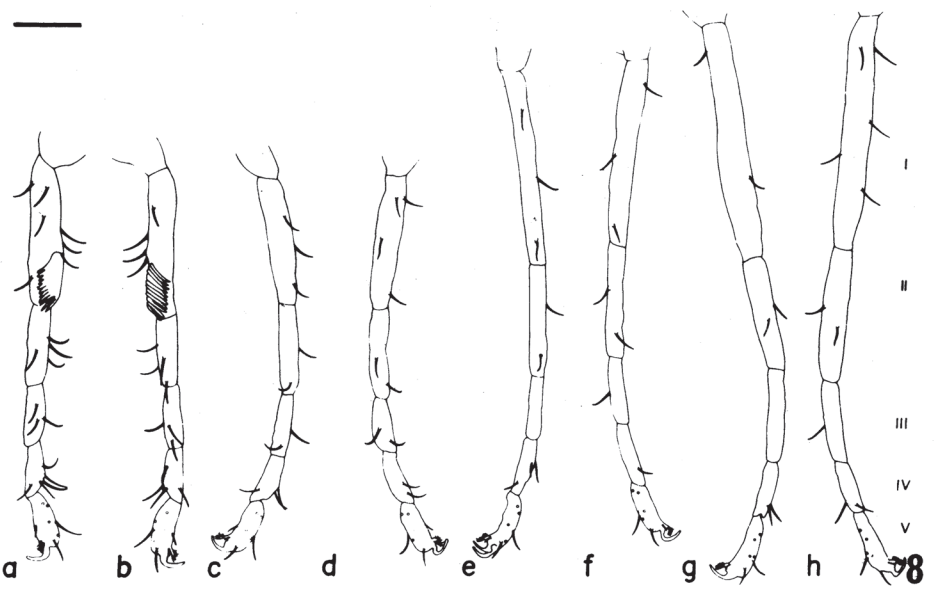

Figure 8 : Diagram showing positions of silver-stained bristles on tarsal segments of legs of Drosophila males and females. Prothoracic tarsi : (a) male, medial view; (b) male, lateral view; (c) female, medial view; (d) female, lateral view. Tarsal segments are marked in Roman numerals and bractless bristles refractile to silver stain are marked o. These abbreviations are applicable to corresponding regions of Fig. 8 (a-h). Mesothoracic tarsi: (e) males, medial view; (f) male, lateral view. Metathoracic tarsi : (g) male medial view; (h) male, lateral view. Scale = 50 um.(Nayak and Singh 1983).

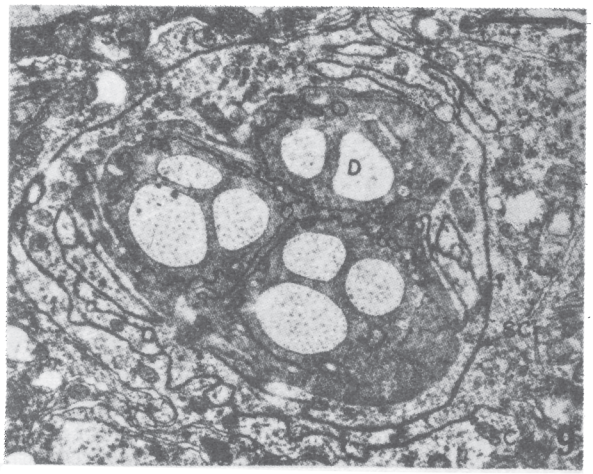

Figure 9 : Dendrites in compound sensillum separated in 3 groups, two triplets and a pair. D = dendrite, SC1 - SC3 = sheath cells. Scale = 1 um. (Nayak and Singh 1983).

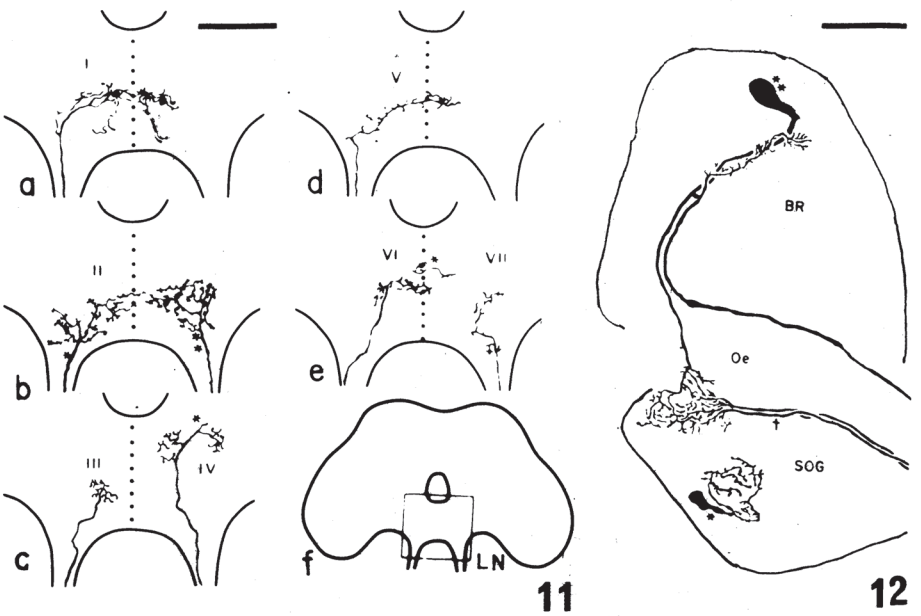

Figure 11 : Different types of labellar sensory fibres projecting in suboesophageal ganglion of *Drosophila* in frontal plane. (a) Type I, coiled fibres; (b) Type II, shrubby fibres, * marked is ipsilateral and ** marked extend to contralateral side, (c) Type III, ipsilateral ventral fibre, * marked type IV, ipsilateral dorsal fibre, (d) Type V, contralateral ventral fibre, (e) * marked type VI, contralateral dorsal fibre, and type VII central fibre, (f) outline of frontal section of Drosophila brain without eyes. Boxed area is the region of suboesophageal ganglion shown in Fig. 10 a-e. Scale = 50 um. (Nayak and Singh 1985).

Figure 12 : Diagrammatic representation of interneurons possibly connected with gustatory perception, sagittal plane. LN = labial nerve, Oe = oesophagus, SOG = suboesophageal ganglion, BR = brain. Scale = 50 um. (Nayak and Singh 1985).

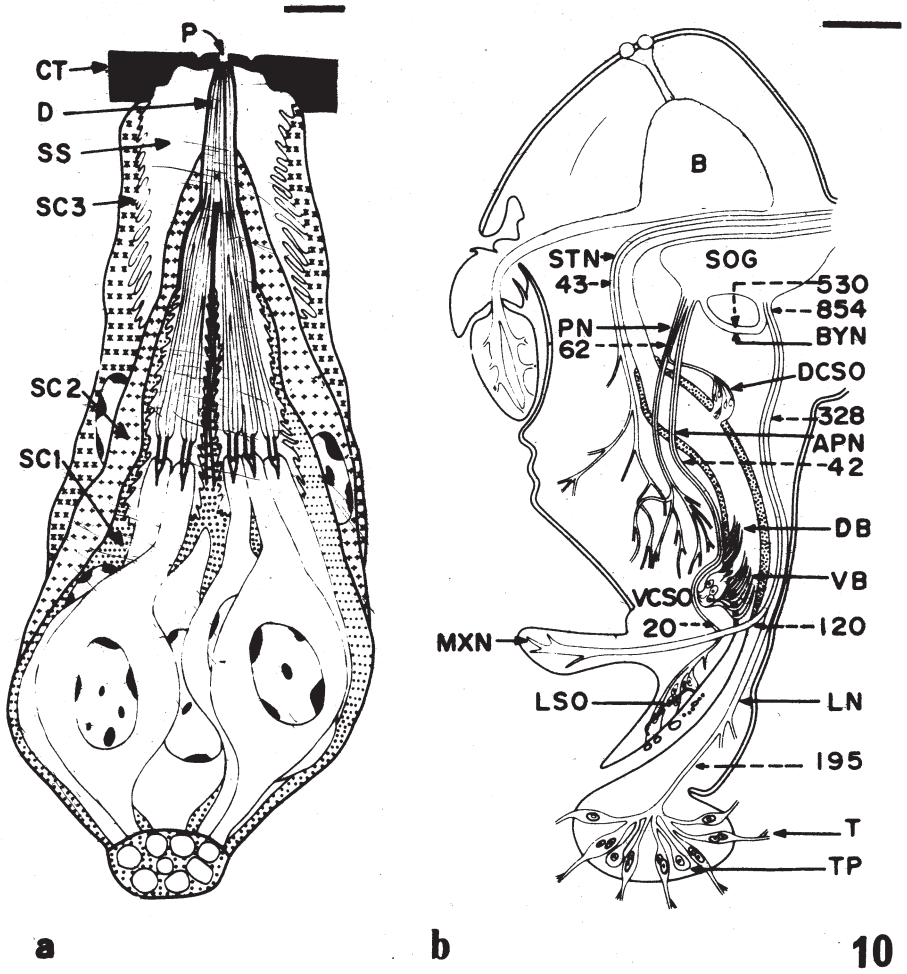

Figure 10 : (a) Diagram of sensillum number 7, the compound sensillum labral sense organ reconstructed from a series of micrographs. The pore is exaggerated 2 times compared to the diagram. Scale = 2 um. (b) Sensilla and prominent nerves of mouthparts, including the bypass nerve loop. Number of axons present in nerves is also given. Broken arrows indicate levels at which axon counts were made. Diagram is partly based on Fig. 1 of Stocker and Schorderet (1981) and partly on our findings. Y = prongs of medial labellar bristles are shown exaggerated. Scale = 100 um. APN = accessory pharyngeal nerve, B = brain, BYN = bypass nerve, CT = cuticle, D = dendrite, DB = dorsal bristles, DCSO = dorsal cibarial sense organ, LSO-labral sense organ, LN=labial nerve, MXN = maxillary nerve, P = pore, PN = pharyngeal nerve, SC1 - SC3 = sheath cells, SF = suspension fibres, SOG = suboesophageal ganglion, SS = sensillar sinus, STN = stomodaeal nerve, T = labellar taste hair, TP = taste peg, VB = ventral bristles, VCSO = ventral cibarial sense organ. (Nayak and Singh 1983).

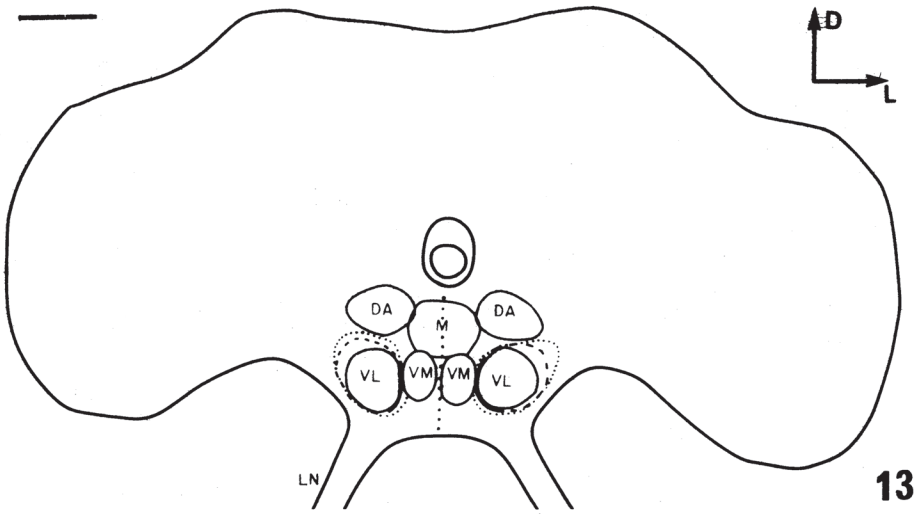

Figure 13 : Diagram of *Drosophila* - brain through LSN of the SOG in frontal plane showing the relative position, shape and size of 7 glomeruli identified by HRP plus diamino benzidine treatment. Three consecutive sections of 15 um thickness were used for this reconstruction. Continuous line..... = more anterior section; broken line..... = medial section; dotted line ..... = posterior section. The terminology roughly indicates relative positions of glomeruli within LSN. A = anterior; D = dorsal; L = lateral; LN = labial nerve; LSN = labellar sensory neuropil; M = medial; * = oesophagus; SOG = suboesophageal ganglion; V = ventral. Scale = 50 um. Figure 14 : Compound sensillum in the pharynx of Drosophilalarva, innervated by six dendrites, which are arranged in two groups of 2 and 4. D = dendrite. Scale = 0.25 um.

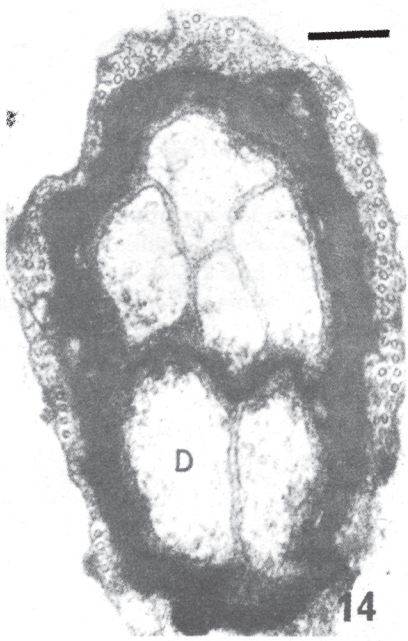

Figure 14 : Compound sensillum in the pharynx of *Drosophila* larva, innervated by six dendrites, which are arranged in two groups of 2 and 4. D = denrite. scale = 0.25 um. (Singh and Singh 1984).

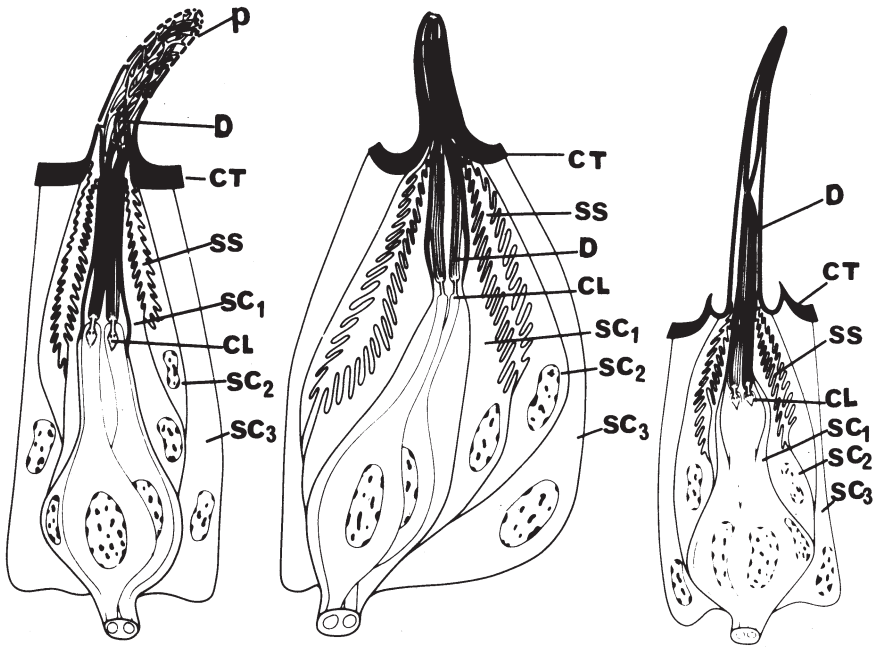

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Figure 1 : Diagrams of three main types of sensilla present on the third antennal segment of Drosophila. CL = ciliary region, CT = cuticle, D = dendrite, P = pore, SC1, SC2 and SC3 = sheath cells 1,2 and 3 respectively, SD = small diameter dendrite, SO = socket, SS = sensillar sinus.

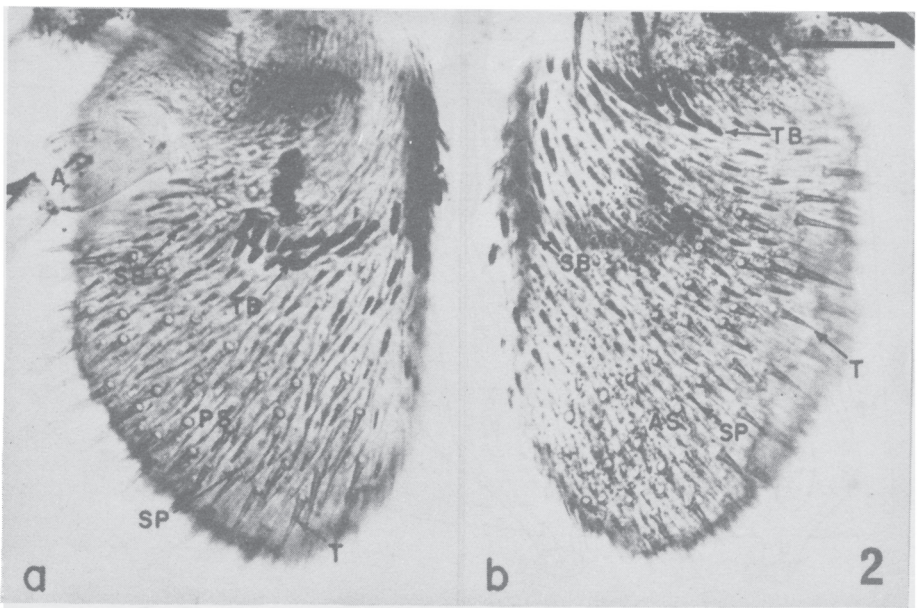

Figure 2 : Photomicrograph of an ethanolic silver nitrate-stained whole-mount preparation of an antenna showing darkly stained sensilla basiconica. (a) Posterior surface, (b) Anterior surface. A = arista, AS = anterior surface, PS = posterior surface, SB = slender sensilla basiconica, SP = spinules, T = sensilla trichodea, TB = thick sensilla basiconica. Scale = 25 um.

Fundamental neurophysiology

T. Desiraju

Outstanding trails and influences

Modern neurophysiological researches in India were started in the 1940s by B.B. Dikshit, a pharmacologist and who was later the first director of the All India Institute of Medical Sciences, New Delhi. He had worked with Sir Henry Dale, the Nobel Laureate while he was working on chemical transmitters at synapses. Dikshit worked on the synaptic transmitter-acetylcholine (1933).

In the early 1950s, B.K. Anand carried out experiments on the frog's heart to show that acetylcholine in small amounts activated the pacemaker and in larger amounts inhibited it - a dual para-sympathetic mechanism. He later went to Yale University and participated in the study of the role of the hypothalamus and limbic system in the regulation of feeding behaviour conducted by John Fulton and J.R. Brobeck . They discovered what is since known as the hypothalamic feeding centre (1951a,b). On returning to India, Anand worked at the Lady Hardinge Medical College, New Delhi and later, from its inception, at the Department of Physiology, All India Institute of Medical Sciences, New Delhi. He introduced new experimental techniques and approaches for the study of brain and behaviour in India. These include the methods of stereotactic placement of electrodes for making local electrolytic lesions, electrical stimulations, recording of depth EEG, evoked potentials and single unit potentials with microelectrodes, and the usage of un-anaesthetised and free moving animals for behavioural experiments. Using these tools, he studied the hypothalamic and limbic system to understand their roles in the homeostatic regulatory mechanisms of visceral and behavioural functions. A large number of postgraduates and research scholars were trained under B.K. Anand. Some of these later on became leading contributors to neurophysiology (Dua-Sharma, G.S. Chhina, K.N. Sharma, S.K. Manchanda, Usha Nayar, T. Desiraju and others). Baldev Singh was associated with Dr. Anand's studies all throughout and inspired many of them.

At about the same period (1950s) A.S. Paintal was working at Edinburgh on the physiology of sensory receptors and nerves of the visceral organs. On his return, he worked initially at Lucknow Defence Research

laboratories, and later at the Department of Physiology, All India Institute of Medical Sciences, New Delhi, and still later at the Patel Chest Institute of the University of Delhi. A.S. Paintal opened a new era in the study of the properties of visceral receptors of the gastro-intestinal, cardiovascular and respiratory systems. He has introduced in India new methods of recording impulses of single nerve fibres, and other advanced experimental and electrophysiological technology. His papers (1953-1970) on visceral sensory nerves and receptors and to the characterisation of cardiopulmonary and juxta-pulmonary receptors (j-receptors) are now termed classics. A number of investigators (Senapati, Marcus Devandan, Pritam Gill, P.D. Gupta and others) have been trained or influenced by Paintal. His work on respiratory and cardio-pulmonary afferent receptors has advanced understanding in the fields of respiratory and cardiovascular medicine, pulmonary oedema at high altitudes and other related problems.

P. Brahmayya Sastry is another distinguished researcher. He worked with F.C. MacIntosh at the Physiology Department of McGill University, Montreal from 1953-57, studying acetylcholine turnover in brain, sympathetic ganglia and nerves and added new knowledge on the role of acetylcholine as a synaptic transmitter in nervous tissue (Grafstein et al 1957,Macintosh et al 1956). After his return in 1957 to the Department of Physiology of the Andhra Medical College, Visakhapatnam, he initiated researches in this difficult field in India. Those were the years when acetylcholine as a chemical transmitter at synapses was being studied with enormous interest in neuroscience. He introduced in India for the first time the most advanced experimental methods for studying the factors influencing acetylcholine synthesis, storage and release in nervous tissue, using the perfused superior cervical ganglion preparation of cat. This ganglion was like a microcosm of the central nervous system made available for experimentation. A large number of scholars (including this author and Nirmala) were trained in his laboratory. He also studied epileptiform electrical discharges in cerebral cortical slabs in the cerveau isole preparation of cat -a method then popular in leading European laboratories. A range of outstanding contributions on cholinergic neuro-transmission (Brahmayya Sastry et al 1976; Desiraju 1966a,b; Nirmala et al 1979) and on cortical epileptiform electrical discharges (Brahmayya Sastry 1975; Desiraju 1966c; Grafstein et al 1957) have been made from his laboratory.

Some well-recognised contributions

In recognition of their contributions, three Indians have been invited to deliver the prestigious invited lectures in the following World Congresses of the International Union of Physiological Sciences: B.K. Anand on nervous regulation of food intake (Buenos Aires, 1959), A.S. Paintal on type J pulmonary receptors (Munich, 1971), and T. Desiraju on neurophysiology and consciousness (Sydney, 1983). These and a few other members have also been invited speakers in the official symposia of the Congresses of other years.

Areas of contributions

Neural Basis of Feeding Behaviour

The large number of studies made by Anand and his colleagues (see above) over the years (Anand 1960b,1961, 1963a; Anand et al 1951 a,b,1955,1958,1961d,1962,1965, 1966,1967; Chinna et al 1971a,b; Desiraju et al 1968a; Glavcheva et al 1972; Khanna et al 1972; Malhotra et al 1973; Oomura et al 1975; Sabberwal et al 1965a,b) established that the lateral hypothalamus facilitates feeding behaviour. In contrast the medial hypothalamus inhibits it. The midbrain reticular formation, amygdala, caudate nucleus and other regions of the forebrain have also been investigated and their modulatory roles in the regulation of feeding behaviour have been identified. They further studied the role of circulating metabolites on the hypothalamic regions and concluded that of the metabolites of lipids, proteins and carbohydrates providing energy, the utilization of glucose was the primary modulator of the neuronal activities of hypothalamic feeding mechanism. This was verified by studying the effect of a specific glucose metabolic blocker, 2-deoxy-D-glucose, in altering the unit activities of ventromedial and lateral hypothalamus (Desiraju et al 1968a). These studies resulted in the central glucostatic theory of regulation of food-intake.

Sharma et al contributed particularly to the understanding of the role of signals from peripheral alimentary receptors on the control of the nutritional state. They characterised the various factors that influence excitability of the peripheral receptors (Sharma et al 1961,1962,1967,1972) and gastric chemoceptive neurons in the brainstem of frog (Ramakrishna et al 1975,1978) and highlighted the role of taste (besides that of calories) in the regulation of feeding behaviour (Jacobs et al 1969).

Peripheral receptors for sensing functional state of visceral organs

As noted, Paintal contributed significantly to the characterization of the properties of sensory receptors of the alimentary, cardiovascular and respiratory systems (1953-1955).

Central nervous regions that influence visceral endocrinal and behavioural functions

Anand et al used electrical stimulation or ablation to study the visceral, endocrine, metabolic and behavioural regulatory functions of different regions of hypothalamus, limbic system, cerebellum, striatum and brainstem (Anand 1963b,1966,1970; Anand et al 1957a,b,c, 1959a,bc; Gupta et al 1969; Sen et al 1957a,c; Sharma et al 1963; Thomas et al 1970).

Manchanda et al studied the autonomic nervous control of cardiac and visceral functions (Manchanda 1970a,b). Manchanda and Bhattarai contributed to the understanding of central nervous control of venous tone (Manchanda et al 1974-1975, Mukherji et al 1978). Manchanda, Bilquis Rasheed et al demonstrated the role of cerebellum on vegetative functions (Manchanda et al 1972b,c;1979, Rasheed et al 1970; Sharma et al 1959; Tsuchiya et al 1974). Manchanda, Stevenson, Oomura et al studied the mechanisms related to feeding (Glavcheva et al 1972, Oomura et al 1975). He has also studied the swallowing center (Manchanda et al 1972a).

Chhina et al contributed to the understanding of metabolic factors that influence the activity of neurons in the hypothalamic feeding centre (1971a,b; Garg et al 1978) and to the studies of Anand referred above. They have also worked on affective behaviour (Chinna 1959), the role of hormones on genitally evoked responses of neuronal units of immature and mature brain areas (Chinna et al 1968, Mangat et al 1978) and the interactions of medial preoptic area of hypothalamus on ovulation (Bagga et al 1981,1984; Kaur et al 1986). Ramakrishna et al studied the role of septal regions in the production of urine in dogs (1971b).

Gogate, Mascarenhas et al studied the role of medial preoptic area, striatum and zona incerta in reproductive function.(Mascarenhas et al 1974,1985,1986b) They also studied hoarding and aggressive behaviour (Morker et al 1987,Mascarenhas et al 1978).

Dhume, Gogate et al studied the circadian motor activity rhythm and the role of hippocampus in spatial, cognition dependent motor behaviour (Dhume et al 1976,1980,1983a,b, 1982,1986; Nagvekar et al 1987). They have also studied the alterations of visceral functions (Dhume et al 1975,1976;Gogate et al 1970,1974,1975).

Maiti et al studied the role of cerebellum and its nuclei on gastric pathology (Ghosh et al 1980a;Guha et al 1978,1979a,b, Maiti et al 1974,1978) and gastric secretion.

Analysis of functional organisation of the hand

Devanandan et al contributed to the study of muscles, nerves and sensory receptors of the joints of the hand in monkey (1980,1983). They have also contributed to the understanding of weight perception in the hand of normal subjects and in patients with leprous neuropathy (Victor Raj et al 1985). Devanandan and R.M. Eccles had earlier contributed to the understanding of motor units of mammalian muscle (1965) and reflex organisation and presynaptic inhibition.

Synaptic potentials of specific (motor) and general (medial) thalamic nuclei

Desiraju, Purpura et al studied the excitatory and inhibitory processes in

gating synaptic transmissions exerted reciprocally between lateral and medial thalamic nuclei, and the synaptic responses of the neurons of these thalamic nuclei to inputs from cerebellum and basal ganglia (Desiraju 1970,Desiraju et al 1969a,b,1970, Purpura et al 1968).

Brainstem effects on sensory cortical neurons, and midline thalamic unit activities:

Mohan Kumar, Mancia et al, studied the patterns of synaptic potentials evoked by stimulations of brain stem reticular formation in sensory cortical neurons. (Mohan Kumar et al 1979, Schieppati et al 1983) Mohan Kumar et al studied the effects of electrical stimulation of different regions of hypothalamus and reticular formation on the midline thalamic unit activities (Abdul Aleem et al 1986, Mohan Kumar et al 1987).

Neural mechanisms of sleep states:

Desiraju has studied the changes that occur in the brain during different sleep states (Baldev Singh et al 1966; Desiraju et al 1966,1967,1968b,1971, 1972a,b,c, 1973b,c, 1974a,1975b,1976a,1980,1981,1982; Mancia et al 1968).

He analysed the patterns of alterations in the electrical rhythms of different regions of the brain. His study of regional evoked potentials and lesions helped to identify dynamogenic and hypnogenic regions of reticular formation and of other parts of brain and excitability alterations in sleep states.

He has also described the characterestics of alterations of single unit impulse discharges in cerebral association cortex (parietal and prefrontal) for all the stages of the primate (monkey) sleep-wakefulness cycle. These studies were the first to show the changes occurring in sleep states in the neuronal activities of the highest cerebral areas involved in thinking or mentation.

Mohan Kumar et al studied the medial preoptic region in the sleep-wakeful states and in EEG synchronization (Datta et al 1985,1987,1988; Mohan Kumar et al 1984a, 1986).

Preoptic and anterior hypothalamic areas

Mohan Kumar, Chhina et al contributed to the understanding of discharge patterns of neurons of preoptic areas (Mallick et al 1983,1984,1986; Mohan Kumar et al 1980,1984b,1985a,b) and their correlations with cortical EEG synchronization and desynchronization. They reported the effects of electrical stimulation of brain stem and reticular formation and those of injections of chemical modulators in causing changes in preoptic neuronal activities, and also of temperature and sleep state.

Prefrontal associative cerebral cortex organisation

Desiraju has analysed the fundamental properties of operations of thalamo-cortical and cortico-cortical projections of the evolutionarily recent dorsolateral prefrontal cortex of monkey (1973a,d,e,1974b, 1975a, 1976b, 1979,1981a,b,1984a,1985). The effects of stimulations of nucleus medialis dorsalis of thalamus, and of medial and intra-laminar thalamus were studied. The operational relations of cingulate and dorsolateral prefrontal cortex were also investigated to add to the understanding of linkages between limbic and neocortical regions. These were the first such studies and attracted special attention in view of their relevance to functions of the conscious state.

Desiraju has also described the patterns of changes occurring in the neuronal unit activities in different states of sleep in the primate (monkey) prefrontal and parietal association areas.

Developing brain and factors influencing it

Nayar et al studied the electrophysiology of cerebellum during postnatal growth of undernourished rat and showed that undernutrition caused retardation in the neuronal activity of cerebellum (Outhuraya et al 1980a,b). They described changes in visual evoked potentials, reduction in conduction velocity of sciatic nerve and in the number and size of motor neurons of gastrocnemius muscle. Neurons of rat ventromedial hypothalamus developed normal glucose sensitivity at about 21 days of age. This could be preponed to 15 days of age by administering glucose to the rat pup from 5th day of age. Responses of lateral hypothalamic neurons to glucose in younger ages were opposite to that in the adult age (Mathur et al 1983,1986).

Desiraju et al have studied the major changes occurring in the course of ontogeny of visual and motor cortices of rat using electrophysiological, morphological and neurotransmitter assessment. They described the effect of nurture (caloric undernutritional state through F2 generation) in causing deviations in the cited parameters of normal course of brain ontogeny and development and the effect of rehabilitation on all the measures of assessment (Annamma et al 1988; Desiraju et al 1984; Gundappa et al 1988; Mascarenhas et al 1986a; Rajanna et al 1984,1987). An initial lag in development of undernourished brain was followed in later age by an excess development of some of the parameters which could be of adaptive importance in chronically deprived nurture. Rehabilitation had little effect in preventing consequences of early undernutritional nurture. They are studying the effect of environmental pollutants including lead, manganese and pesticides on the course of ontogeny.

Brain tissue transplantation

Kavitha Murthy et al have described the scope of growth and differentiation of graft neurons and possible aberrant graft-host relations (1988).

Gopinath et al found survival of grafts of different regions transplanted in to other regions.

Hippocampal neuron changes during learning experience

Desiraju et al studied the synaptic and spine morphology of hippocampus, and the changes occurring in pyramidal neurons of hippocampus when a juvenile is learning a task by operant conditioning (Ibata et al 1971, Mahajan et al 1988).

Modelling language behaviour

Narasimhan has drawn attention to the computer modelling approach in language behaviour (Barlow et al 1972; Narasimhan et al 1978;1981). He has analysed behaviour so that the informal modes of communication can be understood in contrast to the machine-type formal modes. He argues that behaviour modes must satisfy phylogenetic continuity, physiological realisation, and be complete enough to articulate all aspects of behaviour.

Theory of consciousness

Desiraju has formulated the non-dualistic evolutionary theory of the conscious state (1984b), based on the knowledge of some of the principles of organization of brain and its higher cerebral areas (1976,1977a,b, 1981a,b,1984b).

Neural mechanisms of 'pleasure' evoking systems of brain

Desiraju et al have been analysing the components and mechanisms of neural systems that form a basic foundation for drive, motivation and rewards-incentives controlling behaviour. They have been investigating (in rat self-stimulation experiments) the role of receptors of opioid and other types of peptides and of amine neurotransmitters on the so-called pleasure-evoking regions of brain (Rao et al 1988; Singh et al 1988a,b).

Neurophysiology of visceral operant conditioning

Bindu et al resolved the controversy on whether it is feasible to volitionally condition heart rate slowing (a visceral regulation) without involving reflexes created by somatic muscular manipulations. They showed that it is feasible (1988).

Neurophysiology of Yoga

Anand, Chhina, Baldev Singh, Wenger and Bagchi have contributed to the earlier basic research in India on physiological changes in senior yogis (Anand et al 1961a, b,c; Wenger et al 1961,1963).

Desiraju et al have continued the study using a complex range of assessments, advanced computerised methods of EEG, evoked potentials, autonomic functions, and biochemical and psychological tests to characterise the nature of changes that could probably be brought out by practices of pranayamas and meditations in normal individuals (Joseph et al 1986,1987a,b; Natarajan et al 1985; Sukumaran et al 1987; Telles et al 1987). In contrast to findings by earlier researchers, their data shows that yogic practices produce changes differently in different individuals, rather than similar types of changes in all practitioners. Desiraju hypothesized that it is perhaps due to yoga causing changes appropriately in each individual according to his homeostatic conditions and potentials, rather than forcing the internal system of all to a similar stereotype. The data from this complex study is expected to be ready for analysis by 1990.

Changes due to stress of high altitude

H.S. Nayar, M.S. Malhotra and several others of the Defence Institute of Physiology have worked on altered physiology at high altitudes (Malhotra et al 1976). B.K. Anand helped them in the initial years. Selvamurthy et al studied the autonomic responses of inhabitants of plains and of those living at high altitudes in their original environments, after transposing the two groups and again after returning back to their original habitats (1981). They have also studied changes in EEG during acclimatization to high altitude (1978) and sleep patterns at high altitude during acclimatization (1986). Yoga helped in the adaptation of the subjects to a cold environment and cold tolerance (Joseph et al 1981). An initial reduction of slow wave sleep with frequent episodes of arousal was seen. These became normal later on.

Tonic pain mechanisms

Usha Nayar created a model for the study of tonic pain by injecting formalin into the skin of monkey (Alreja et al 1984). Analgesic agents like morphine and pethidine were tested. Analgesic reaction to immobilization stress resembled opiate analgesia. A study on non-narcotic analgesics was under way.

Nayar also studied EEG changes after administration of clonidine and other drugs (Kulkarni et al 1986; Malhotra et al 1973; Parale et al 1986).

Brain regions influencing aggressive behaviour

Balasubramaniam et al assessed the effects of amygdaloid and hypothalamic lesions in patients with behavioural disorders (Arjundas et al 1971; Balasubramaniam 1975; Balasubramaniam et al 1967,1970,1973,1975,1976). They have shown that hypothalamotomy helps in quietening the patients thereby reducing medical and social problems. Amygdalotomy reduces hyper-kinetic behaviour. In severe cases, hypothalamotomy and amygdalotomy may be necessary. Cingulumotomy was shown to be useful in curing drug addiction. Depth electrode studies (Kanaka et al 1980) on human brain have a high relevance in understanding the fundamentals of human cerebral organisation and for extending the principles noted in animal experiments to humans.

Manchanda et al observed that electrical stimulation of perifornical regions of hypothalamus in the carnivore cat evoked different varieties of aggressive behaviour: flight, defence, attack. The responses depended partly on the environmental stimuli and partly on the strength of electrical stimulation. Attack responses were also elicited by stimulation of midbrain sites. Experiments were done to assess cholinergic and other mechanisms in the aggressive behaviour.

Experimental epileptogenesis

Brahmayya Sastry studied the preparation of neuronally isolated slabs of cerebral cortex of cat in both acute and chronic states and evaluated the qualities of stimuli that trigger the epileptiform electrical after-discharges in the slabs. The spread of discharges ephaptically from contralateral cortex in the acute preparation and the prevention of such spread by callosal sectioning was also investigated (Desiraju 1966c).

Maiti, Snider et al studied the cerebellar inhibition of forebrain seizures of amygdala and hippocampus, septal-discharges, and caudate spindles and seizures (Maiti et al 1975,1977; Snider et al 1975). They have also studied the projections from cerebellum to amygdala and brainstem (Ghosh et al 1980a; Maiti et al 1974). They also produced penicillin-induced epileptic foci in avian brain, to understand seizure susceptibility and its modulation by paleocerebellum (Ghosh et al 1979,1980b).

Sharma et al have reported the EEG power spectra of penicillin induced focal cortical discharges (1987).

Mukherjee et al studied the relationship between stress and convulsive brain activity (1971).

Pathak et al studied changes in GABA transminase and succinic semi-aldehyde dehydrogenase in epileptogenic foci induced by cobalt and iron in rat (1984).

Joy David et al have worked on the monkey model of absence (petit mal) type of seizures by implanting aluminium hydroxide in pre-motor frontal cortical areas and stimulating thalamic regions to produce the seizures. They have also studied the temporal lobe epileptic discharges in monkeys after aluminium hydroxide injections into the temporal lobe. Kindling of seizures in amygdala of rats were studied by using repeated, low intensity electrical stimulation. On all these models, they tested the differential efficacies of anticonvulsant drugs. Their studies have relevance to understand both normal and abnormal functional patterns of the brain. (1977a,1978,1982)

Pineal gland function

Parvathi Devi et al studied the effects of stress on pineal gland responses (1977b) and have reported the action of lithium on the pineal gland (1977a). Melatonin levels were estimated in depressed patients during treatment and when they were deprived of REM sleep (Venkoba Rao et al 1984). Hypofunctioning of pineal gland was seen in some depressed patients.

Changes in biogenic amines during physical stress and brain oedema

Dey et al studied effect of heat stress and immobilization stress in rat. The resulting dysfunction of blood-brain barrier and cerebral oedema correlated with serotonin increase. Prostaglandin synthetase inhibitors modified this impairment (Dey et al 1983; Mohanty et al 1979,1980; Sharma et al 1981,1984,1986a,b, 1987,1988).

Opioid analgesia

Dey et al have reported on analgesia produced by morphine injected experimentally into cerebrospinal fluid (Dey et al 1976,1975; Ray et al 1980). They also compared the resulting hyper-glycaemic effect with that of adrenaline.

Paul et al studied the relation between action of morphine and that of acetylcholine (1959).

Biogenic amine changes in stress and disease and therapeutic use of Yoga

Alterations of biogenic amines in neurological and behavioural disorders were studied by Sarada Subrahmanyam et al (Subrahmanyam 1980; Subrahmanyam et al 1980). They have also studied the therapeutic effect of yogic practices in preventing stress induced disease (Subrahmanyam et al 1983).

Effects of pulsed magnetic field

Sarada Subrahmanyam et al have studied the application of pulsed magnetic field as therapy (Rajeshwari et al 1985; Sanker Narayan et al 1984,1985; Subrahmanyam et al 1985a,b). They applied pulsating magnetic fields (in the frequency range of 0.01 - 20 Hz with amplitude of ± 5 and ± 50 gamma using a 4 member Fanselau-Braunbeck coil system), on animals, as well as on humans, with ambient magnetic fields of 40 K gamma and 20 K gamma and orienting the subject with respect to earth magnetic field. In experimental rats, various parameters (EEG, ECG, tail blood flow, biogenic amines of brain and adrenals, motor activity, and body temperature) were assessed. The magnetic exposure caused a reduction in brain EEG and in certain biochemical changes in normal human subjects oriented northwards. Subjects oriented eastwards had calm, blissful alertness. Beneficial effects of the magnetic field therapy were reported in a variety of patients with disorders of brain. Arthritic patients also benefited.

Enzymatic changes in muscle atrophy

Swami et al have examined the changes in enzyme systems concerned with metabolism of protein and carbohydrate in the frog gastrocnemius after inducing muscular atrophy by sectioning the sciatic nerve (Bojji et al 1971; Govindappa et al 1965; Krishnamoorthy et al 1954; Sreelakshmi et al 1972). Activity of proteolytic enzymes increased, and the energy producing enzyme systems decreased. They also noted that the enzymes involved in energy production possess positive electrical charge in contrast to the degradative enzymes having negative electrical charge. External cathodal electric fields applied to denervated muscles retarded the process of atrophy, whereas external anodal field hastened atrophy. Protein synthesis could be augmented by externally applied cathodal fields in normal muscles too.

Human peripheral nerves in disease

Dastur et al have reported on the relationship between patterns of nerves distributed in a region and the sensation contributed by the region (1955,1961).

Antia et al used teased fibre and tissue culture preparations to examine cutaneous nerves in leprosy. Immunohistological, ultra-structural, and other methods were also employed. (Antia et al 1975; Jacobs et al 1987; Shetty et al 1977) Their studies indicted lipid or lipoprotein receptors on the membrane of Schwann cells of peripheral nerves as routes of entry of the bacterium M-leprae (Mukherjee et al 1980).

Cerebral blood flow and metabolism

Dastur has correlated changes in cerebral circulation and ageing (Butler et al 1965; Dastur et al 1963,1971).

Effects of pollution and other agents toxic to nervous tissue

Dastur et al have reported on lathyrism (1962)and on experiments on rats and monkeys to assess the pattern of distribution of manganese in central nervous system (1969,1971).

Chandra and her colleagues have described changes in catecholamines and serotonin in different parts of brain after consumption of manganese (Mustafa et al 1971) and other neurotoxins (Mahdi Hassan et al 1977). The effects of manganese in altering seizure susceptibility, various neurochemical constituents and developmental and behavioural aspects have been studied in depth (Chandra et al 1981; Mohamed Ali et al 1985; Seth et al 1984).

Desiraju et al studied the effects of food contaminated with lead, manganese and pesticide on the biogenic amine neurotransmitter levels in different regions of brain and spinal cord in developing and adult rats.

Misra et al have reported on nerve conduction and reflexes in workers spraying pesticide (Misra et al 1985).

Short studies in various other fields

Rai et al observed hippocampal effect on hypothalamo-pituitary -seminiferous tubular axis in experiments on rats (1983).

Kesava Ram et al studied the effect of graded compression of lumbar spinal cord on EEG. They observed an initial increase in delta EEG followed by its reduction when the compression was complete (1987).

Bhaskar studied the effect of music on EEG of human listeners. He has exposed subjects separately to western music and to its constituent components of melody and rhythm. Augmentation of alpha rhythm was seen to a greater degree in those who had a taste for music than in naive subjects.

Bhaskar observed that L-Dopa therapy in patients with Parkinson's disease caused recovery of P100 latency of visual evoked potentials (pattern reversal checks) from slow to normal. However, grating stimulus evoked potentials were not improved (1986).

Banerjee et al observed that tryptophan administration caused increase in urinary 5-HIAA in mentally ill patients, suggesting that serotonin synthesis and catabolism are accelerated in them. Elevated synthesis of nicotinic acid was also seen. The eosinopenic response of schizophrenic patients to injections of epinephrine was lower than normal. It was higher in cases of depression. ACTH effect on eosinopenic response was also lower in schizophrenics (Banerjee et al 1958; Nandi et al 1958).

Roy et al (1983) have studied the enzyme changes in subcellular fractions of brain during ageing. They have also studied enzymatic changes in hypothalamus during insulin induced hypoglycemia, and after giving para- chlorophenylalanine and other agents (Kaur et al 1983). Singh et al have described histochemical methods for detecting lipids and phospholipids (1964a,b).

Koley et al have been studying electrophysiological properties of receptors of visceral organs, and mode of working of autonomic nerves and reflexes

Subhra Datta (1988) observed in unanesthetized rabbit that repeated auditory stimulation plus subcutaneous electric shock caused initial augmentation of unit activities of CA3 hippocampus but in about 10 stimuli, the original level was restored, perhaps due to habituation.

Chandrasekaran et al studied the effect of light on the social synchronization and circadian rhythms in the bat. Satpal Singh et al studied the audiograms of a south Indian bat and the inferior colliculus neuronal properties in sound reception by bats (Nevweiler et al 1984; Schlegel et al 1983).

Nervous system organization in invertebrates

Babu et al have described the anatomical organization and cholinesterase activity of the scorpion ventral nerve cord, the conducting pathways, interneurons and microanatomy of the 7th abdominal ganglion and nerves related to the ventral nerve cord of the scorpion (1967, 1972, 1985, Vasantha et al 1977; Venkatachari et al 1968, 1970, 1975; Yellamma et al 1982,1983). Similar studies on the nervous system on the snail (Murali Mohan et al 1969,1976), cardiac ganglion of spiny lobster (Pampapathi et al 1969), the 6th abdominal ganglion and giant fibres of the nerve cord of cockroach have also been described by them (Babu et al 1979,1981; Murali Mohan et al 1980; Vijayalakshmi et al 1977).

Ramakrishna has studied arachnids (1970,1971a,1977,1983). In the median eye of scorpion the outer segment of the receptor cell acts as a current sink while the cell body acts as a source during exposure to light. The influence of the central nervous is greater on the 'b' wave of its electro-retinogram than on the 'c' wave.

Pandey et al (1983) have also studied the nervous system of cockroach.

Neurobiology of Drosophila Mutants

At the molecular biology unit of Tata Institute of Fundamental Research, Bombay, Naresh Singh, Siddiqui, Veronica Rodriques and their colleagues

have been identifying in different mutants of drosophila the gustatory receptors of sugar neurons, the genes involved in regulation of neurons of olfactory pathways and odor coding, and the distribution patterns of olfactory sensory structures: antennae, maxillary palps, gustatory sensillae located on the legs and mouth parts, larval sensillae. The electrical responses of taste receptors of X-linked gene mutants of drosophila defective in pyranose receptors, chemosensory dendrites of labellar taste bristles, and axonal counts of all the prominent nerves of mouth parts have been described by them. A new type of compound sensillum was observed in the labial sense organ. The primary sensory projections from sensillae of antenna and maxillary palp, were found to converge in the lobes of the brain. Seven types of sensory fibres were observed in the projection from labellar sensilla to the brain (sub-oesophageal ganglion).(Nayak et al 1983; Rodrigues et al 1978,1980, 1981,1984; Singh et al 1985; Venkatesh et al 1984).

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Neurochemistry

P.S. Sastry

Introduction

All phenomena which characterize life processes should ultimately be amenable to explanation in chemical and physical terms. The functioning of nervous system, the most challenging among biological phenomena, is no exception. Even higher functions of the brain such as thought and memory will have to be explained eventually in terms of the chemistry of the constituent molecules and their physical properties. Therefore, neurochemistry - the chemical approach to the study of the nervous system- would be vital to our understanding of the nervous system.

Though the primacy of brain among the organs of the body has been accepted and it is recognized as the seat for cognitive, intellectual and emotional experiences from ancient times, no effort appears to have been made to study the brain analytically in India, using modern scientific methodology, until very recently. It was only in the early sixties that centres devoted to neurochemistry were established at Baroda, Calcutta, Delhi and Vellore. Subsequently neurochemical investigations were also initiated at Bangalore, Bombay, Hyderabad, Trivandrum and in a few other places. These investigations covered several aspects of the nervous system and the results were reported in a large number of publications. Here the important findings in these studies are summarised with selected references to original publications. Studies which pertain to developmental neurobiology, ageing of brain and clinical neurochemistry have not been included here as they are covered elsewhere in this volume. Every attempt has been made to include all the significant findings.

Nucleic acid and protein metabolism

Nucleic Acids: In one of the earliest studies in India, the regional distribution of nucleic acids in monkey's brain was investigated in Talwar's laboratory. There was no difference in the neocortical regions but appreciable variations were seen in the different parts of the limbic system. In general DNA and RNA content was commensurate with cell density (Sadasivudu and Talwar 1961). In a series of experiments on convulsions induced with metrazole, it was found that brain nuclear RNA content

decreases either due to increased ribonuclease activity or due to the transfer of RNA to the extra nuclear compartment in the convulsive state (Talwar et al 1961). RNA and protein content appeared to increase at the onset of spike activity, decrease during the phase of active spike activity and return to normal levels in the post-spike phase (Chitre and Talwar 1963). Experimental rats sacrificed at the peak of convulsions induced by intraperitoneal injections of metrazole suggested a transfer of RNA from nuclei to the cytoplasm where it was hydrolysed (Chitre et al 1964). Ghosh and Ghosh (1969) showed the presence of acid ribonuclease activity in the CNS with an improved histochemical method. From experiments on the incorporation of adenine-9-^{14}C, Sharma and Singh (1970) demonstrated precursor-product relationship between nuclear and cytoplasmic RNA. Protein content in the occipital cortex was found to correspond to sensory stimuli, increasing in developing rabbits after the eyes - hitherto kept shut - were allowed to open (Talwar et al 1966a). Similarly, there was an increased RNA turnover in cortical tissue in response to flickering light. (Talwar et al 1966b) Brain DNA increases in rats subjected to long term training at avoiding shock (Ahuja and Subrahmanyam 1978).

Subba Rao and his colleagues studied DNases and DNA polymerases in developing brain in a variety of species. These are reviewed elsewhere in this volume. An acid DNase was shown in human foetal brain (Subba Rao 1973). Acid and alkaline DNases were demonstrated in developing chick brain and these exhibited maximum activity during the phase of rapid cellular proliferation (Shrivastaw and Subba Rao 1975). Inhibition of thymidine kinase, the first enzyme in the salvage pathway for DNA synthesis, by hydroxyurea was also noted (Kaplay et al 1983). This inhibition was dependent on the developmental stage and was seen only during the cell proliferative stage both in the cerebellum and cerebrum (Prabhakar et al 1984). Hydroxyurea inhibits DNA synthesis by its action on ribonucleotide reductase. Thymidine kinase also appears susceptible to this compound. Subba Rao and Subba Rao (1984) found increased DNA polymerase beta activity in aged rat brains which explains the spurt in DNA content in aged brains. These observations were confirmed through studies on neurons isolated from young and very aged mice (Subba Rao et al 1985). DNA polymerase showed high infidelity and may contribute to the ageing process.

Ribosomes

The effect of neuropharmacological drugs on the stability of cerebral cortical and hypothalamic ribosomes was investigated by Ghosh and his colleagues. Ribosomes isolated from goat cerebral cortex slices treated with strychnine sulfate or picrotoxin sulfate were more susceptible to breakdown into their constituents and the drugs affected the secondary structure of RNA (Ghosh et al 1965). Similarly delta^9 tetrahydro-cannabinol given in *vivo* or in *vitro* also affected the H-bonded structure in ribosomes making them more

susceptible to breakdown but only at high doses (10-50 mg/kg in *vivo* or 5 mg/gm tissue in vitro or 10 mg/kg/day for 21 consecutive days). No significant effect was observed at a low dose of 2 mg/kg (Poddar et al 1978). Similar observations were made with goat cerebral cortex slices treated with mescaline. (Datta and Ghosh 1970a) This drug lowered the H-bonded structure of the ribosomal 28S RNA of the brain (Datta and Ghosh 1970b). This destabilizing effect of mescaline on ribosomes was prevented by spermidine (Datta et al 1971). Ribosomes of brain cortex contain small amounts of spermidine and spermine and the enhancement of their content by in vitro treatment leads to increased stability of the ribosome structure (Datta et al 1969b). Mesçaline also inhibited the binding of E. Coli phenylalanine - tRNA to goat cortex ribosomes (Datta et al 1974).

D'Monte and Talwar (1967) attempted to identify and characterize brain-specific proteins. They extracted occipital, motor and sensory cortices from monkey with 1.5 M urea at 4oC to obtain sustances linked by weak interactions. These extracts contained RNA and protein. As many as 14 to 15 protein bands were observed on polyacrylamide gel electrophoresis in each brain area of which some were common in all the areas. Subsequently a brain specific ribonucleoprotein was isolated from goat brain and immunological experiments showed its presence in brains of a wide variety of animals but not in other tissues (Sharma and Talwar 1973).

Proteins: Mukherjee and coworkers investigated the ontogenic pattern of protein, nucleic acids and amino acids in the human foetal brain. The DNA content showed a fluctuating pattern in the various brain regions investigated. RNA accumulation was steady in the cortex and cerebellum but showed a polyphasic pattern in other regions (Mandal et al 1981). Striking developmental changes were found in the levels of aspartic acid in the medulla-pons and spinal cord; glycine in the spinal cord; GABA in the cerebral cortex; glutamic acid in the cerebral cortex, midbrain and spinal cord and taurine in the medulla-pons and spinal cord (Datta and Mukherjee 1983). During the early period of gestation, the content of soluble protein in the cerebral cortex was higher than that of insoluble protein. This decreased later. The brain specific S-100 protein appeared in early foetal life and constituted a major part of the soluble fraction. A new protein similar to S-100 was found in the human foetal brain (Sinha et al 1980).

The assembly of neurotubules is required for the growth of axons and dendrites and the neurotubule protein, tubulin, is the major protein in the cellular processes of the maturing neurons. In addition, several proteins designated as 'microtubule associated proteins' and tau-proteins are involved in tubulin assembly. Sarkar and his group at the Indian Institute of Chemical Biology, Calcutta, are investigating neurotubule proteins. They have separated the microtubule associated proteins of goat brain from tubulin and showed that the tubulin- assembly-promoting activity resides

in the tau-proteins (MW 55 - 77 kda) and a class of lower molecular weight (25-35 kda) proteins (Majumdar et al 1982). From studies in organ cultures of brain from newborn rats as well as embryonic chicks, it was demonstrated that the synthesis of tubulin is controlled by triidothyronine (T3). From the temporal correspondence of the sensitivity of the rat brain to T3 with the period of normal rise in the level of tubulin, it is concluded that thyroid hormones modulate the synthesis and accumulation of tubulin in the early phase of brain development (Chaudhury and Sarkar 1983, Chaudhury et al 1983). The rapid induction of tubulin is due to the dual effect of the hormone on tubulin metabolism - an increase in the rate of synthesis and a decrease in the rate of turnover (Chaudhury et al 1985). The level of tubulin is significantly less in hypothyroid neonatal rat brain and these brains showed much higher sensitivity to T3 indicating that the regulation of tubulin synthesis by this hormone in the developing brain is a natural ontogenic phenomenon (Mazumdar et al 1985). Glial cells appear to be the target cells for the T3 induced synthesis of tubulin in the newborn rat brains (Chatterjee and Sarkar 1986). T3 stimulates tubulin synthesis in oligodendrocytes during the period of myelino-genesis in rats. The hormone sensitivity appears around the day 11 after birth, reaches a maximum at day 15 and disappears by day 25 (Sil and Sarkar 1987). To further substantiate the role of the thyroid hormone, Haidar and Sarkar (1984) demonstrated thyroid-hormone receptors in the nuclei of developing chick brain. A single class of high affinity binding sites for tri-iodothyronine and thyroxine was found at all embryonic ages and in adults but a definite ontogenic increase in the level of the receptor was noted. Studies on the developmental alterations in alpha and beta tubulin mRNA in polysomes from brains of -3 days (foetal) to 30-day-old rats showed a coordinate expression of the alpha and beta tubulin mRNA with a maximal level around day 5 after birth which represents the mid phase of synaptogenesis (Bhattacharya et al 1987). Bhargava et al (1985) noted a increase in taurine content during brain development which ceases at weaning,when the tissue has acquired adult number of cells. Taurine could be a growth regulator.

Ramamoorthy and Balasubramanian (1985) have investigated the phosphorylation of endogenous proteins in the basal ganglia in the brain of monkey and produced evidence for the existence of a Ca2+/Mg2+ independent protein kinase which phosphorylates a 45 kda protein and a Ca2+ dependent protein kinase which phosphorylates a 75 kda protein. Reserpine is an effective inhibitor of protein phosphorylation in brain (Chakrabarthi et al 1986b) while phenobarbitone greatly enhances protein phosphorylation in brain in vitro (Kumar and Shankar 1987).

Lipid Metabolism

Lipids constitute about 10% of the fresh weight and half the dry matter of the brain. A large variety of lipids occur in neural tissues.Their content and complexity increases during the early phase of brain development,

particularly during myelination. Abnormal metabolism of several lipids causes conditions of severe mental retardation. Indian investigators have broadly covered glycolipids, particularly the sulfatides; ethanolamine plasmalogens (which are the major phospholipid components of the myelin membranes), phosphoinositides and cholesterol. Sastry (1985) has reviewed research in the entire area of nervous tissue lipids.

Glycolipids: Aruna and Basu (1974) studied the changes in various glycolipid components and their degradative enzymes in the developing human brain. They found a marked increase in ganglioside content when neuronal and glial cells multiply. When formation of neurons slows down, ganglioside content decreases with a concomitant increase in the degradative enzymes viz. beta-galactosidase and beta-hexosaminidase. Cerebrosides, sulphatides and sphingomyelin also increase indicating myelination. N-acetyl-beta-hexosaminidase A was purified from human and monkey brains and its glycoprotein nature was established (Aruna and Basu 1975). They have also purified beta-hexosaminidase B, an enzyme deficient in Sandhoff's disease (variant O) from monkey brain.(Aruna and Basu 1976) The two forms of acid beta-galactosidase whose deficiency causes GM1 gangliosidosis and Krabbe's disease have been purified from monkey brain (Alam and Balasubramanian 1978a) and their properties described (Alam and Balasubramanian 1980).

Bachhawat and coworkers studied some of the enzymes involved in ganglioside biosynthesis in brain. These include the enzymic synthesis of N-acetyl neuraminic acid (Joseph and Bachhawat 1964) and their regional distribution in sheep brain (Shoyab and Bachhawat 1965). Alam and Balasubramanian (1976) extracted a neuraminidase from sheep brain with Triton X-100 which was shown to act upon gangliosides with sialic acid as one of the products. The reports from this group on sulfatides are described in a later section.

Ethanolamine plasmalogens : The biosynthesis of ethanolamine plasmalogens, the main phospholipid components of the myelin membrane, was investigated in this author's laboratory. Experiments on developing rat brain showed hexadecanol to be the precursor for the long chain ether moiety in plasmalogens. The incorporation of (1-^{14}C) hexadecanol into 1-0-alkyl dihydroxyacetone phosphate was demonstrated in cell-free systems of 10-day old rat brain. The biosynthetic pathway for the plasmalogens was thus delineated (Natarajan and Sastry 1975). Rat brain preparations actively acylate 1-0-alkenyl glycero-3-phosphoryl ethanolamine which explains the specific fatty acid composition found in these lipids (Natarajan and Sastry 1973). The acyltransferase activities to 1-alkyl-,1-alkenyl- and 1-acylglycero-phosphoryl ethanolamine increase progressively during the myelinating period in rat brain (Natarajan and Sastry 1974). More importantly, **they demonstrated for the first time the conversion of (1-^{14}C) palmitic acid to (1-^{14}C) hexadecanol with**

rat brain microsomes. This fatty acid reductase was specific towards NADPH and showed the greatest activity with palmitic acid. Maximal activity was found in 15-day old rat brain when myelin synthesis was at its maximum (Natarajan and Sastry 1976). Jagannathan and Sastry (1981a) determined the 0-alkyl dihydroxy acetone phosphate synthetase and the fattyacid reductase levels in the neuron and glial enriched fractions during the myelinating period in rat brain and showed the role of glia in ethanolamine plasmalogen biosynthesis during myelination. They discovered a new cholesterol esterifying enzyme in the developing rat brain which required coenzyme A and ATP for esterification. This enzyme was found only in the myelinating brain and is probably involved in the transport of cholesterol from its site of synthesis to the myelin membrane (Jagannathan and Sastry 1981b). It was observed that the NADPH -dependent fattyacid reductase is insensitive to anticonvulsants such as sodium valproate and phenobarbitone while the cytosolic NADPH-dependent fatty aldehyde reductase is completely inhibited by these drugs (Turner et al 1982). Sastry and coworkers developed a method to hydrolyse sphingomyelin to ceramide with hydrofluoric acid which caused no alteration in either the fattyacid composition or the stereochemical configuration of the sphingosine moiety of the ceramide formed (Reddy et al 1976).

Phospholipids and cholesterol : Enzymatic acylation of lysophospholipids is an important reaction in obtaining the specific fattyacid composition of membrane phospholipids. The existence of this reaction in brain was shown by Subbaiah et al (1970). Brain is especially rich in polyphosphinositides and these are now implicated in signal transduction mechanisms across the membrane. Uma and Ramakrishnan (1983a) showed that polyphospho-inositides exist in two pools in brain: a metabolically active pool that is rapidly hydrolyzed and an inert pool which is hydrolyzed only at a slower rate. The two pools increase during brain development. Lalitha et al (1988) studied the effect of maternal alcohol consumption on the lipid composition of CNS in the offspring and showed that maternal alcohol consumption at a level that does not affect calorie intake increases the content and synthesis of cholesterol in the brains of newborn rat pups. Continued consumption of alcohol during lactation leads to an increase in myelin lipids and their synthesis in the pups. It appears that increased synthesis of lipids prevents fluidization of the membranes by alcohol.

The accumulation of phenolic compounds is detrimental to brain function. Ranganathan and Ramasarma (1974) observed inhibition of cholesterol synthesis by phenyl and phenolic acids. Both inhibit mevalonate-5-pyrophosphate decarboxylase. Phenolic acids also inhibit mevalonate-5-phosphate kinase on pre-incubation of brain preparations (Bhat and Ramasarma 1979).

Lipid peroxidation : **Lipid peroxidation in brain appears to have been studied for the first time in Indian laboratories.** Thermostable factors present in brain cytosol were shown to act on substrates located in the mitochondrial and microsomal fractions and liberate lipid peroxides (Sharma and Krishna Murthi 1968). This factor was subsequently identified as ascorbic acid (Sharma and Krishna Murthi 1976). Phospholipids (particularly phosphatidylcholine) are the main substrates for lipid peroxidation in rat brain mitochondria. Neutral lipids do not undergo peroxidation (Sharma 1977). Bishayee and Balasubramanian (1971) found ascorbic induced nonenzymic peroxidation in all subcellular fractions, maximal being in microsomes. In contrast NADPH dependent enzymic lipid peroxidation was found mainly in microsomes. NADH could replace NADPH and Fe^{2+} (but not Fe^{3+}) stimulated this enzymic reaction. Patole and Ramasarma (1988) showed the occurrence of lipid peroxidation in brain microsomes in the presence of NADH and polymeric form of vanadate. After this reaction, the binding of quinuclidinyl benzilate, a muscarinic antagonist, to brain membranes was reduced. Reserpine very significantly inhibits lipid peroxidation in brain homogenates (Chakrabarti et al 1986).

Nagarajan et al (1988) produced experimental focal cerebral ischemia by occlusion of the right middle cerebral artery and studied the release of the lysosomal enzymes, production of free fattyacids and lipid peroxidation. They showed that in ischemia, lipid peroxidation, which damages the lysomal membrane, causes the release of lysosomal hydrolytic enzymes.

Metabolism of sulphated compounds

Bacchawat and his colleagues studied extensively the metabolism of active sulfate (3-phosphoadenosine-5'-phosphosulfate, PAPS), transfer of sulfate to acceptors such as cerebrosides and mucopolysaccharides and arylsulfatases in brain. **They were the first to demonstrate the enzymatic formation of PAPS in young rat brains.** The activity profile of this enzyme correlated with myelin synthesis (Balasubramanian and Bachhawat 1961). PAPS was also shown to be degraded to inorganic sulfate and 3',5'-diphosphoadenosine by a partially purified enzyme from sheep brain (Balasubramanian and Bachhawat 1962). The PAPS synthesizing enzyme and PAPS degrading enzyme show marked differences in their respective activities in the grey and white matter in the different regions of the brain (Balasubramanian and Bachhawat 1963a). Farooqui and Balasubramanian (1970) identified an enzyme which dephosphorylates PAPS to adenosine 5'-phosphosulfate in the brain. This enzyme was partially purified and its physiological role was suggested to be regulation of PAPS levels in the brain.

Balasubramanian and Bachhawat (1965) demonstrated the formation of

cerebroside sulfate from PAPS with sheep brain extracts. This enzyme was present mainly in the white matter and appeared to use galactocerebroside as the acceptor. The products were identified as kerasin and phrenosine sulfates. The acceptor was present in a protein-bound form (Bhandari and Bachhawat 1972). Neonatal thyroidectomy in rats reduced the levels of cerebrosides and sulfatides and also decreased sulfate transfer from PAPS (Kokrady et al 1972). The enzymatic transfer of sulfate from PAPS to mucopolysaccharides was also observed in young rat brains (Balasubramanian and Bacchawat 1964). In this reaction, heparitin sulfate and chondroitin sulfate B acted as good acceptors while chondroitin sulfate C and hyaluronic acid were inactive. A similar sulfotransferase activity in rat brain towards weakly-sulfated glycosaminoglycans isolated from normal human brain was also identified (George et al 1970). Formation of phenolic sulfate and steroid sulfate from endogenous substrates was also observed on incubation of rat brain extracts with PAPS (Balasubramanian 1975).

Arylsulfatases are a group of enzymes which metabolise sulfuric acid esters of organic compounds. **In one of the earliest studies on these enzymes, Balasubramanian and Bachhawat (1963b) identified and partially purified an arylsulfatase from human brain which catalysed the hydrolysis of phenolic esters.** The activities of arylsulfatase A and B were distinguished and they were partially purified from brains of a number of species. The results suggested a relation between arylsulfatase A and sulfatides and between arylsulfatase B and mucopolysaccharides (Farooqui and Bachhawat 1971). Arylsulfatase A was purified from chicken brain and shown to hydrolyse sulfatides (Farooqui and Bachhawat 1972). A method to purify a number of brain lysosomal enzymes, including arylsulfatase A and B, using concanavalin A - sepharose column chromatography was also developed by this group (Bishayee et al 1973). With this method, arylsulfatase A from sheep brain was purified to homogeneity and it was shown to be a glycoprotein (Balasubramanian and Bachhawat 1975). Arylsulfatase A of chicken brain showed differences in kinetics in its action against sulfatides and phenolic sulfates (Farooqui and Bachhawat 1975).

Balasubramanian and Bachhawat (1976) also purified arylsulfatase B from sheep brain and showed it to be a glycoprotein. It appears that a distinct minor anionic form of arylsulfatase B, denoted as 'arylsulfatase Bm' exists specifically in brain tissue. This enzyme was demonstrated in human and monkey brains (Lakshmi and Balasubramanian 1980) and separated from arylsulfatases A and B. The content of the three enzymes differs in infant and adult brains. The anionic form of arylsulfatase B increases in the developing rat brain and it was shown to be a phosphorylated protein.(Mathew and Balasubramanian 1984). The purification of arylsulfatase Bm and evidence of its phosphoprotein nature were described by Lakshmi and Balasubramanian (1984).

Balasubramanian (1976) compared arylsulfatase C, esterone sulfatase and dehydroepiandrosterone sulfatase activities in sheep brain. The results suggested that one enzyme is responsible for arylsulfatase C and esterone sulfatase activities while a different enzyme is involved in the hydrolysis of dehydroepiandrosterone sulfate. The arylsulfatase C of sheep brain was solubilized with chaotropic agents (Lakshmi and Balasubramanian 1979). From studies on the susceptibility to phospholipase action, it was concluded that one enzyme is not responsible for both the arylsulfatase C and esterone sulfatase activities. (Mathew and Balasubramanian 1982) The distribution of arylsulfatase C, esterone sulfatase and dehydropiandrosterone sulfatasein a number of areas of primate brain was studied by Lakshmi and Balasubramanian (1981).

Studies on enzymes

Enzymes of carbohydrate metabolism: The presence and properties of a number of enzymes for carbohydrate metabolism in brain were investigated. Damse et al (1961) found hexokinase activity in the lateral parietal cortex, lateral frontal cortex, hypothalamus, corpus callosum, hippocampus and cerebellum of monkey. The activity was not uniform,being least in the cerebellum. Joshi and Jagannathan (1968) purified brain hexokinase and studied its properties. Two key enzymes of gluconeogenesis, viz., glucose-6-phosphatase and fructose-1, 6-biphosphatase were shown to be present in the cerebral cortex, cerebellum and brainstem (Kaur et al 1981). Fructose-1,6 biphosphatase was purified to homogeniety from human foetal brain and found to exist as a dimer. Interestingly, 5'-AMP a known allosteric inhibitor of this enzyme in other tissues, had no effect on the brain enzyme (Biswas et al 1985). A distinct N-acetylglucosamine kinase which did not show hexokinase activity was purified from sheep brain (Pattabhiraman and Bachhawat 1961a). An enzymic inter-conversion of N-acetyl glucosamine-6-phosphate and N-acetyl glucosamine-1-phosphate has been demonstrated in rat brain (Pattabhiraman and Bachhawat 1962a). They have also purified uridinediphospho N-acetyl glucosamine pyrophosphorylase from sheep brain. This enzyme catalyzes the formation of UDP-N-acetylglucosamine from UTP and N-acetylglucosamine 1-phosphate (Pattabhiraman and Bachhawat 1961b). UDP-N-acetylglucosamine is an important intermediate in the interconversion of various aminosugars and it is also a precursor for aminosugars of mucopolysaccharides. In addition, glucosamine-6-phosphate N-acetylase of sheep brain and glucosamine-6-phosphate deaminase (which degrades glucosamine-6-phosphate reversibly to fructose 6-phosphate and ammonia) of human brain have also been purified (Pattabhiraman and Bachhawat 1961c, 1962b). Basu and Bachhawat (1961 a,b) purified UDP-glucose pyrophosphorylase from human brain and UDP-glucose glycogen transglucosylase from sheep brain.

Alpha-L-fucosidase is an important enzyme responsible for the hydrolysis of oligosaccharide chains of complex glycoconjugates and is absent in fucosidosis, an inheritable neurovisceral storage disease. This enzyme has been purified from monkey brain and resolved into 3 molecular forms of activity which appear to be trimer, dimer and monomer (Alam and Balasubramanian 1978b). These molecular forms were separated using a simple affinity system consisting of a alpha-L-fucose coupled to Sepharose 4B,(Alam and Balasubramanian 1979) Alpha-D-mannosidase is a glycosidase involved in the degradation of glycopolymers and multiple forms of this enzyme having acid, neutral and intermediate activities are known to occur. Mathur and Balasubramanian (1981) separated and purified the acid and neutral alpha-D-mannosidase from monkey brain. Subsequently they separated two forms of acid alpha-D-mannosidase from monkey brain,one containing only high mannose oligosaccharides and the other both high mannose and complex oligosaccharides (Mathur et al 1984). They have also devised a method for the purification of brain neutral alpha-D-mannosidase by cobalt-ion chelate affinity chromatography (Mathur and Balasubramanian (1964).

Dehydrogenases and Oxidases: The ontogeny of lactate dehydrogenase was studied by Mahajan et al (1984) in human foetal brains during growth from 8 to 760 gms body weight. The activity of this enzyme was higher in the cerebral cortex than in spinal cord, increased with age and showed a biphasic developmental pattern. Similar results were obtained with succinic dehydrogenase in human foetal brains with a cranio-caudal pattern of development (Mahajan et al 1982). In a study on the regional distribution of cytochrome oxidase in monkey brain Tolani and Talwar (1961) observed highest activity in the temporal tip, hippocampus and lateral frontal cortex. The corpus callosum showed the least activity.

The enzyme monoamine oxidase is implicated in migraine, depressive disorders and in the process of ageing of the brain. It is bound to the mitochondrial outer membrane. Two forms-A and B-are thought to exist. Anna Oommen and Balasubramanian (1976) solubilized the membrane-bound enzyme from monkey brain and obtained evidence for the presence of both A and B type of activity in this tissue. Mayanil and Baquer (1984) compared the properties of semipurified mitochondrial and cytosolic monoamine oxidases from rat brain. Kinetic and stability studies suggested that the two enzymes are different. They showed that monoamine oxidase regulates Na+, K+ATPase of rat brain. 3-methoxy-4-hydroxy benzaldehyde, an analogue of 3-methoxy-4-hydroxy phenylacetadehyde (a product of monoamine oxidase on dopamine), activates Na+, K+ATPase and this activation seems to involve a cAMP-dependent protein kinase (Mayanil and Baquer 1985).

Lysosomal hydrolases: A number of degradative enzymes are implicated in the storage diseases of the brain and these are localized in lysosomes.

The purification, characterization and biosynthesis of the lysosomal enzymes is a major area of interest at Vellore. Five lysosomal enzymes; arylsulfatase A, acid phosphatase, beta-N-acetyl hexosaminid·.se, beta-galactosidase and beta-glucuronidase; were shown to bind to concanavilin A suggesting their glycoprotein nature and enabling their purification (Bishayee and Bachhawat 1974). Alvares and Balasubramanian (1982) purified the microsomal and lysosomal beta-glucuronidases of monkey brain by Con A-Sepharose affinity chromatography and studied their interrelationship. They also isolated a binding protein for the four lysosomal enzymes; namely, beta-hexosaminidase, beta-glucuronidase, alpha-L-fucosidase and arylsulfatase; from the lysosomal fraction of monkey brain by phosphomannan - sepharose chromatography. These results suggest that the receptor is specific for the mannose-6-phosphate recognition marker on the enzymes (Alvares and Balasubramanian 1983). The binding requirements of the lysosomal enzymes to their protein have been investigated (Alvares and Balasubramanian 1986). The binding protein undergoes phosphorylation on serine and tyrosine residues and can also act as a tyrosine kinase, phosphorylating tyrosine residues in histone. The phosphorylated receptor binds lysosomal enzymes to a lesser extent than the unphosphorylated receptor and it is suggested that phosphorylation is the mechanism for shedding lysosomal enzymes from the receptor and recycling the receptor.

Some of the pioneering investigations on brain lysosomal enzymes, conducted at Vellore, were described by Professor Bachhawat in his Presidential address at the 22nd Annual Conference of the Neurological Society of India (Bachhawat 1974).

Phosphatases: Datta et al (1969a) observed acid and alkaline phosphodiesterase activities in goat cerebral cortex ribosomes. The alkaline activity was greater and it is firmly bound to the ribosomal particles.

Significant alkaline phosphatase activity was found in human foetal tissue. This enzyme was present both in cytosol and microsomal fractions and showed a progressive increase with gestational age (Chatterjee et al 1979). Saraswati and Bachhawat (1963) purified a pyridoxal phosphate phosphatase from human brain. Later, they separated two similar alkaline phosphatases from sheep brain. One of these showed higher affinity towards pyridoxal phosphate and AMP than the other (Saraswati and Bachhawat 1966). A specific O-phosphoserine phosphatase has been reported to exist in rat brain (Subrahmanyam 1963).

Acetylcholinesterase and its associated arylamidase activity: Acetylcholinesterase is one of the most important enzymes in the brain because of its role in hydrolysing acetylcholine released at nerve terminals during impulse propagation. Kaplay and Jagannathan (1970) purified a particulate acetylcholinesterase from the caudate nucleus of the ox.

It specifically hydrolysed acetylcholine and showed no activity towards butyryl choline. Anna Oommen and Balasubramanian (1977,1978) purified an arylacylamidase from sheep and monkey brains and observed that this enzyme is closely related to acetylcholinesterase. The two activities have many properties in common. Arylacylamidase is associated with acetylcholinesterase in monkey brain (Anna Oommen and Balasubramanian 1979). The interesting property of the arylacylamidase is that it is inhibited by serotonin. Anna Oommen and Balasubramanian (1980) also presented evidence for the identity of the serotonin-sensitive arylacylamidase with acetylcholinesterase in sheep basal ganglia, electriceel and human erythrocytes by a number of criteria. Both the enzyme activities were shown to contain phosphatidylinositol moieties which anchor the enzyme to the membrane. Some of the phosphatidylinositol moieties also appear to be essential for the catalytic activity (Majumdar and Balasubramanian 1982). The effect of chemical modification of the acetylcholinesterase and arylamidase activities of the purified enzyme from electric eel and basal ganglia was investigated (Majumdar and Balasubramanian, 1984). These results suggested that the active centres for the two activities are situated at different loci but have histidine and tyrosine as common residues. Apparently, phenacetin-N-deacetylase of monkey brain is an enzyme different from the aryl acylamidase (Oommen and Balasubramanian 1980).

In insects, acetylcholinesterase exists in several forms. Two distinct classes of this enzyme are known to occur in the fruit fly drosophila melanogaster- one soluble and the other particulate. The soluble species shows heterogeneity. Zingde et al (1983) studied the molecular properties of drosophila acetylcholinesterase. Their results suggest that this enzyme exists in the monomeric, dimeric and tetrameric forms. From studies on mutants they concluded that the native viable enzyme consists of a tetramer composed of two units of 64,000 daltons and one each of 60,000 and 57,000. The dimeric association by disulphide bonds occurs exclusively between 57,000 and 60,000 dalton units (Zinde et al 1983).

Glutathione-5-transferases: These are a group of multifunctional enzymes which catalyze the conjugation of glutathione to a variety of compounds as a mechanism for their biotransformation and detoxification. While the presence of these enzymes in many tissues has been reported, **this enzyme was observed in the mammalian and avian brain for the first time at the Industrial Toxicology Research Centre, Lucknow** (Dixit et al 1981). They also reported the conjugation of glutathione with acrylamide, a potent neurotoxin (Dixit et al 1980). Glutathione-5-transferase in the brain was found in relatively lower concentrations in male mammals (rat and mouse) than in females (Das et al 1981). In contrast, in the aves (pigeon, kite, vulture and crow), males showed higher activity than females. In rat this enzyme activity increased during the first three weeks after birth.

Hormones and Enzymes

The effect of hormones, particularly insulin, has been investigated in detail at Jawaharlal Nehru University, Delhi. During insulin-induced hypoglycemia, the type I and type II hexokinases showed significant changes in cerebrum, cerebellum and brainstem (Kaur et al 1983). In alloxan diabetes, the particulate hexokinase activity decreased while that in the soluble fraction increased. These changes were normalised on insulin treatment (Kaur et al 1985). Aminobutyrate aminotransferase decreased while succinate semialdehyde dehydrogenase increased in insulin-induced hypoglycemia.(Gupta and Baquer 1984) In alloxan diabetes, marked changes were noted in malic enzyme,(Murthy and Baquer 1983), monoamine oxidase (Mayanil et al 1982), aspartate aminotransferase, malate dehydrogenase (Kazmi and Baquer 1985) and these were generally restored on insulin treatment. In several areas of the brain, the level of active form of pyruvate dehydrogenase was markedly influenced by the thyroid status of the animal while the total concentration of the enzyme was generally not affected (Murthy and Baquer 1982).

Significant changes in the activity of hexokinase isoenzymes were observed in some regions of the rat brain during thyroid deficiency (Kaur et al 1987).

Urea cycle enzymes and ammonia toxicity

Enzymes of the urea cycle in brain and the effects of ammonia toxicity have been extensively studied by Sadasivudu and his colleagues. To study the metabolic and functional significance of urea cycle intermediates, Sadasivudu and Indira (1974a) determined the distribution of arginosuccinate synthetase, arginosuccinate lyase, arginase, carbamoyl-phosphatase and aspartate transcarbamylase in the various regions. Arginosuccinate synthetase was generally higher in all the regions. The brain stem showed the least activity of all enzymes. In another study, they (Sadasivudu and Indira 1974b) investigated the regional distribution of arginase, arginine-glycine transaminidase, arginine-GABA transaminidase, ornithine-alpha-keto glutarate aminotransferase and ornithine-glycoxalate aminotranferase which are involved in the disposal of arginine and ornithine. The results showed that cerebellum has very high activities of arginase and ornithine-alpha-ketoglutarate aminotransferase suggesting that the major fate of arginine is to give rise to glutamic acid. Citrulline (30 mg/kg i.p.) increased the glutamine synthetase and ornithine aminotransferase in the cerebral cortex indicating that it may alleviate toxicity in hyperammonemic states (Sadasivudu and Indira 1976).

Several studies have been conducted on the enzymes of glutamic acid and glutamine metabolism. Pattabhiraman and Bachhawat (1959) purified glutamic oxaloacetic transaminase from human and ox brains.

Administration of hydrocortisone (10 mg/day per mouse) for five days caused an increase in aminoacids of glutaric acid family and in glutamate dehydrogenase (Sadasivudu et al 1977a).

Bhargave and Telang (1986) reported that glutamate dehydrogenase, glutamic acid decarboxylase and glutamine synthetase were stable upto 12 hours after death in young and adult brains. GABA-transaminase was stable only upto 30 minutes postmortem. Glutamine synthetase activity is very low in rat brain until day 13 after birth, rises sharply between days13 and 15 and slowly thereafter. Most of the protoplasmic astrocytes - the cells involved in glutamine synthetase - are formed by day 12. Glutamine synthetase activity in the developing brain is under steroidal control (Chatterjee and Sarkar 1984a).

Pal and Ghosh (1969a) observed that phenothazine tranquilizers markedly inhibit ammonia formation in rat brain homogenates. AMP deaminase activity was noted to increase in cerebral cortex, cerebellum and brain stem during convulsions and in the preconvulsive stage. (Sadasivudu et al 1980) Guanine deaminase was purified from rat brain (Mansoor et al 1963). This enzyme activity was highest in thalamus, fairly abundant in cerebral cortex but could not be detected in the cerebellum.

Experiments on the acute and chronic administration of ammonium salts conducted by Sadasivudu et al (1977b) showed that Na+, K+ ATPase was elevated in many parts of the brain probably as the primary responses to hyperammonemia. Cerebral glutamine synthetase remained unaltered under these conditions but glutamate dehydrogenase increased in the brainstem. Alpha-ketoglutarate dehydrogenase activity also increased in brainstem and cerebellum of male rats administered ammonium acetate (Sadasivudu and Rangavalli 1981). Monoamine oxidase (Sadasivudu and Murthy 1978), adenosine deaminase and phosphodiesterase (Sadasivudu et al 1981) were also considerably decreased in ammonia toxicity. The accumulation of adenosine may be the basis for depression in brain function in these cases.

Jessy and Murthy (1985) found a significant increase in the levels of aminotransferase activities of branched-chain aminoacids, particularly leucine and isoleucine in acute ammonia toxicity and suggested that these aminoacids may be a source for glutamate required for glutamine synthesis in these conditions. Citric acid cycle enzymes viz., pyruvate-, ketoglutarate- and succinate dehydrogenases and citrate synthase are elevated while isocitrate dehydrogenase, asparate- and alanine aminotransferase decreased in acute ammonia toxicity (Ratnakumari et al 1986).

Subbalakshmi and Murthy (1985a) studied the distribution of enzymes of glutamate metabolism in astrocytes, neurons and synaptosomes of the

cerebral cortex in rat. High glutaminase acitivity was found in astrocytes but none in neuronal perikarya. Glutamine synthetase was present in synapatosomes and neuronal perikarya. High glutamate dehydrogenase activity was noted in synaptosomes. Glutamate metabolism may be different in the two organelles (Subbalakshmi and Murthy 1985b). Studies on the acute effects of ammonia in organelles suggest that primary detoxification occurs in neuronal perikarya and not in astrocytes. Further detoxification occurs in both neurons and glia (Subbalakshmi and Murthy 1983a). These experiments were repeated with methionine sulfoximine (instead of ammonium salts) to cause hyperammonemia. The same changes were observed in enzyme levels showing that the metabolic shifts were due to hyperammonemia irrespective of its etiology (Subbalakshmi and Murthy 1981, 1983b, 1984; Ratnakumari et al 1985; Jessy and Murthy 1988).

Neurotransmitters, their receptors and opiate receptors

One of the most interesting areas of neurochemical research is the study of neurotransmitters, their levels, metabolism and receptors. In a study on the cholinergic system, Iqbal and Talwar (1971) assayed acetylcholinesterase in the brain at different stages of development of the chick embryo to correlate the ontogenesis of electrical activity with the appearance of the enzyme. The enzyme was associated with the synaptosomal fractions, increased progressively with age and existed as 3 isoenzymic forms. In rats, however, a single enzyme species of acetylcholinesterase was observed at all ages (Moudgil and Kanungo 1973a). The enzyme could be induced with 17 beta-estradiol in immature and adult rat cerebrum and cerebellum (Moudgil and Kanungo 1973a). Acetyl-choline-esterase of brain was also shown to exhibit a diurnal rhythm which changed with age (Moudgil and Kanungo 1973b). Ravikumar and Sastry (1985a) studied the ontogeny of the muscarnic cholinergic receptors in human foetal brains. They analysed several normal human brains of gestational ages from 16 to 40 weeks and postnatal ages from 5 to 50 years. (3H)-quinuclidinyl benzilate (QNB) was used as the specific ligand in these studies for the characterization of the muscarinic receptors. Their identity was further established by detailed pharmacological experiments. The ontogeny of muscarinic receptors in the frontal cortex showed 3 distinct phases. In phase I, they appear between 16 and 18 weeks and increase slowly upto 20 weeks. Phase II is a lag period between 20 and 24 weeks when the receptor concentration does not change perceptibly. Phase III is a rapid, nearly three-fold, increase of receptors occurring in the third trimester. After birth the receptor concentration declined and the values in adult frontal cortices are 50% of that at birth indicating synapse elimination postnatally. Affinity of the receptor to QNB did not change during foetal development. Sodium chloride and GIP decreased the agonist affinity even in 16-18 week foetal brains. The modulatory elements seem to appear simultaneously with the receptors. Ravikumar and Sastry (1985b) also investigated the ontogeny of muscarinic

receptors in human foetal striatum, brainstem and cerebellum to establish the general principles of synaptogenesis. In the corpus striatum QNB binding sites were present at 16 weeks of gestation, increased slowly upto 24 weeks and rapidly during the third semester. In brainstem, the muscarinic receptors showed the maximum concentration by 16 weeks of gestation and then declined gradually. In cerebellum, except for a slight increase at 24 weeks of gestation, the receptor concentration remained nearly constant throughout foetal life. The ontogeny of muscarinic receptors thus varies in the different regions of the brain and occurs principally inthe third semester. Das et al (1986a) studied the effect of acute and chronic administration of morphine on the muscarinic receptors in different regions of the brain in rats using (3H)-QNB as the ligand. These receptors were unaffected by administration or withdrawal of morphine. Similarly, acute or chronic administration of the two peptides: proline-leucine-glycine-NH_2 and its analog cyclo-(leucine-glycine) to mice and rats did not effect the (^{3}H)-NB binding characteristics or quantity in striatum (Das et al 1986b). The earlier reported anticholinergic activity of these compounds is, thus, not mediated through the muscarinic receptors.

Sastry and Ravikumar (1987) analysed the corpora striata from normal human foetal brains (ranging in gestational age from 16 to 40 weeks) and postnatal brains (ranging from 23 days to 42 years) for the ontogeny of dopamine receptors using (^{3}H)-spiroperidol as the ligand and 10 mM dopamine hydrochloride in the blanks. These receptors were characterized as D_2 type. During the foetal age of 16 to 40 weeks, the receptor concentration remained nearly the same with no discernible ontogenic pattern but it increased two-fold postnatally reaching a maximum at 5 years. Significantly, at lower foetal ages (16-24 weeks) the receptors contained low affinity and high affinity components but after 24 weeks all showed a single high affinity. This result is in contrast to the ontogenic pattern of muscarinic receptors in humans reported earlier by these workers. D_2 receptor binding was also influenced by GTP in foetal life suggesting that the regulatory elements of this receptor also appear simultaneously. Kazmi et al (1986b) reported the solubilization and characteristics of the D_2 receptors of bovine striata. The soluble preparations showed the same potency rank order of agonists and antagonists as membranes. They obtained evidence for the presence of low and high affinity components as well as the guanosine nucleotide binding sites in the soluble preparations. **They also demonstrated high affinity binding of the agonist (^{3}H)-N-propyl-norapomorphine in these preparations for the first time.** Ray and Poddar (1985) found that the acute administration of the anticholinesterase agent, carbaryl, produces tremors which are significantly reduced by prior treatment of the rats with L-DOPA and were exacerbated by haloperidol. They suggested a central cholinergic-dopaminergic interaction in carbaryl induced tremors. Chatterjee et al (1984) studied the interaction of several dihydroxy-2-aminotetralin derivatives with rat brain D_2-dopaminergic, alpha-and

beta-adrenergic receptors by measuring the inhibition of spiperone, prazosin and clonidine binding, respectively. All the components showed significant inhibition of clonidine and spiperone binding but not that with prazosin. Poddar and Deway (1980) showed that delta 9-tetrahydrocannabinol, cannabinol and cannabidiol stimulate the release and uptake of (^{3}H)-dopamine and (^{3}H)-norepinephrine by synaptosomes prepared from rat brain corpus striatum and hypothalamus at 10^{-7}M concentration. Higher concentrations inhibited these processes. Intraperitoneal administration of a single dose of delta^9 -tetra hydrocannabinol or cannabis extract increased rat brain dopamine and decrease noradrenaline levels (Poddar and Ghosh 1976a).

The levels of serotonin are altered by drug treatment. Poddar et al (1977) found that a single dose of pentamethylenetetrazole administered to rabbits increased serotonin content in brain. It also inhibited enzymes metabolising serotonin. They concluded that the effect of this compound on serotonin metabolism is related to its convulsive effect. PGE, administered subcutaneously, also increased serotonin levels in brain within one hour but they tended to normalize within 4 hours (Debanath et al 1978). Krishnan and Balaram (1976a) made a nuclear magnetic resonance study of the interaction between serotonin and mixed gangliosides prepared from monkey brain. They observed a specific and strong interaction between serotonin and gangliosides which is not mimicked by other lipids.

Poddar and coworkers made interesting investigations on gamaaminobutyric acid (GABA) binding sites in brain during sleep and wakefulness cycles. Membranes isolated from brains of sleeping (non-rapid eye movement) and awake hamsters show equal amounts of (^{3}H)-GABA binding in several areas of brain. This binding decreased when brain cytosol of animals kept awake was added. The brain of sleeping hamsters contain a thermostable GABA binding activator whose concentration goes down as wakefulness progresses (Poddar et al 1980a). They found evidence for the presence of endogenous small molecular weight sleep or wakefulness induced substances in human urine (Chandra and Poddar 1986). Similar factors affecting diazepam binding also exist in sleep-wakefulness cycles (Poddar et al 1980b). Chakrabarthi et al (1986a) investigated the effect of electroacupuncture analgesia on GABA in the mammalian CNS and observed that in rats exposed to electroacupunture, analgesia started within 2 minutes and remained at this level for 15 minutes. GABA levels increased in the hypothalamus and thalamus during this period. GABA transferase activity increased in pons-medulla and it may be involved in analgesia.

Sharma and colleagues at Delhi have studied the biochemistry of opiate receptors with special reference to the molecular basis by which opioid peptides bring about tolerance and dependence. They found that in neuroblastoma x glioma hybrid cell line (NG 108-15)- with stereospecific

morphine receptors closely resembling those in rat and human brain-ascorbate suppresses the delayed etorphine-induced compensatory increase in the levels of cyclic AMP without affecting the early response of these cells. The cells show a transient decrease in cyclic AMP levels on treatment with etorphine (Sharma and Khanna 1982). Ascorbate, coadministered with morphine, suppresses the development of tolerance and dependence on the drug without affecting its analgesic property in mice. Ascorbate may be useful in the prevention of tolerance and dependence on narcotic analgesics (Khanna and Sharma 1983). Ascorbate may be acting at the level of the Ni protein which links the receptor to the adenylate cyclase in the membranes and has GTPase activity associated. By inhibiting the low Km GTPase, ascorbate keeps the receptor in the low affinity state(Bhatia et al 1988, Sharma et al 1989).

In their studies on biochemical changes due to narcotic receptor mediated phenomena, they observed a decrease in striatal fructose 1,6-biphosphate levels on short term treatment with morphine in mice. On addition of morphine, fructose 1,6-biphosphate levels returned to control values but decreased markedly on withdrawal. These results show perturbations in glucose metabolism in narcotic drug addition. (Sharma et al 1985) Kinetic study on the thermal inactivation of adenylate cyclase in neuroblastoma X glioma hybrid cells showed that the enzyme contains two components which differ in their sensitivity to heat (Sharma 1985). This finding helps explain the differential response of the enzyme to prostaglandins and etorphine.

Kazmi and Mishra (1986) demonstrated the occurrence of mu and delta types of opioid-binding sites in human neuroblastoma SH-SY 5Y cells. These receptors were well characterized. Their regulation by guanine nucleotides and NaCl was also observed. They suggested that this cell line would be useful for the biochemical and pharmacological characterization of brain opiate receptors.

Effect of drugs and toxins on brain

A number of drugs profoundly affect brain function: tranquilizers, opiates, anaesthetics and blockers for neurotransmitters. Elucidating their mode of action is very important. In a series of investigations on the effect of delta-9-tetrahydrocannabinol in Ghosh's laboratory it was found that acute (10 mg/kg i.p.) or chronic (10 mg/kg for 15 days) administration of this compound to rats led to a decrease in many lipid components in mitochondrial, synaptosomal and myelin fractions but increased lipid components in the microsomal fraction (Sarkar and Ghosh 1975). In the microsomal and synaptosomal fractions, the sialoglycoprotein content increased while the gangliosidic sailic acid content decreased significantly (Sarkar and Ghosh 1976). Delta-9-teta-hydrocannabinol profoundly affected a number of enzyme activities in brain: monoamine oxidase

(Banerjee et al 1975), Na^+, K^+-ATPase, acetylcholinesterase and glutamine synthetase (Poddar and Ghosh 1976b,c). There were significant differences in the effects produced by acute and chronic treatment. The site of action for delta-9-tetrahydrocannabinol is the neuronal membrane. Chronic administration of morphine decreased the brain microsomal ATPase level. This could be restored to some extent by Mg^{2+}. Nalorphine hydrobromide reversed the morphine effect on ATPase. Morphine probably inhibits the catalytic activity of the enzyme by its effect on the binding sites for cationic activators (Ghosh and Ghosh 1968).

The mycotoxin citreoviridine, from *Penicillium citreoviride* affects metabolism in brain. It inhibits glycogen synthetase but does not affect glycogen phosphorylase or glucose-6-phosphatase (Datta and Ghosh 1981a). It also inhibits Na+, K^+-ATPase and alters the kinetic parameters such as V_{max} and K_m of acetylcholinesterase in synaptosomes (Datta and Ghosh 1981b). Citreoviridine reduces GABA levels in cerebrum and cerebellum and increases GABA-transaminase activity (Datta and Ghosh 1983).

In vivo administration of carbaryl, 1-naphythyl N-methyl carbamate, enhanced catacholamine synthesis and breakdown in the striatum and hypothalamus (Ray et al 1984) while phenothiazine tranquilizers significantly inhibited monoamine oxidase (Pal and Ghosh, 1969b). Poddar and coworkers reported that lignocaine inhibits monoamine oxidase and acetylcholinesterase by increasing the lipid fluidity of synaptosomal membranes (Haque and Poddar 1983). Brain ATPase has been investigated in some detail in Ghosh's laboratory. The addition of imiprine to brain microsomal and synaptosomal preparations caused considerable inhibition of ATPase. This was counteracted by spermine (Nag and Ghosh 1973) while strychnine increased this enzyme activity two-fold in cortical microsomes (Nag and Ghosh 1968). Shankar (1973) noted that ouabain, an inhibitor of ATPase, enhances anaerobic glycolysis in brain cortex slices. Chronic administration of reserpine increases K^+ level in brain by about 25% (Shankar and Mishra 1974).

Bacquer's group made a series of studies on the effect of 6-aminonicotinamide (an important intermediate in pyridine nucleotide synthesis) on brain metabolism. It caused selective changes in glutamate dehydrogenase, glutamate oxalacetate transamine and malate dehydrogenase, these being related to the conclusive polyspike activity observed in EEG patterns in these animals (Kazmi et al 1986a). It also decreased monoaminooxidase and ATPase activity in cerebral hemispheres (Mayanil et al 1984) as well as particulate hexokinase and lactate dehydrogenase activities (Kaur et al 1984). Metrazol (pentamethylene tetrazole), another drug that induces convulsions, inhibited brain phosphorylase (Biswas and Talwar 1968). Pandey and Singh (1985) investigated the effects of isonicotinic acid hydrazide and mercaptopropionic acid on the GABA system in cockroach brain. Both compounds inhibited glutamic acid decarboxylase. Isonicotinic acid

hydrazide also showed a total inhibition of the GABA transaminase activity. In the cockroach brain, tryptophane hydrolase and 5-hydroxytryptamine decarboxylase, two enzymes of the serotonin biosynthetic pathway, are strongly inhibited by p-chlorophenylalanine and 3-hydroxybenzyl hydrazine (Pandey et al 1983).

Rajalakshmi and Patel (1968) found that tranquilizers such as fluphenazine increase the ascorbic content in brain. The olfactory lobes and hypothalamus showed the maximum increases in ascorbic levels while basal ganglia, visual cortex and the dorsal cortex showed minimum increases.

Neurolathyrism is prevalent in some parts of India and has therefore received attention. **Beta-N-oxalyl-L-alpha beta-diamino propionic acid (ODAP) has been identified as the major neurotoxic aminoacid** in ***Lathyrus sativus*** **seeds** (Rao et al 1964; Murti et al 1964). Nagarajan et al (1965), Rao and Sarma (1967) showed that ODAP is neurotoxic to young animals. It is a potential glutamate antagonist (Lakshmanan and Padmanaban 1974). Rao and Sarma (1967) found that adult animals are refractory to the effect of ODAP but respond to the neurotoxin if it is administered in the immediate environment of the brain by intracranial, intracisternal or intrathecal route. Adult animals were also shown to be susceptible to the effects of neurotoxin when treated with drugs or chemicals which induce an acidotic state (Cheema et al 1969). Intra-thecal administration of ODAP to adult monkeys was shown to produce paraplegia (Rao et al 1967; Nagarajan 1969) and polioclastic neuropathological lesions (Mani et al 1971). Rao (1978), using (^{3}H)-ODAP, has shown that it enters the CNS of the rhesus monkey whether or not there is acidosis. He also found the toxin in the CNS of non-susceptible species like the adult rat and in the CNS of a susceptible species like the day-old chick to the same extent. Jacob et al (1967) found that ODAP given intraperitoneally (30 mg) to day-old chicks produced complete paralysis in 4 hours. Recovery from paralysis required between 12 to 24 hours. The period of complete paralysis was associated with a fall in the activity of L-glutamate-NAD oxidoreductase. This was restored to normal on recovery. ODAP administration in 12-day old rats led to liberation of ammonia, increased levels of adenylic deaminase, glutaminase, acid protease and transglutaminase in brain. Glutamate dehydrogenase, aspartate-alpha-ketoglutarate transaminase and aspartate-pyruvate transaminase were also affected in ODAP treated rat brains (Cheema et al 1971).

Myelination, synaptogenesis and neural membranes

Myelination and synaptogenesis are two fundamental neurobiological processes on which the ultimate function of the brain depends. These have not received much attention in India. Most of the work conducted on the biochemistry of myelin lipids viz. the ethanolamine plasmalogens,

sulfatides, gangliosides and cholesterol has already been described. (See **Lipid Metabolism**) Natarajan et al (1984) investigated the biosynthesis of long chain alcohols in the developing and regenerating rat sciatic nerve. The fatty acid reductase level increases considerably in the adult rat sciatic nerve after crush injury during Wallerian degeneration and regeneration (when myelinogenesis occurs). Experimental allergic encephalomyelitis (EAE) is considered a good model for producing demyelination in animals. Vasan et al (1971) found a significant decrease in the concentration of cerebrosides, sulfatides and glycosaminoglycans in the acute stage of EAE produced in rats. The incorporation of radioactive sulfate into sulfatides andglycosamino-glycans was also much higher at this state of EAE. The levels of sulfatides could be correlated with the changes in the activity of arylsulfatases at the various stages of EAE (Vasan and Bachhawat 1971). Jagannathan and Sastry (1981c) studied several enzymes of ethanolamine plasmalogen biosynthesis during the various stages of EAE produced in rats. The enzyme levels fell during the onset of demyelination and reached their normal levels during the recovery period. **They attributed these effects to the damage to glial cells which produce myelin. They also demonstrated a cholesterol ester synthetase active at pH 7.4, which they discovered, is mainly responsible for cholesterol ester synthesis in demyelination conditions.** Nag and Ghosh (1984, 1985) studied the effect of sumithion on myelin lipids in pigeons. This compound produced hind leg paralysis and ataxia, decreased the levels of cerebrosides and sulfatides and increased cholesterol ester content suggesting the onset of demyelination.

Sastry and colleagues have studied the biosynthesis and phosphorylation of myelin proteins and their localization within the membrane. To determine the developmental pattern and possible synchrony in the synthesis of various proteins during myelination, Valli and Sastry (1988) purified the basic proteins, proteolipid protein and wolfgram proteins from rat brain and raised specific antibodies to these proteins. They used these specific antisera for the immunoprecipitation of nascently synthesized proteins. Homologous and rabbit reticulocyte lysate protein synthetic systems were utilised. Myelin protein synthesis by brain total polysomes isolated from rats of age 5 to 30 days was studied. It was found that the rat brain has the capacity to synthesize all the three proteins much before myelin can be detected. Wolfgram proteins may be the first to be synthesized and may be the prerequisite for the initiation of the myelination process. They further showed that both basic proteins and wolfgram proteins (but not proteolipid proteins) are phosphorylated by endogenous kinases in myelin. **The wolfgram protein phosphorylation was shown for the first time** and a serine residue was found to be phosphorylated (Valli and Sastry, unpublished). Nag and Ghosh (1985) reported decreased proteolipid protein and wolfgram protein content in the myelin of pigeons treated with sumithion and an enhanced phosphorylation of the myelin proteins (Nag and Ghosh 1986). Marutimohan and Sastry

(1987) subjected the rat myelin membrane to controlled proteolytic digestion. The basic proteins were completely hydrolyzed in a short time but the proteolipid protein remained largely intact for 1 hour of incubation. The wolfgram protein was progressively hydrolysed with the simultaneous appearance of a 35 KDa M.W. fragment. On western blot analysis they showed that the 35 KDa M.W. protein is the only major breakdown product. From these experiments they concluded that the major fragment (35 KDa M.W.) is located in the hydrophobic milieu of the bilayer, relatively inaccessible to trypsin, whereas a portion (about 20 KDa M.W.) is exposed to the cytoplasmic side (major dense line) like the basic proteins. It is likely that an interaction between the acidic wolfgram protein and basic protein at the cytoplasmic surface is the initial event in myelination. They also found that the 2′-3′-cyclic nucleotide 3′-phosphodesterase activity, a myelin specific enzyme believed to be identical with wolfgram proteins, is not lost on proteolytic degradation of the wolfgram proteins implying that a smaller fragment of this protein exhibits the enzyme activity.

Krishnan and Balaram (1976b) described a simplified procedure for the isolation of plasma membrane from monkey and rat brains. These membranes contained proteins which resembled erythrocyte ghost proteins but not myelin proteins. The cation binding to brain plasma membranes using anionic sulfonate fluorescent probes was also studied (Krishnan and Balaram, 1976c). Ion affinity sequences followed the order $Mg^{2+}>Ca^{2+}>>K^{+}>Cs^{+}>Na^{+}>Li^{+}$. Evidence was presented for a role for proteins in binding hydrophobic probes. In similar studies, Chakrabarti et al (1983) showed that beta-endorphin causes release of Ca^{2+} from synaptosomal membranes but not from rat brain mitochondria indicating some functional significance for this differential effect.

Nutrition and brain development

Several important events such as cellular proliferation, dendritic arborization, myelination and synaptogenesis occur in the early phases of brain development. Realising the importance of adequate nutrition during this critical period and recognizing the widely prevalent nutritional deficiencies in India, several groups have investigated the consequences of undernutrition on brain development. These reports have been summarised by Sastry and Murthy (1984). A general article on *Nutrition and Brain Function* has been published by Rajalakshmi and Ramakrishnan (1972).

Nucleic acids and proteins : Mehta and Chakravarti (1971a) studied the effect of protein deprivation on weaning rats and observed that it decreases the DNA, RNA and protein content in the brain. Recovery of these parameters was not complete 4 weeks after rehabilitation. They also investigated the effect of protein - calorie malnutrition on suckling rats and noted significant decreases in the weight, protein and alpha-amino

nitrogen contents in brain (Mehta and Chakravarti 1971b). Rats subjected to dietary protein restriction from 3 to 7 weeks of age were also found to contain reduced DNA in the cerebrum but not in other regions. Some increase in cell number may occur in cerebrum even after weaning and may be affected by protein malnutrition (Mehta and Chakravarti 1973). In a study on the effect of protein-calorie malnutrition on young rhesus monkey, no change in DNA, protein and total lipids was noted in the brain but RNA decreased. Here protein-calorie malnutrition was initiated at a later stage when the brain development might have been complete and therefore no effect was observed on these growth parameters (Mehta et al 1981). Katiyar et al (1975) produced undernutrition in rats by withdrawing the young ones from their mother for 12 hours every day from the age of 6 days onwards. In these animals too decreased DNA, RNA and free alpha-amino nitrogen levels in brains were recorded. This group also investigated the effect of the quality of dietary protein on foetal brain development in rats (Agarwal et al 1981a; Prasad et al 1980). It was concluded that wheat and Bengal gram diets isonitrogenous with 10% casein, fed to pregnant rats, results in lower DNA, RNA and protein in foetal brains and reduced RNA/DNA ratio indicating decreased protein synthesis. These effects could be countered by supplementing the diet with the deficient aminoacids.

Subba Rao et al (1980) and Subba Rao and Subba Rao (1982a) reported that the specific activity of acid and alkaline DNAases was not effected in rat cerebellum by early postnatal undernutrition but the total activities were lowered and this effect was reversed on rehabilitation. White matter is markedly vulnerable to undernutrition while the grey matter is unaffected (Subba Rao and Subba Rao 1982b).

Bakshi and Kumar (1979) reported that undernutrition throughout the weaning period in rats reduces the DNA content in brain as well as the (3H)-thymidine incorporation into DNA and DNA-dependent DNA-polymerase activity. Protein phosphorylation in developing rat brain was also affected by undernutrition (Kumar and Shankar 1985).

Sarma and Subba Rao (1974) studied the biochemical composition of the brain from small-for-date infants. These brains were reduced in size. On a percentage basis, the cerebellum and medulla oblongata were affected more than the cerebrum. Cellularity (as estimated by DNA content) was affected only in the cerebrum. RNA level decreased significantly in the cerebrum of small-for-date babies but other parameters did not change significantly. Sarma and Subba Rao (1976) analysed human foetal brains from poor income families. Moisture content decreased sharply during the last weeks of intrauterine life and the DNA increase in different areas of the brain did not occur at the same rate and time. These authors postulated three phases of brain development: one of rapid cell proliferation lasting upto 22 weeks, a lag phase upto 32 weeks followed by a rapid growth phase.

This is one of the few systematic studies made on brain development in human foetuses. Ganguly et al (1972) studied the composition of brains of children who had suffered from kwashiorkor and marasmus and observed reduced levels of DNA, RNA and protein in these brains.

Lipids: Rajalakshmi and Nakashi (1974) reported that maternal protein deficiency in rats during lactation leads to significant reduction in brain weight, body weight and total lipids but not lipid concentration in the brains of the offspring. They (Rajalakshmi and Nakashi 1976) also found that in the spinal cord, total lipid concentration was not affected by neonatal protein malnutrition until two weeks but there was a reduction by the end of the third week. Rajalakshmi et al (1974b) observed that cholesterol and cerebrosides were reduced in the brain of rats undernourished during the weaning period. These were further reduced when the undernutrition is continued upto the 8th week after birth. Undernutrition in the post-weaning period does not seem to affect brain lipids. In general, the nutritional effects are more pronounced on white matter than on grey matter (Reddy and Ramakrishnan 1982a) and nutritional rehabilitation reverses the deficit observed in grey matter (Reddy et al 1982). Srinivasa Rao (1979) reported that lignoceric and nervonic acids (which are characteristic of cerebrosides) and polyenoic fattyacids (such as arachidonic acid) are reduced in the brains of undernourished rats. Reddy and Sastry (1978a) found that the ganglioside concentration in the brain was significantly reduced by undernutrition but this deficiency was corrected on rehabilitation. (^{14}C)-glucosamine incorporation in vivo into brain gangliosides was not affected by undernutrition. Bhargava et al (1984) reported a significant reduction of ganglioside content and neuraminidase activity in several parts of the brain in undernourished rats, the hypothalamus being maximally affected.

Reddy and Sastry (1978a) found that the phospholipid content of rat brain undernourished upto 8 weeks after birth was about 7 to 9% less than in control animals. This deficit could not be made up on rehabilitation indicating the permanent nature of the damage. Phospatidyl ethanolamine and ethanolamine plasmalogen were the most affected components in the brains of undernourished rats. Uma and Ramakrishan (1983b) found that neonatal undernutrition reduces the level of structural phosphoinositides and metabolically inert phosphatidyl inositophosphate but not the metabolically active phosphatidyl inositoldiphosphate. Rehabilitation reverses this effect.

Shankar et al (1975) showed that the in vivo incoporation of (^{14}C)-acetate into lipids was unaffected by undernutrition but in experiments with homogenates Subba Rao et al (1978) found a drastic reduction in the incorporation of (U-^{14} C)-glucose into mongalactosyl diglyceride, a myelin component. Reddy and Sastry (1978a) reported a higher incorporation of

(^{32}P) into phospholipids by brain homogenates of undernourished rats and suggested that it may be related to heightened emotion, a characteristic manifestation of perinatal malnutrition. Reddy and Sastry (1979a) also showed that stimulation of phospholipid metabolism by neuro-transmitters in cerebral tissues is a valid biochemical correlate of synaptogenesis in the developing brain and from such studies, **they concluded that the cholinergic, adrenergic and serotonergic synapses are unaffected in the cortex but are significantly affected in the brain stem by undernutrition.** In the cerebellum of undernourished rats the adrenergicand cholinergic are altered but not the serotonergic systems. Chauhan et al (1980) found an enhanced incorporation of (^{14}C)-acetate, (^{14}C)-palmitate into phospholipids, cholesterol, cerebrosides and sulfatides into the brains of malnourished rats in vivo compared to controls.

Shalini et al (1972) noted considerably lower levels of cerebrosides and sulphatides in children aged 4 years or more who died of kwashiorkor. Sarma and Subba Rao (1974) observed significantly lower cholesterol and phospholipid contents in the cerebrum, and medulla oblongata in small-for-date infants. Srinivasa Rao and Subba Rao (1973) determined the fattyacid profiles of phospholipids in the cerebrum, cerebellum and brainstem of human foetuses and noted an accumulation of long chain unsaturated fattyacids towards term. Polyunsaturated fatty acids increased to a greater extent in the cerebellum than in other areas. Sarma et al (1983) reported a reduction in total lipids, longchain fatty acids of cerebrosides and polyenoic fattyacids of phospholipids in the brains of children who died of kwashiorkor and chronic starvation. Significant changes in glycosaminoglycans have also been reported in the brains of children who died of kwashiorkor (Chandrasekharan et al 1971). While most of the above mentioned reports indicate impairment of myelination, direct evidence for a nutritional effect on myelinogenesis was provided by Sastry and coworkers. Reddy et al (1979b) demonstrated that undernutrition produced 16% and 35% reductions in myelin content at the ages of 3 and 8 weeks respectively, while protein malnutrition caused the more drastic reduction of 27% in myelin content at the age of 3 weeks. These effects were only partially restored on rehabilitation. Under-nutrition did not alter the relative composition of myelin proteins but protein malnutrition resulted in a significant reduction in proteolipid content. Vitamin A deficiency (Bhat and Rama Rao 1978) and Vitamin E deficiency (Pappu et al 1980) were also shown to affect myelinogenesis in the developing rat brain. Similarly, Rajalakshmi and Nakashi (1975) reported that pantothenic acid deficiency leads to reduction of brain lipids from reduced growth in these animals. In contrast, thiamine deficiency was found to reduce brain lipids significantly (Reddy and Ramakrishnan 1982b). Undernutrition causes peroxidation of membrane lipids (Chakrabarti and Sankar 1984).

Neurotransmitters, enzymes and amino acids Ramamurthy (1977) determined the levels of serotonin, dopamine, norepinephrine and histamine in undernourished foetal and postnatal brains upto 5 weeks of age in rats. Serotonin, dopamine and norepinephrine levels were not altered in the undernourished brain during gestation and upto one week after birth but declined thereafter. The level of histamine, on the other hand, increased two-fold during the first 5 weeks after birth in these animals. Tryptophan hydroxylase, tyrosine hydroxylase and monoamine oxidase -enzymes of neurotransmitter metabolism - increased from the 14th day of postnatal life in the brains of undernourished rats (Kalyana Sundaram and Ramanamurthy 1981,1983). Tryptophan level was found to be high at birt hand upto 7 days postnatal but decreased from the 14th postnatal day in undernutrition (Kalyana Sundaram 1976). Pups born to protein restricted mothers did not show any alteration in amino acid levels at birth but from day 14 onwards there was a significant increase in the levels of taurine, glutamic acid and glycine and a decrease in the level of GABA (Kalyana Sundaram and Ramanamurthy 1982). These studies showed that the precursor amino acids for catecholamines were not altered in undernutrition but the amine levels show alterations. Katiyar et al (1976) found enzymes of glutamic acid metabolism to be affected by undernutrition. Similar results were also reported by Rajalakshmi et al (1974c and d).

A number of enzymes in brain have been found to be affected by undernutrition. Thus Katiyar et al (1978) demonstrated a significant increase in the neutral protease activity in protein-energy malnutrition. Kaplay (1977) found that the cholinesterase activity is increased in the brains of small-for-date infants. Rajalakshmi et al (1974a) observed that preweaning undernutrition did not alter acetylcholine levels but post-weaning undernutrition upto 4 weeks reduced acetylcholine level in brain. Reddy and Sastry (1978b) studied the effect of malnutrition on the ouabain-sensitive and ouabain-insensitive Na^+, K^+, ATPases in rat brain. Undernutrition as well as protein-malnutrition significantly reduced the ouabain-insensitive enzyme but not the ouabian-sensitive enzyme. Mishra and Shankar (1980) also made similar observations. The activity of 2',3'-cyclic nucleotide 3'-phosphohydrolase, a myelin specific enzyme was investigated in undernourished rats by Reddy and Sastry (1979). Undernutrition did not affect this enzyme but protein-malnutrition caused a 25% reduction at 3 weeks which was totally reversed by rehabilitation.

Ramamurthy and Srikantia (1970) showed that the brain serotonin levels are lowered in experimental animals fed sorghum diet or casein diet supplemented with 8% leucine. The rate of synthesis was not altered but the degradation of serotonin was high in these rats. Uptake of serotonin into synaptic vesicles was inhibited in rats fed iron deficient diets. (Kaladhar and Narasinga Rao 1977) (^{14}C)-glycine uptake by cerebral cortex slices was found to be higher in malnourished rats but this effect was abolished by reserpine (Mishra and Shankar 1975).

Biochemical characterisation of human brain tumor antigens using monoclonal antibodies.

Shail Sharma and colleagues used the immunological approach to identify cell surface molecules that may be involved in vital cellular processes such as differentiation, de-differentiation and malignant transformation. Brain tumor cells were chosen as a model system since they offer a consistent and constant source of defined antigenic ensemble and the ease with which they could be morphologically and biochemically differentiated in the presence of effector agents.

C6 glioma cells in culture, on addition of 3':5' cyclic monophosphate (cAMP) show two distinct types of morphological changes: a) Cell bodies become rounded with multipolar processes and beadings after 30 minutes as cAMP levels in the cells show 70-80 fold increase. b) Cell bodies become elongated with extended bipolar processes after 24-48 hours as cAMP concentration in the cells drops. The morphological differentiation of the cells results in retardation of cell growth, diminished uptake of ^{3}H-2-deoxyglucose and abolition of enhanced synthesis of cAMP by lectin-concavalin A (Sharma and Raj 1987). Rapidly proliferating cells had higher concentrations of glucose-6-phosphate, fructose-6-phosphate and fructose-1,6-biphosphate compared to morphologically differentiating cells. At maximally activating conditions the specific activity and V_{max} of hexokinase and phosphofructokinase were reduced by approximately 3 and 28 fold respectively in differentiated cells, without any change in Km values. These results suggest that hexokinase and phosphofructokinase occupy special control positions and the rate of glycolysis is correlated with cellular priliferation of C6 glioma cells (Dastidar and Sharma,1989).

There is a relative increase in the amount of proteins (MW 65000-80000) in the rapidly proliferating C6 glioma cells. Differentiation may enhance the turnover of some proteins in this group. Proteins with MW 58000 daltons became progressively more prominent after differentiation (Sharma et al 1983). In studies using mice hyperimmunised with C6 glioma cells, clones have been obtained which specifically recognise proteins on differentiated cells (Sharma et al 1987). C6 glioma cells secrete a putative growth factor which promotes the growth of hybridomas in culture. (Gomathi et al 1986)

Studies with hybridoma clones isolated using whole U87-MG (human glioblastoma multiforme) cells as antigenic stimulant, it was noted that intermolecular antigenic competition led to limited antibody production, minor antigenic components having vital roles to play in cellular function being obscured by poor response. To a certain extent passive immunisation overcame such immune suppression. Antigenic determinants recognised by monoclonal antibodies have been shown to be glycoproteins. **Antibodies**

did not cross-react with human non-neural cell lines or normal fetal and adult human brain tissue and thus appear to be different from those reported in the literature (Sharma et al 1988).

Other Investigations

Bachhawat and coworkers conducted a series of investigations on glycosaminoglycans of the nervous tissues. They fractionated the glycosaminoglycans of human brain and showed that it contains hyaluronic acid, chondroitin 4-sulfate, dermatan sulfate, heparin sulfate and two unidentified low sulfated compounds (Singh et al 1968). Similar studies have also been carried out on brains of different species (Singh et al 1969). In the spinal cord and peripheral nerve of the monkey, glycosaminoglycans containing uronic acid have been identified (Chandrasekharan and Bachhawat 1969). Pattabhiraman and Bachhawat (1964) studied the regional distribution in the various areas of the brain of uridinediphosphoacetyl glucosamine pyrophosphatase, N-acetylglucosamine kinase and gluccosamine-6-phosphate deaminase -enzymes associated with aminosugar metabolism. Their results showed the importance of these enzymes in maintaining regional concentrations of gangliosides. Mary D'Souza and Datta (1986) purified to homogeneity a hyaluronic acid binding protein from normal rat brain. Hyaluronic acid is now believed to be involved in cell-cell interactions, tissue remodelling and morphogenesis.

Generation of H_2O_2 by mitochondria is an important physiological process but this reaction could not be shown *in vitro* with sucrose-Tris buffers until now. Patole et al (1988) demonstrated generation of H_20_2 by brain mitochondria using succinate and glycerol-1-phosphate as substrates in phosphate buffer. This system was shown in the brains of a number of species, the maximum levels being in the cerebellum.

Vertebrate CNS contains several neuroglial cell types with specialized functions. To facilitate the study of these functions, it will be necessary to devise methods for the isolation of a given cell type in pure form. With this aim, Chatterjee and Sarkar (1984b) devised a procedure for the isolation of protoplasmic astrocytes involving controlled trypsin digestion of the tissue and percoll gradient centrifugation. They obtained 97-98% pure populations of intact protoplasmic astrocytes. Chatterjee et al (1987) have also developed five monoclonal antibodies against neuronal cell surface antigens by immunoaffinity chromatography. These will be of potential use in the isolation of neuronal sub-populations.

Overview

Beginning in the early sixties, neurochemical research in India has made

many significant contributions to our understanding of the nervous system. During the past two and a half decades, over five hundred publications have emerged from Indian laboratories. Even a selected reference to the more significant findings described in this article resulted in a bibliography of over three hundred published papers. Many important questions have been addressed and the investigations cover many areas. These were broadly classified into eleven areas. In the field of nucleic acids and proteins, the investigations on the RNA metabolism in the convulsive state, the relation between protein content and sensory stimuli and on the role of DNAases in the developing and ageing brain are noteworthy. The experiments on the stability of ribosomes on drug treatment, particularly with cannabis are very interesting. Significant contributions were made to the biochemistry of the neurotubule protein, tubulin and on the role ofthyroid hormone. The lipids of the nervous tissue (particularly the metabolism of ethanolamine plasmalogens, the main phospholipid components of the myelin membrane) have been extensively studied. That polyphosphoinositides exist as a metabolically active pool and as an inert pool in brain is a significant finding. Studies on lipid peroxidation have provided new leads to the understanding of role of lipids in neural membranes. A major area where Indian laboratories have made substantial contributions is the metabolism of sulphated compounds. Many enzymes have been purified from nervous tissues using simple and novel methods. The investigations on acetylcholinesterase and its associated other enzyme activities added new knowledge. Ammonia toxicity in nervous tissue and urea cycle enzymes have been thoroughly investigated.

In the area of neurotransmitter receptors, the ontogeny of cholinergic muscarinic receptors and dopamine receptors in human foetal brains was determined contributing significantly to the neurobiology of developing human brain. Similarly, important investigations were reported on the opiate receptor. Studies on acupuncture and on sleep-wakefulness states are pioneering. Several investigations were made on the effect of drugs and toxins on brain and the most important of these were on the neurotoxin from lathyrus sativus. Nutritional effects, particularly malnutrition, on the developing brain has been studied in considerable depth and the adverse effects of malnutrition were amply demonstrated. More recently investigations on the molecular biology of myelin were initiated and already some very useful insights into the process of myelination were obtained. It mat be hoped that future research effects will be directed towards understanding challenging phenomena such as myelination, synaptogenesis, structure and function of receptors, learning, memory and the biochemical basis for complex behaviour.

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Biochemistry and molecular biology of ageing of the brain

M.S. Kanungo

Introduction

The activities of all organisms deteriorate after attainment of adulthood. The elucidation of the basic mechanism of this process, which is one of the frontier problems in biology, shall be a great breakthrough with immense benefits. It may then be possible to manipulate the onset and rate of ageing, and prolong adulthood. Diseases of the brain such as senile dementia, Alzheimer's and Parkinson's diseases and Huntington's chorea, which usually set in after 60, may be postponed. By enabling individuals to enjoy health over a longer period, such research will 'add life to years'.

There has been a rapid increase in the average human life span in all countries due to improved economy, public health and medical care. When we gained independence in 1947, the average life span in India was only about 30 years. Now it is 56. (In the developed countries it is around 75.) At present those over 60 constitute about 6.5% of the population in India. By the year 2000, they may constitute 7.5%,and number 75 million in a population of around 1000 million. Such a large, continuously increasing section of the population of old, retired and vulnerable persons will pose a great burden on society. The immensity of this problem can easily be visualised.

Ageing is manifested as a gradual deterioration of function of various organs after attainment of adulthood. The time of onset and the rate of deterioration are different for different organs. The manifestations of ageing are more clearly expressed in postmitotic cells (which stop dividing soon after birth and get terminally differentiated) such as those of the brain and skeletal muscle . An understanding of the types of changes occurring in the genes with advancing age may give an insight into the basic mechanisms of ageing.

It was with this objective that researches on the biochemistry and molecular biology of the ageing process were initiated at the Banaras Hindu University in 1964. Our work on rats has included the study of the changes in the isoenzymes of lactate dehydrogenase (LDH) of the brain, induction

of enzymes, structural and functional changes in the chromatin, and presently, expression of genes. K. Subba Rao and his group in the University of Hyderabad have studied the enzymes involved in the metabolism of DNA of the brain of the chick during ageing. R. Singh and his colleagues in the Jawaharlal Nehru University, New Delhi, have been studying the enzymes involved in neurotransmitter synthesis and the effects of anti-ageing drugs on the function of the brain. M. Hasan of Aligarh Muslim University works on electron microscopic and histochemical studies of the age pigment of the rat brain. S.P. Sharma and his colleagues (Guru Nanak Dev University, Amritsar) are studying the enzymes of insects during ageing. S.P. Sharma of Kurukshetra University studies histochemical changes in the rat. Ageing is taught as a topic at the M.Sc level at the Banaras Hindu University and as a course at the M.Phil. level at Guru Nanak Dev University, Amritsar.

Changes in enzymes of the brain

We have carried out extensive studies on several enzymes of the brain. The brain is a highly aerobic organ as its cells, especially the neurons, cannot withstand the absence of oxygen for more than a few minutes. When oxygen supply to some regions of the brain is cut off as by a clot, M4-LDH, one of the five isoenzymes of LDH, converts pyruvate to lactate and helps in the supply of energy to the cells by anaerobic glycolysis. We have shown that the level of M4-LDH decreases significantly in the brain of the rat with advancing age (Kanungo and Singh 1965; Singh and Kanungo 1968). The availability of energy to the cells is reduced. Their capacity to withstand the absence of oxygen decreases and they may die. This may be the reason for the higher frequency of infarction from strokes in old age. The decrease in M4-LDH may be due to a decrease in the expression of the gene for the M subunit of LDH.

Choline acetyl transferase (CAT) is essential for the synthesis of the cholinergic neurotransmitter (NT), acetylcholine (ACh), from acetyl-CoA and choline. Its deficiency has been implicated in the causation of Alzheimer disease (AD), a brain disorder of old age in which cognitive functions and recent memory are impaired, and disorientation, emotional lability and irritability are common. The level of CAT is significantly lower in AD, especially in the nucleus basalis of Meynert (nbM). This may be due to the death of neurons in the region (Coyle et al, 1983). Our studies show that the level of CAT is nearly 60% lower in the cerebral cortex of old rats. However, intraperitoneal administration of sex steroids, 17beta-estradiol and testosterone, 10 micrograms/100 g body weight, to ovariectomized old rats raises the level of CAT to that of the adult. (James and Kanungo, 1978) Sex steroids act by binding to specific protein receptors in the nucleus. These then bind to promoter regions of specific genes. This causes stimulation of transcription of the genes. Analysis of 17B-estradiol receptor in the brain showed that the high affinity receptor level decreases

with age (Kanungo et al, 1975). It is likely, therefore, that concomitant decrease in transcription of genes occurs as the rat ages. This may lower the levels of enzymes which are coded by these genes and is in line with the recent finding that continuous intracerebral infusion of the nerve growth factor (NGF) to old rats over a period of four weeks partly reverses the atrophy of cholinergic neurons and improves their memory and behaviour (Fischer et al, 1987).

Another interesting age-related change occurs in acetylcholinesterase (AChE). This enzyme has a circadian rhythm in the brain of the rat. In the immature rat, its activity is highest at 6.00 A.M. and lowest at midnight. In the adult, its activity is highest at midnight and lowest at 6.00 A.M. This may be correlated with the high activity of adult rats at midnight and low activity during the day (Moudgil and Kanungo 1973).

Pyruvate kinase, an important enzyme of the glycolytic path, shows age and sex-related decrease in the cerebral hemisphere of the rat (Chainy and Kanungo, 1976,1978). Orchiectomy and ovariectomy decrease its level in male and female rats respectively, the decrease being more in the latter. 17B-Estradiol raises its level, especially in the female. Testosterone does not produce similar changes.

Several proteins responsible either for synthesis of neurotransmitters or their action are also found to be reduced in the brain of rats with advancing age. For example, both tyrosine hydroxylase (needed for the synthesis of epinephrine) and beta-adrenergic receptor (that binds to (-) 3H-dihydroalprenolol, an antagonist of NEp) decrease with increasing age in the rat (Paulose and Kanungo 1982). Likewise, both acetylcholinesterase (AChE) and the muscarinic receptor in the synaptosomal fraction that is measured by 3H-atropine binding are found to be reduced (James and Kanungo 1976,1978). Ornithine decarboxylase, the rate limiting enzyme in the polyamine biosynthetic path and polyamines spermine and spermidine, which are required for cellular growth and differentiation, are found to be reduced (Das and Kanungo 1982).

To see if the enzymes synthesised in the old are structurally the same as those in the young, they were purified from young and old rats and studied as regards their kinetics, antigenicity and peptide mapping. No differences were seen in any of these parameters (Kanungo and Gandhi 1972). Since the primary structure of these proteins does not change with age but their levels drop, this can only be due to the changes in the expression or transcription of the genes coding for them.

K. Subba Rao and associates have been looking at the changes in DNA, RNA and protein and the levels of certain enzymes concerned with DNA metabolism in the brain of the chick. There is a definite increase in the DNA content in old age as compared to that in the adult and the young.

Further, two DNases, one with an optimum at acidic pH and another at alkaline pH show changes in their activity with age. The acid DNase shows highest activity during the embryonic stage of the brain with a precipitous decrease in its activity during postnatal life and further progressive decrease in old age. On the other hand, the alkaline DNase, has high activity not only in the early stages of life, but also in old age (Srivastava and Rao 1975). These early experiments were later extended to different regions of the brain (Rao and Srivastava 1979) and different cell fractions (neuron, astroglia and oligodendroglia) isolated from different ages (Rani et al 1983; Rani and Rao 1986). These studies show that acid DNase may have a role in DNA-replication while alkaline DNase may have a role in DNA repair process that continues in cells with no relation to DNA-replication. The work with isolated cells (Rani and Rao 1986) also shows that the increase in DNA content in the aged brain is probably due to proliferation of glial cells in old age and not polyploidy.

Acid DNase was purified to homogeneity from the brain of both young and old chicks and its properties studied (Singh et al 1982). Many of the properties of 'young' and 'old' enzymes were similar. However, the 'old' enzyme showed a markedly reduced specific activity. Circular dichroism spectra of the enzyme indicate that the 'old' acid DNase molecules are more rigid and have a more helical structure than the 'young' enzyme. This suggests that the decrease in specific activity of the 'old' enzyme may be due to conformational changes in the enzyme molecules (Singh and Rao 1984).

The possible roles of the two DNases in DNA-repair and the changes in their activities have also been examined in the rat. The observations made on the chick brain were confirmed. Acid DNase is seen to be involved in RNA replication and alkaline DNase for DNA repair that occurs throughout life, especially in old age (Rao and Rao 1982a; Rao and Rao 1982b; Rao and Rao 1984). In line with the high alkaline DNase activity in the old brain, a second peak of DNA polymerase activity, generally considered to be a repair enzyme, was also noticed around 1-1/2 years of age in the rat (Rao and Rao 1984) showing that DNA repair activity remains at a significant level even in the old brain. That the old brain possesses good DNA repair machinery not only in terms of quantity but also in quality, has been demonstrated by assaying the fidelity of neuronal DNA polymerase. The fidelity of mouse neuronal DNA polymerase was studied using a natural template (an amber mutant of 0 x 174). It was observed that there was no age-dependent decline in the fidelity of this enzyme, although the enzyme is basically error prone, making one mistake in 5000 in selecting the complementary base (Rao et al 1985).

Further studies on DNase and DNA repair in the brain show that the so called acid DNase is actually an enzyme that only attacks native DNA or that irradiated by ultraviolet light while alkaline DNase prefers either the

single-stranded DNA or depurinated DNA. The activities of these enzymes along with that of DNA polymerase (as markers of DNA repair) in cells isolated from young and old brain and challenged with mutagens in vitro are being measured. Rameshwar Singh and associates have been studying age-related changes in the levels of anti-oxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, glucose-1-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase) in various regions and sub-cellular fractions of the brain of the rat during ageing (Roy and Singh 1983; Roy et al 1983; Roy et al 1984). The enzymes of the particulate fraction are more age-sensitive than those of soluble fraction. Catalase activity is not affected by age. Lipid peroxidation and accumulation of age-pigment in different regions of the brain depend on the levels of the activities of the anti-oxidant enzymes.

Changes in chromatin of the brain

Our findings on enzymes led us to the study of the chromatin (which is a complex of DNA and chromosomal proteins, histones and non-histone chromosomal (NHC) proteins) and houses the genes. Histones with positively charged amino acids, lysine and arginine, are bound to the negatively charged phosphate groups of DNA at physiological pH. The expression of genes, that is, transcription of messenger RNA from DNA, requires that histones dissociate from DNA transiently. Covalent modifications such as acetylation, phosphorylation and ADP-ribosylation of histones decrease their net positive charge and dissociate them from DNA. This is supported by the finding that when histones are acetylated, transcription increases. When nuclei from the cerebral cortex of young and old rats were incubated with 3H-acetyl-CoA, the degree of acetylation was significantly lower in the old. Also. transcription, as measured by the incorporation of 3H-UMP into RNA, was lower. Thus, chromatin becomes increasingly compact in the ageing brain cells. This is expected because the neurons stop dividing in the rat at around day-14 after birth. No DNA synthesis occurs after day-14 except for DNA repair. This may account for the lower transcription and lower enzyme levels in old age (Thakur and Kanungo 1978; Kanungo and Thakur 1979).Compaction of chromatin of the brain has been further probed by digesting it by the endonuclease DNase I, that cleaves the chromatin DNA at intervals of 10 base pairs (bp) and its multiples. 10 and 20 bp fragments are far less common in the old as seen by polyacrylamide gel electrophoresis (Chaturvedi and Kanungo 1985a).

Compaction of chromatin-DNA with advancing age was also studied by nick-translation in which nicks (cuts) were produced in the DNA by an endonuclease. Subsequent incorporation of 3H-dCMP into the DNA was measured in the presence of DNA polymerase I and other dNTPs. Such measurements show that the incorporation of 3H-dCMP after DNase I digestion is far less common in the old. Nick-translation was also studied

after digesting the chromatin DNA by the restriction endonuclease (RE) Eco RI, that cuts DNA in the palindromic sequence 5'GAATTC3'.

The number of such sequences does not change with age. Incorporation of 3H-dCMP after Eco RI digestion is nearly 50% less common in the old. Incorporation measured after digestion with the REs, Msp I, that cuts DNA at 5'C^mCGG3'and 5'C^CGG3'sequences, and Hpa II that cuts at only 5'C^CGG3' is also far less in the old. The difference in the incorporation after Msp I and Hpa II digestion is significantly higher in the old. It shows that 5'CCGG3' sequences get methylated to 5CmCGG3' with increasing age. Higher methylation of DNA has been correlated with higher compaction of chromatin. Increasing methylation of cytosines in the DNA may contribute to increasing compaction of chromatin in old age. This may decrease the expression of genes (Chaturvedi and Kanungo 1985b) and lower the levels of enzymes in old age.

The above findings have been supported by the recent studies on the methylation of repetitive DNA sequences (RDS) of the genomic DNA of the brain of 15 and 88 week old rats. Digestion of the DNA by methyl-sensitive REs, HPaII and MspI show that mCpG and mCpC doublets are more, not only in the CCGG sequences but also in the entire genome of the old brain. Such increasr in DNA methylation may alter chromatin conformation and gene expression in old age (Rath and Kanungo 1989).

Changes in gene expression

Whether or not gene expression actually changes with age has been studied by us using genetic engineering techniques. Poly-A+ mRNA was purified from the brain of young and old rats. Plasmids carrying the genes for thymidine kinase (TK) and NGF were end-labelled with 32P and hybridized to the mRNA by northern and slot blot. It is seen that the mRNA levels for TK and NGF genes in the brain decrease with increasing age. TK is essential for DNA synthesis. Its decrease may be the reason why DNA synthesis stops early in the brain. NGF is essential for the growth of sympathetic nervous system. Its decrease may reduce the regenerating capacity of this part of the nervous system (Kanungo et al 1988).

The reason for the lower expression of the NGF gene of the brain in old age has been analysed by Southern hybridisation (Singh 1988). Genomic DNA was digested by DNase I and resolved by gel electrophoresis. 32P-labelled NGF gene was hybridised to the DNA fragments. The gene is less DNase I sensitive in the old. Also, digestion by MspI and HpaII followed by Southern hybridisation show that the gene is more methylated in the old.

These facts support the gene regulation theory of ageing (Kanungo 1975,1980) which proposes that sequential activation and repression of

genes are responsible for growth, differentiation and attainment of adulthood. The expression of genes is modulated by gene products. Specific levels of various gene products are necessary for maintaining the homeostatic functioning of genes required for adulthood functions. As a result of reproduction, various types of stresses and malnutrition, some gene products such as steroid hormones are depleted. The organism may be unable to replace them. It may also be unable to get rid of factors like the components of age pigment which then accumulate. These destabilize the homeostatic functioning of genes and result in the repression of some and stimulation of others. Certain undesirable genes such as oncogenes may get expressed. A gradual deterioration of various functions follows and manifests as ageing. This explains the variability in ageing seen not only in the brain, but in all organs and the organism as a whole. Ageing is not programmed. It is due to the breakdown of the homeostatic functioning of genes. Steps that can prevent this destabilization may prolong adulthood or defer the onset of old age.

Even though the proto-oncogenes, c-myc and c-fos, are necessary for cell growth, proliferation and differentiation in the early period of development, their uncontrolled and over-expression have been implicated in tumour formation. Slot-blot studies using ^{32}P labelled c-myc and c-fos genes show that their expression is greatly increased in the old brain. This may be one of the reasons why the frequency of brain tumour is higher in old age. On the other hand, the expression of proto-oncogenes, c-Ha-ras, c-mos and c-abl, is lower in the old brain (Rath 1988).

Age pigment in the brain

Rameswar Singh and associates have studied the neurochemical mechanisms of action of drugs known to have anti-ageing effects. The effects of dimethylaminoethanol, centrophenoxine, and chlorpromazine with particular reference to antioxidant enzymatic system, membrane lipid peroxidation and age-pigment accumulation were examined. These drugs were seen to produce their antiageing effects by activating antioxidant enzyme systems (and inhibiting the formation of age-pigments, preventing or reducing lipid peroxidation) in the brain or by preventing age-related decline in the activity of the enzymes. This has elucidated the mechanism(s) for the removal of the age-pigment by these drugs.

Anti-ageing influence of the well known psychotropic drug, chlorpromazine, suggests that the improvement it produces in psychiatric disorders may be due to its anti-lipidperoxidation and anti-lipofuscin effects. (Roy et al 1983, 1984; Singh and Mukherjee 1972)

Electrophysiological studies of the ageing brain

Changes in electroencephalographic activity and multiunitary action

potentials due to ageing were examined and their response to treatment with the anti-ageing drug centrophenoxine were investigated. The drug prevented age-related deterioration of the electrophysiological function of the brain. (Roy and Singh 1988) This effect is probably due to effects of the drug on the membrane.

Experiments were also conducted to determine the nature of the deterioration of neurotransmitter systems in the ageing brain. Age-related increases in the imbalance between inhibitory and excitatory neurotransmitters were seen. Pharmacological data showed that age-associated deterioration of neurotransmitter metabolism can be corrected by the use of drugs: vincamine and centrophenoxine.

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Neural transplantation

Gomathi Gopinath

Neural transplantation at All India Institute of Medical Sciences, New Delhi

Introduction

We were stimulated by the reports of A. Bjorklund and G.D. Das (at the First Congress of the International Brain Research Organisation held at Lausanne, Switzerland in 1982), showing that embryonic neural transplants not only grow and differentiate in the brain of adult rats but also help in the recovery of lost function in damaged regions of the brain and the kind offer of G. D. Das of Purdue University, U. S. A. to teach his techniques at different centres in India. With financial support from the Biotechnology Board (now the Department of Biotechnology) of the Department of Science and Technology (DST), Government of India, we arranged for a national workshop conducted by Professor Gopal Das in 1985. Soon after work was started in our laboratory. Based on our preliminary experience, DST was approached to create a national facility for research and training in this field. Under their programme of "Intensification of Research in High Priority Areas" (IRHPA) such a unit was sanctioned under Professor P. N. Tandon in 1986. A multidisciplinary team consisting of neurosurgeons (P.N. Tandon, A.K. Mahapatra), neuroanatomists (Professor G. Gopinath) and neurophysiologists (Professors U. Nayar and V. Mohan Kumar) was constituted. Several other faculty members have later joined the team.

The main aim was to initiate research in neural transplantation and impart training so that several centres for such work could be started in the country.

To start with neural transplantation was standardised in different areas of the brain in rat using embryonic neocortex. Following the standardisation of the technique and the morphological investigations of the transplants in rat, the method was standardized in primates.

Reports of recovery of specific lost functions after graft therapy prompted

a closer look at the long-term behaviour of such transplants especially since the recovery reported so far is partial and transient. Moreover, neurobiological explanations even for the transient recovery are not determined so far. Donor tissues for these studies are obtained from adrenal medulla and fetal substantia nigra and are used currently for trials in experimental models of Parkinson's disease and in patients with this disease.

Further work has been initiated to produce a model of Parkinson's disease in rhesus monkey. Nigral cells are studied at different periods after treatment with MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine). The model is also used to evaluate the quality of recovery following transplantation of fetal substantia nigra.

Behavioural and electrophysiological studies are also underway in rodents after kainic acid-induced lesions of preoptic area and caudate nucleus and with lesions and transplants.

Material and methods

Stock-bred Wistar rats are used in the study of rodents. Dated fetuses are obtained by programmed breeding of the rats. This is achieved by examining the vaginal smear after caging the male and female together overnight. In most of the experiments conducted, 15-17 day old fetuses were used unless otherwise mentioned. Hosts are 4-10 months old rats except in some experiments where neonates are used.

Donor tissue is taken from fresh embryos removed from the mother after anaesthesia. The embryonic brain is removed immediately and immersed in chilled Ringer's lactate solution. The meninges are carefully removed along with the blood vessels to avoid contamination of the graft with connective tissue. The area to be transplanted is then aspirated into a glass capillary needle attached to a syringe. The capillary tube is calibrated so that the volume of the embryonic tissue can be determined. In some experiments tissue is taken in glass capillary tube connected to a Hamilton syringe through a polythene tube to enable direct measurement of the volume and for convenient handling of the capillary tube with the donor tissue. The injection of the donor tissue is carried out either directly or indirectly using stereotaxic coordinates depending on the sites at which transplantation is done.

For standardisation of the technique embryonic neocortex was transplanted into the cerebellum, lateral ventricle, third ventricle, striatum, hippocampus, tectum and the anterior chamber of the eye in rat.

For lesion studies in rat, 0.8 and 3 microlitres of kainic acid are injected into preoptic area and striatum respectively to destroy neurons. The behavioural deficits are recorded before transplanting tissue from the same

areas from the embryo. Following transplantation behavioural and electrophysiological studies are done.

Fetal substantia nigra and adrenal medullary chromaffin cells are transplanted into the intact and lesioned striatum, lateral ventricle and anterior chamber of the eye for following up the long term behaviour of these cells. Both autografts and allografts are used in case of the medullary cells.

A monkey colony for breeding was first established with cycling female monkeys. They are allowed to mate only after confirming regular cyclicity by examination of vaginal smear. Vaginal smear is tested for sperm positivity after mating for dating the fetus. The pregnancy is further confirmed by rectal palpation on the 30th and 40th day after positive vaginal smear. On the day of transplantation the pregnant monkey is anaesthetised and the fetus of the desired date is delivered by Ceasarean section under aseptic conditions. The CR length of the fetus is determined before removing the brain. The brain is immersed in chilled Ringer's lactate and tissue obtained for transplantation as described above.

In rhesus monkey, transplantation was done in striatum, neocortex and the cerebellum for standardisation. Fresh and preserved neocortex was used as donor tissue. For preservation, tissue was either frozen at sub-zero temperature or incubated in tissue culture medium for 4 days. Difficulty in the preparation of a sufficient number of hosts at a time has necessitated preservation of tissues.

To produce an experimental model of Parkinson's disease in monkey, either systemic or unilateral intracarotid injection of 1 methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) was done. Intramuscular injection of MPTP at a dose of 0.5 mg/kg body weight for 5 days was repeated at an interval of 10-15 days till signs of Parkinsonism developed.

Because of the problem of maintaining the total Parkinson models, a hemiParkinson model has been produced by injecting MPTP (1.75 mg/kg body weight) in a single intracarotid dose or in 3 doses on consecutive days.

After standardising the signs and symptoms in these animals over 4-12 weeks, transplantation of the fetal substantia nigra into the striatum is done using stereotaxic coordinates. Fetal nigra is taken from animals at gestation periods of 45 to 60 days.

In another experiment a block of motor cortex representing the upper limb is removed using electric cautery before transplanting the same area of the fetal cortex.

For morphological investigations techniques used are:
1. Nissl stains for cytoarchitecture.
2. Electron microscopy (EM) studies.

3. Golgi stains for detailed morphology of the individual neurons.
4. Fluorescence for catecholamines using glyoxylic acid.
5. Immunohistofluorescence and immunolabelling using peroxidase-antiperoxidase technique. Antisera against the relevant neurotransmitters and neuropeptides specific to the transplanted neurons are used.
6. Immuno-gold labelling to localise the neurotransmitters and neuropeptides in the neuronal cytoplasm and synapse under EM.
7. HRP labelling for neuronal tracing and connectivity.
8. Quantitation using automatic image analyser for neuronal size, density and neuron/glia ratio in the transplant.

Observations and conclusions

Standardisation of technique in rat

There was 85 to 90% survival of transplants grown from embryonic neocortex at various sites in the rat brain. The transplants in the host cerebellum, striatum were of smaller size than transplants in the ventricle or the eye chamber till the end of the 4th month. Lamination, normally seen in the adult neocortex, was clearer in ventricular and ocular transplants than in transplants grown at other sites in the brain. Most of the neurons in all the transplants matured to show phenotypical characteristics. Though there was an apparent integration between the transplants and the host tissues without the interference of glial scar, very few processes were seen bridging the two. Neuropil in the transplants was very well developed showing all the characteristics of the adult cortex including synapses. As the age of the transplants advanced some of the neurons became hyperchromatic- an indication of early degeneration. These findings showed that allografts survived and matured heterotopically and for the morphological maturation of these neurons specific afferent input was not required.

Neocortex of 13th gestation day was transplanted into the anterior chamber of the eye in one set of adults. They developed isolated patches of tissue resembling retina in the maturing neocortex graft. During the early days mitotic figures were seen in the outer nuclear layer of the retinal tissues, which raised doubts that the retina could have developed from the embryonic neocortex and not from invasion by the host retina since it has been categorically shown that beyond 12th postnatal day mitosis is absent in the rat retina. Moreover the photoreceptors were very prominent and bulbous in appearance and pigment epithelium was absent. As the age of the transplant advanced the neuronal components of the retina slowly disappeared leaving only isolated patches of photoreceptors and outer nuclear layer by the 90th day after transplantation. These findings have been reproduced and investigations are on to confirm the genesis of the retina.

Kainic acid lesion in rat

Different doses of kainic acid were injected to produce a standardized lesion in the adult striatum before transplanting embryonic striatum. It was found that 3 microgrammes of kainic acid produced a satisfactory lesion without significant mortality in rats. Successful striatal transplants are grown from embryonic striatum at the lesion sites in these rats. These transplants are being used for electrophysiological recording to investigate the neuronal characteristics.

Kainic acid, in a dose of 0.8 microlitre, produced neuronal death in the medial preoptic area of the adult rats. Following such lesions, persistent cornification of the vaginal epithelium and lower resting body temperature were recorded. These rats showed steeper rise in body temperature on exposure to hot environment compared that in the prelesion state. After transplantation with embryonic preoptic area/anterior hypothalamus, improvement was seen within 5 to 40 days. Estrous cycle was resumed and the basal body temperature returned to prelesion levels. After 80 to 90 days of transplantation increase in body temperature on exposure to hot environment was also much less in these rats. These models are now being used for electrophysiological investigations of the transplanted neurons.

Long-term investigations of the transplants grown from fetal substantia nigra and adrenal medulla (allografts and autografts)

1. Substantia nigra

a. In the anterior chamber of the eye: There was 80% success rate at this site. Only a few rats showed complications like corneal opacity, cloudiness, or cataract and such rats were not included in the study. The size of the transplant continued to increase till the end of the first month and thereafter remained more or less stationary. Our study with 17 to 21 days old embryos showed that the tissue from younger embryos achieved the best size, but the size of the individual transplant varied making it difficult to obtain a linear growth pattern, even though fixed amount of the donor tissue has been used for transplantation.

Many of the transplants had the cytoarchitecture of the normal intact substantia nigra showing compact and reticular divisions. The neurons of the fetal nigra matured and increased in size till the end of the first month. When the size and shape of the neurons in the transplants and that of the age-matched control were compared using an automatic image analyser it was found that there was no significant difference. A large number of myelinated and unmyelinated fibres and synapses were present in the transplant in addition to the dendrites, glia and glial processes. Most of the synapses had clear round vesicles and morphology typical of the

intrinsic connections of the normal substantia nigra. Many of the axons and synapses showed dense core vesicles of noradrenergic type mixed with the clear type.

A significant number of neurons fluoresced for monoamines. Immunogold labelling after treating with antidopamine serum demonstrated a few dopamine positive cells and dendrites. HRP introduced into the anterior chamber was picked up by a large number of neurons showing retrograde axonal transport. In Golgi-stained preparations the neuronal morphology was comparable to that of the intact substantia nigra, but the dendritic processes were wavy and curved and remained in the vicinity of the perikarya.

Glial cells were randomly distributed and the oligodendroglial cells were seen in close association to the myelinating axons. Blood vessels were restricted to the periphery.

In addition to the normal features already cited, there were some observations which were not commonly encountered in the normal substantia nigra. Closely opposed double neurons with gap junction could be seen randomly distributed in the transplants. From 60 to 360 days, the period studied so far, an increasing number of neuronal soma and dendrites showed clear spaces in the cytoplasm. There was a concurrent decrease in the total and fluorescing neurons in the transplant.

b. In the lateral ventricle: In this region too,the success rate of the transplant was 80%. As in the anterior chamber, nigral cells from 16-17 gestation days gave the best results in the ventricle also. The transplants gained attachment to the ventricular wall and not to the choroid plexus without showing preference to any particular site in the ventricle. No attempt was made during transplantation to deposit the tissue in the ventricular wall. Ependymal proliferation was noticed at the site of attachment. Transplants 30-90 days old had closely packed neurons and as the days advanced the neurons were more dispersed. At 270-360 days transplants showed a number of shrunken neurons with pyknotic nuclei. Number of fluorescing neurons and the intensity of fluorescence decreased as age advanced. Tyrosine hydroxylase positivity was demonstrated in many of the neurons till 360 days.

Neuronal processes were seen between the host tissue and the transplant. Dendritic spread of the individual neurons was much better in these transplants. The unusual features seen in the anterior chamber were also seen in relation to the neurons in the ventricular transplants.

c. In the striatum: The rate of success here was less than at the other sites. The size of the transplants was comparatively much less making its identification difficult. Many of the features already described were seen

at this site too. Immunolabelling with antiserum against tyrosine hydroxylase demonstrated a large number of positive neurons till the end of the 12th month in the transplants and in isolated neurons in the adjacent regions of the host striatum. HRP injected into the neighbouring region of the host striatum was picked up by neurons in the transplants confirming extension of processes into the adjacent host tissue from the transplants.

Conclusion

Embryonic nigral cells survive and mature and achieve phenotypical features irrespective of the sites of transplantation and the age of the host. In the absence of the specific afferent input, maintenance of the neurons may be influenced by the intrinsic connections mutually established by neurons of the transplants. Degenerative changes in the older transplants suggest that continued survival of the neurons is dependent on the native environment rather than the artificial medium provided. Migration of the nigral neurons into the target striatum shows the trophic action between nigra and striatum. Establishment of synaptic connectivity still needs to be explored.

2. Adrenal medulla

a. In the anterior chamber of the eye: 80% of the transplants survived at this site and vascularisation took place during the first week at the end of which the size of the transplant reduced. Chromaffin cells were comparable to intact medullary cells in all the cytological details and monoaminergic content till the 90th post transplantation day. The compact arrangement of the cells slowly disappeared and small clusters were seen instead with spaces in between. Beyond the 90th day of transplantation the number of chromaffin cells reduced gradually and the ones present were in close association to the sinusoids developed in the transplant. Many of the cells had assumed elongated shape with short, fine processes. The aminergic vesicles also started degenerating in the cells present in the transplant.

A few of the allografts showed lymphocytic infiltration and more rapid degenerative changes and decline in cell number. In the autografts lymphocytic infiltration was absent. Degenerative changes and cell loss appeared much later and progressed very slowly.

b. In ventricle and striatum: Chromaffin cells from the allografts lasted till 180 days, after which only connective tissue was visible at the site of transplantation in the ventricle. In transplants from autografts, cells were slower to disappear. The intact cells fluoresced. Very few cells identifiable by monoamine fluorescence were retained in the striatum.

Conclusions: Chromaffin cells are unable to survive for long in an alien

environment. These cells had not developed any neuronal morphology as claimed by earlier workers.

Studies in primates: Before standardising the technique in primate using neocortex as the donor tissue, it was necessary to determine the gestation day at which sufficient number of dividing cells and immature migrating neurons ideal for transplantation were available in the cortex. Neocortex between 50 to 100 gestation days was studied and a mixture of dividing and immature neurons was seen during the period of 50 to 70 days. On transplantation of fresh and preserved neocortical tissue at various sites in the adult host brain, we found that only two hosts with preserved donor tissue had surviving transplants in the striatum. Many of the neurons remained rather immature 4 months after transplantation, showed multiple nucleoli and were not comparable to neurons of the neonatal period. Neuronal clusters were frequent and no proper integrations were visible between the transplant and the host except for a very few fibres.

Conclusion: Our preliminary studies have indicated that transplantation in higher mammals especially primates may not be as feasible as it is in rodents. Fresh embryonic tissue had not survived in any of the host monkeys.

Following the initial studies in the primate it was decided to produce lesions before transplantation. Since Parkinson model in primate was already established by others it was decided to produce this model in rhesus monkey for transplanting nigral cells into the striatal region.

Animal model of Parkinson's disease

Adult rhesus monkeys developed rigidity, akinesia, and apathy within a week of injecting MPTP. Subsequently intermittent tremor of the forelimbs could also be seen. The condition of some of the animals deteriorated. They needed to be fed during the 2nd and 3rd week. By 4th week, 3 of the 4 monkeys improved sufficiently to handle food while one had to be sacrificed. In this monkey most of the nigral neurons on both sides had degenerated. Another monkey which had improved also had the same type of nigral morphology as the previous one, showing that signs did not depend on the histological nature or the aminergic fluorescence of the nigral neurons.

Of the two monkeys transplanted with nigral neurons from fetuses at the 50th gestation day, one died within 3 days and the other one was sacrificed after 100 days. Both had cluster of aminergic neurons at the transplanted site in the striatum. The monkey which survived for 100 days had recovered from many of the symptoms except from occasional tremor. Movements were still slow and clumsy compared to the prelesion period. The condition of the substantia nigra was the same as the other MPTP treated monkeys.

Because of the difficulty in maintaining the total Parkinson model it was decided to produce hemi-Parkinson monkeys by injecting MPTP into the carotid unilaterally. These animals developed rigidity, and akinesia of the opposite side of the body within 2 weeks after injection. Two animals were sacrificed after 8 weeks to study the substantia nigra. Nigral cells of the control side was comparable in cytological appearance, number and fluorescence to the nigra of control monkeys which had not received MPTP injection. Nigra from the injected side showed few normal cells among the degenerating neurons.

One hemiparkinson monkey was transplanted with nigra from a fetus of the 50 gestation day and one with neocortex alone. The monkey with nigral transplant started showing improvement after one week while the other had to be sacrificed due to complications. The latter monkey and the former after 8 weeks of transplant had normal nigral cells on the control side and a large number of hyperchromatic degenerating cells on the injected side. Fluorescing aminergic neurons were present in the striatum of the monkey transplanted with fetal nigra.

Conclusion: From these studies it is not clear whether the improvement in these models are due to the transplanted neurons or because of the nigral neurons still remained inspite of MPTP treatment.

Future plan

1. Electrophysiological studies are to be standardized.
2. Detailed studies of medullary and nigral transplants to explore host-transplant interaction.
3. Behaviour of medullary and nigral cells when transplanted at sites with prior lesion.
4. Studies in primate to be continued.
5. Study of the nature of immunologic reaction of the hosts to transplants.

Neural transplantation at National Institute of Mental Health and Neurosciences, Bangalore: (Kavitha Murthy et al 1989)

To understand whether the apparently normal neurons of transplants are really normal and how far they are deviant from normal, quantitative assessment of neurons was initiated following transplantation of fetal hippocampus into the neocortex of neonatal rats.

Materials and methods

Hippocampal tissue from fetus at 18 gestational day was transplanted into a freshly made cavity in the frontal neocortex in neonatal rats aged 18 days. Grafts were studied after 2,3 and 5 months after processsing by rapid Golgi technique, Nissl stain (cresyl violet), histo-fluorescence and ethanolamine phosphotungstic acid method. Neuronal morphology, quantitation of dendritic branching pattern such as intersections and branching orders, dendritic spine density of the different types of neurons were assessed.

Observations and conclusions

The grafted neurons generally showed significant deviations from normal native hippocampal neurons. Aberrations were seen in pyramidal and granule cells. Many cells could not be classified into the known type of the hippocampal neurons. There was a significant deficiency in the dendritic branching of the pyramidal neurons, more obvious in the basal than in the apical dendrites. Sometimes apical dendrites of the grafted neurons had even more spines than that of the neurons in the intact hippocampus. The significant deficiency in the number of spines in basal dendrites was primarily due to deficiency in dendritic branches and spines than the intact hippocampal granule cells. The unclassifiable neurons had generally high dendritic branching and spine density when compared to the other neurons of the graft.

Conclusion: Differentiation of the neurons is influenced by different environmental conditions. The transplanted neurons need not necessarily have the characteristics of the intact neurons.

Neural Transplantation at Post Graduate Insitute of Basic Medical Sciences, Madras: (Muthuswamy et al 1987, 1988)

Embryonic neocortex from monkey and human fetuses were transplanted at different sites in adult bonnet monkey (Macaca radiata) to determine the growth potential, survivability and growth of the embryonic tissue in the monkey.

For dated fetuses in bonnet monkey, ovulation was determined by vaginal smear cytology, estimation of the cervical mucous and by palpation method. During the ovulatory phase female and male monkeys were mated overnight. At times artificial insemination was carried out using freshly collected semen from male monkeys.

Embryonic cortical tissue was transplanted into the visual cortex and cerebellum in adult and juvenile monkey recipients. Cell-mediated immunity was assessed by leucocyte migration inhibition test and T-cell

rosette formation test before transplantation and after 7,15,45 and 90 days of transplantation. The animals were sacrificed, the brain sectioned serially and stained with Nissl and silver stains. The area of transplant was reconstructed graphically and quantified morphometrically in order to assess the growth potential of the donor tissue. Embryonic neocortex showed good growth potential in adult and juvenile monkeys with a 10 fold increase in volume and good interface with host brain. There was no cell mediated immunity in the recipients against the donor tissue.

Neocortex from hysterotomy specimens of human fetuses of age group 14 to 18 weeks was transplanted into the cerebellum of bonnet monkey. Monkeys were sacrificed between 15 and 45 days after transplantation. Nissl and silver stains and graphic reconstruction of the transplants from serial sections were carried out as before.

Transplants grown from neocortex of 14 weeks human embryo showed 5 to 10 fold increase in volume while the tissues form older age group attained only 2 to 5 fold increase in size compared to the initial volume of the donor tissue.

The results of these studies indicate that both monkey and human fetal neocortex survived, grew and integrated with host brain of the adult and juvenile monkeys.

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Neuropharmacology

B.N. Dhawan and G.K.Patnaik

Neuropharmacology has been an area of major research interest to pharmacologists in India and several centres of excellence have developed. The effort has been mainly directed toward understanding neurotransmitter regulation of central mechanisms in normalcy and disease and analysis of drug action in term of neurotransmitter mechanisms. Several laboratories have also been involved in developing new drugs. The initial period was used to develop competence. The fruits in terms of research output has been evident after 1970. To adequately cover various areas of work, the review has been arbitrarily divided into five sections. There is, however, a certain amount of inevitable overlap between the sections.

Putative neurotransmitters.
Basic neuropharmacological studies.
Studies on drugs known to be active in the central nervous system (CNS).
Development of new drugs acting on the CNS.
Study of plants showing CNS activity.

Putative neurotransmitters

Acetylcholine

Acetylcholine (ACh), the earliest definitive neuro-transmitter to be identified in the CNS, has been studied with respect to its role in several neural phenomena.

(a) *Analgesia*: The role of cholinergic mechanisms in the production of analgesia has been extensively investigated. Pilocarpine has been shown to produce analgesia in rats (Naik et al 1981). The analgesic effect of morphine is potentiated by neostigmine bromide (Saxena and Gupta 1957a). The antagonism by atropine and hyoscine (Kulshreshtha and Saxena 1957) further confirms a cholinergic link. Muscarinic receptor stimulation leading to release of endogenous opiate peptides resulting in analgesia has been reported by Sharma et al (1980). Methscopolamine significantly reduced the analgesic effect of analgin and methylatropine partially antagonized the effect (Sen et al 1985). These observations indicate an involvement of acetylcholine in nociception. The role of the cholinergic system in the brain in the production of nociception has also been studied by Mohan Rao and Bhattacharya (1989).

(b) *Sleep*: The cholinergic mechanism associated with sleep was analysed by Haranath et al (1967) and Haranath and Indiranarayan (1971). Using perfusion of cerebral ventricle in dogs they showed that the release of ACh was decreased before and at the time of sleep and increased during REM sleep (Haranath and Bhatt 1971,1972).

Haranath and Bhatt (1977) produced sleep by intracerebroventricular (icv) administration of cholinergic agonists. The site of action was localised to structures lining the inferior horn of lateral ventricle.

(c) *Convulsions*: Metrazol induced convulsions in mice involved brain acetylcholine (Rastogi et al 1979). Atropine abolished these convulsions and physostigmine restored the convulsion indicating further a competitive antagonism between atropine and physostigmine. ICV nicotine induced convulsion was also linked to cholinergic mechanism by Saxena et al (1976).

(d) *Central vasomotor control*: Cholinergic involvement in the mediation of pressor and depressor response of drugs through its action on the vasoactive area on the ventral surface of the medulla has been demonstrated by Srimal et al (1977,1980b) and Raghubir et al (1981). The muscarinic cholinoceptors had an inhibitory action on cardiovascular control whereas the nicotinic cholinoceptors at the hypothalamic, medullary and spinal levels played a facilitatory role (Bhargava et al 1978).

(e) *Other studies*: The levels of acetylcholine and acetylcholine esterase activity were studied in the rat brain in starvation and protein restriction (Venkataraman et al 1984,1985).

The possibility of cholinergic mediation in the central integration of emesis was ruled out by Gupta et al (1969). Das and Malhotra (1962) had noticed that the ACh content was reduced during hypothermia.

Catecholamines :

Attention has been focussed on the role of noradrenaline (NA) and dopamine (DA) in view of their selective distribution in large concentrations within the CNS. The development of sensitive techniques for assay of catecholamines has helped greatly. Study of the role of catecholamine and MAO in medoxy-progesterone-acetate-induced changes in brain dopamine levels in rat shows that MAO-B activity is important in the metabolism of dopamine (Gupta et al 1983, Tandon et al 1983).

Analgesia: Singh et al (1976) have analysed the role of dopamine in antinociception. Increase in brain dopamine level after i.p. administration of l-dopa resulted in the production of analgesia. The analgesic action of morphine is potentiated through a dopaminergic link. Saxena and Gupta (1957) showed that the analgesia induced by morphine was potentiated

by ephedrine and amphetamine. More recently Sharma et al (1981a) have shown that analgesia induced by enkephalin is partly mediated through catecholaminergic mechanism.

Central cardiovascular control: Alpha-adrenoceptors have an inhibitory role and beta-receptors an excitatory role in central cardiovascular control in cats (Bhargava et al 1978). Alpha-receptors appear to have a predominant role at the medullary level and the beta-receptors at the hypothalamic level. However, the work of Dhawan and colleagues suggests an excitatory role of alpha-receptors at various brain sites (Dhawan et al 1975a,b; Gulati et al 1978). ICV and intrathecal administration of 6-hydroxydopamine (6-OHDA) in choloralosed cats inhibited reflex as well as direct excitability of the vasomotor loci (Gupta et al 1972). Singh et al (1973) showed that alpha-methyl noradrenaline caused inhibition of central vasomotor loci in cats. It has been suggested that being a weak agonist it acts as an antagonist.

Microinjection of monoamines and some cholinergic agents in the mesencephalic nucleus dorsalis raphe has been shown to modulate cardiovascular activity. The mono-aminergic receptors present in the nucleus dorsalis raphe appear to influence sympathetic preganglionic neurones in the intermediolateral columns of the spinal cord which modulate cardiovascular activity (Saxena et al 1983,1985,1987; Pant et al 1983a-d).

Experimental studies show that for regulation of blood pressure, heart rate and post-coronary ligation arrhythmias, central muscarinic, beta-adrenergic and nicotinic receptors are facilitatory whereas 5-HT and opioid receptors are inhibitory. Central alpha 1 adrenoceptors inhibit baroreflex mechanisms and alpha 2 adrenoceptors facilitate them(Sinha et al 1985; Gurtu et al 1986).

Other effects: Vomiting induced by cardiac glycosides was prevented by catecholamine depleting drugs (Gaitonde and Joglekar 1975). David et al (1977b) have shown involvement of dopaminergic mechanism in acquisition of pole climbing behaviour by isolated weaning rats. This was prevented by treatment with 6-OHDA and haloperidol while apomorphine significantly enhanced the response. Bhattacharya et al (1976b) have shown that the suppression of convulsions, induced by electroshock, by imipramine involves brain noradrenaline. Central noradrenaline is the critical biogenic amine involved in these convulsions in rats. Motor deficits following stroke were shown to be due to the changes in dopamine and its metabolism in the brain (Kuruvilla et al 1986). An excitatory effect of NA has been shown following microiontophoretic application in the cortical neurone of rat by Sharma (1976) and Raghubir and Dhawan (1981). MAO-B activity is important in dopamine metabolism in the brain (Gupta et al 1983). Catecholamines are also involved in thermoregulation. (See the

next section of this review.) Reserpine probably has a direct action on the CT-zone and not through release of catecholamines (Gupta et al 1968).

5-Hydroxytryptamine (5-HT)

The major contributions have been made on its role in sleep, analgesia and convulsions.

Sleep: Bhattacharya and colleagues (1975a) have shown that barbiturate induced hypnosis in rat involved a serotonergic mechanism. PGF1 potentiated hexobarbitone induced hypnosis. This effect was antagonised significantly by PCPA and methysergide (Bhattacharya et al 1973b), which again indicates a serotonergic involvement. Imipramine induced hexobarbitone sleep potentiation has also been shown to be mediated through brain 5-HT (Bhattacharya 1978a).

Analgesia: 5-HT plays an important role in the causation of analgesia by morphine. The antinociception in rat was inhibited by drugs decreasing 5-HT synthesis, those displacing 5-HT from tryptaminergic neurones and by those blocking 5-HT receptors (Bhattacharya et al 1975b). Involvement of brain 5-HT in the antinociceptive action of physostigmine, MAOI, and imipramine (Bhattacharya and Nayak 1978; Bhattacharya et al 1976g,1978), further confirms a serotonergic link in analgesia.

Convulsions: A supportive role of 5-HT in the anticonvulsant action of diphenylhydantion and phenobarbitone has been suggested by Bhattacharya and coworkers (Bhattacharya and Bose 1978; Bhattacharya and Sanyal 1978b; Bhattacharya et al 1978a). PGE1 induced inhibition of metrazol convulsions in rats was also shown to be mediated through brain 5-HT (Bhattacharya 1971,1978a). 5-HT thus inhibits convulsions. Micro-iontophoretic injection of 5-HT predominantly inhibits the cortical neurones of rat (Sharma 1976).

Other studies: Gupta et al (1984) have shown inhibition of the central control of ovulation by 5-HT. Testosterone secretion in rats is also influenced by the central serotonergic system (Biswas et al 1985). The role played by 5-HT in toxaemia of pregnancy has been shown by Sharma et al (1985).

Histamine

Bhattacharya and Parmar (1985) showed that the antinociceptive action of central histamine is mediated via H1 receptors. The histaminergic receptors in the chemoreceptor trigger zone were shown to be responsible for the production of emesis (Bhargava and Dixit, 1968). Both H1 and H2 histamine receptors in the emetic chemoreceptor trigger zone of the area postrema are involved in histamine induced emesis (Bhargava et al 1976). Both types of histamine receptors are also involved in the release of ACTH

(mediated via catecholamine) seen after administration of histamine icv (Palit et al 1979). The component of cardiac arrhythmia induced by toxic doses of digoxin attributed to central action was found to be abolished by histamine receptor blockade in the brain (Tripathi and Tayal 1984). Shukla and co-workers have demonstrated the role of histamine in thermoregulation in pigeons (Shukla et al 1983) and mastomys (Shukla et al 1980,1981a-e).

GABA

Modulation of the nigrostriatal system in Parkinsonism in mice by GABA has been shown by Gulati et al (1980). The inhibitory role of GABA against d-tubocurarine induced CNS stimulation was demonstrated by Dhumal and Bhavsar (1980). The role of GABA in benzodiazepine effects has also been studied. The inhibition of neurotransmission by GABA was shown to be potentiated by benzodiazepines (Kulkarni and Jog 1983). Diazepam induced analgesia was mediated through benzodiazepine and GABA receptors (Kunchandy and Kulkarni 1986b). Central alpha2-adrenoceptors modulate the function of GABA. GABA antagonists inhibit the intake of food (Kamatchi et al 1986,1988). Using receptor binding studies Gulati et al (1986a) showed that electroconvulsive shocks upregulate brain benzodiazepine receptors in rats. Gulati et al (1988) also compared the cortical benzodiazepine, cholinergic and adrenergic receptors between albino rat and mastomys using radioreceptor binding assay.

Purines

Kulkarni and colleagues have studied purinergic transmission in detail in various experimental models. Clonidine and carbamazepine (Kulkarni and Mehta 1984; Mehta and Kulkarni 1986) blocked P1 purinergic receptors. This could explain the antimigraine and anticonvulsant properties of these drugs. These authors have also proposed a purinergic theory of despair behaviour in animals (Kulkarni and Mehta 1985). Digoxin induced convulsions did not involve purinoceptors (Kulkarni and Mehta 1983).

Basic neuropharmacological studies

A large amount of basic work has been done in the more recent years involving different anatomical structures and neurotransmitters and utilizing drugs as tools.

Catalepsy

Several neurotransmitters like histamine, 5-HT, GABA, acetylcholine, prostaglandins and dopamine have been shown to play a direct or modulatory role in the cataleptic behaviour of various animals. Catalepsy induced by several drugs also involves these neurotransmitters.

The modulatory influence of the central histaminergic system on the striatal dopaminergic mechanisms in haloperidol induced catalepsy has been shown by Joshi et al (1979) and Muley et al (1979). Balsara et al (1979) have demonstrated a 5-HT dependent cataleptic effect of haloperidol in rats which was suppressed by 5-HT antagonists. Balsara and coworkers have further shown that naloxone, an opiate antagonist suppressed haloperidol catalepsy and potentiated amphetamine stereotypy. Central noradrenergic and GABAergic systems also seem to play a role in this process (Balsara et al 1984; Gada et al 1983; Muley et al 1983). Chopra and Dandiya (1975) suggested that perphenazine catatonia is induced by the release of acetylcholine and histamine or disturbance of their metabolism in some areas of brain.

Bose and Bhattacharya (1979) and Bose et al (1979) analysed morphine induced catalepsy. Reduction of brain dopaminergic activity or enhancement of cholinergic activity potentiated the morphine induced catalepsy. Their work also suggests a modulatory role for prostaglandins. Bala et al (1978) showed that catalepsy induced by morphine was antagonized by apomorphine while catalepsy induced by chloropromazine, trifluperazine and haloperidol was inhibited by methamphetamine, imipramine and atropine. This indicates that neuroleptics could induce catalepsy by directly blocking dopamine receptors and morphine might act via nonstriatal dopaminergic pathways without the involvement of cholinergic pathways. Morphine induced catalepsy was potentiated by restraint stress. This was found to be prostaglandin modulated and serotonin mediated (Bhattacharya and Parmar 1985).

The cataleptic effect of clonidine in mouse was thought to be mediated through the histamine released from the mast cells in the brain by the stimulation of alpha2-adrenoceptors (Jadav et al 1983). On the other hand clonidine showed anticataleptic effect and potentiated the anticataleptic effect of dopaminergic, anti-cholinergic and GABAergic agents against perphenazine induced catalepsy (Shukla et al 1986a,b). Clonidine also showed central antitremor effect (Shukla et al 1986c) and anticonvulsant effect against morphine and digitalis (Kulkarni and Nagrath 1983; Kulkarni and Mehta 1983).

Prostaglandins were shown to modulate the cataleptic effect of bradykinin which was also affected by various other neurotransitters like acetylcholine, 5-HT and dopamine (Bhattacharya et al 1985,1986). Cataleptic effect of centrally administered prostaglandins was found to be 5-HT mediated (Bhattacharya et al 1984; Bhattacharya and Mohan Rao 1987). The neuroleptic induced catalepsy was also greatly influenced by various prostaglandins (Bala et al 1983) and GABA (Tekur et al 1984).

Stereotyped behaviour

The drug induced stereotype has been analysed by various investigators in mice, rats, guinea pigs and pigeons.

Dandiya and coworkers analysed the influence of hallucinogens, CNS stimulants and antidepressants on the open field performance in rats (Dandiya et al 1969, 1970a). Hallucinogens produced 'simple stereotype' which was also the characteristic behavioural pattern noticed with amphetamine and methylphenidate (Dandiya et al 1970a,b; Gupta et al 1971a,b). Antidepressants failed to modify the behavioural pattern in the open field test. The 'complex stereotype' was mediated by dopaminergic mechanism while the simple stereotype was a function of central noradrenaline (Dandiya and Patni 1973).

Amphetamine induced stereotypy has been suggested as a test for CNS stimulants and depressants (Sethy et al 1967). The intensity of stereotypy induced by meth-amphetamine depended upon the balance between central dopaminergic, serotonergic and histaminergic systems (Joshi et al 1979,1981). A parachlorophenyl analogue of GABA potentiated methaphetamine stereotypy and apomorphine induced cage climbing behaviour in mice (Balsara et al 1981a) possibly by increasing the sensitivity of postsynaptic DA receptor. Gulati et al (1986b), using receptor binding assay, conducted a comparative study on stereotyped behaviour and striated dopamine receptors in albino rat and mastomys. The study indicated that the weaker potency of apomorphine and amphetamine stereotype in the mastomys may be due to a lower affinity of its striatal dopamine receptors in comparison to albino rat. The amphetamine and beta-phenethylamine induced stereotypy in rats was greatly attenuated by testosterone, progesterone and oestradiol (Naik et al 1978). Apomorphine induced gnawing in mice was inhibited by physostigmine (Dadkar et al 1977). Dhawan and Srimal (1977) suggested that the apomorphine induced gnawing syndrome in guinea pigs partially involved a dopaminergic mechanism. A possible catecholaminergic involvement was also suggested by them. Methylphenidate induced gnawing was also analysed by Srimal and Dhawan (1970). The mechanism of potentiation of apomorphine stereotype due to electroconvulsive shock was elucidated by Gulati et al (1987). Apomorphine and amphetamine induced stereotypy has been compared in mastomys and rat (Gulati et al 1986). A dopaminergic involvement in the amphetamine induced behavioural changes in monkey has been suggested by Palit and Bhargava (1984) and Palit et al (1986). Balsara and colleagues have studied the ergometrine induced head twitch in mice involving 5-HT receptors (Balsara et al 1986) and the effect of ergometrine on methamphetamine stereotypy in guinea pigs (Balsara et al 1985; Bapat et al 1985; Joshi et al 1983). Balsara et al (1983) and Dhavare et al (1983) have further shown that drugs which influence central histaminergic mechanism modify the stereotypy induced by indirectly acting dopamine agonist amantadine but failed to modify the effect of apomorphine.

Dhawan and colleagues analysed the apomorphine induced pecking in pigeons (Dhawan and Saxena 1960; Dhawan and Patnaik 1976; Dhawan

et al 1961). Their work suggested non-involvement of dopaminergic mechanism in this behaviour. Dandiya et al (1976) supported these conclusions, whereas Saxena et al (1977) expressed an opposite view regarding the role of dopaminergic mechanisms. Gupta and Dhawan (1965) studied the SAR of 20 phenothiazine derivatives against apomorphine induced pecking. The study also revealed that the antipecking activity paralleled the CAR blocking activity of the drugs.

Aggressive behaviour

The fighting behaviour induced by electrical foot shock was facilitated by increase in brain 5-HT level (Anand et al 1976), dopamine (Kohil et al 1979; Amiraju et al 1979) and histamine (Ray et al 1981). Jain and Barar (1985,1986) also studied the biting (clonidine induced) and fighting (foot shock) behaviour in mice. Steroid hormones, nitrazepam, haloperidol and propranolol were found to modify these aggressive behaviours. Mukherjee and colleagues have studied the effect of various drugs on animal emotion and aggressive behaviour (Dutta et al 1984). Ray et al (1983a,b, 1984,1987) have further studied the involvement of histaminergic and adrenergic receptors in the central control of aggressive behaviour in rats.

Learning and memory

D-amphetamine in small doses increased the retest latencies on the learning trial in rats (single trial passive avoidance response). A higher dose, however, produced the opposite effect. Caffeine showed a marked facilitation of memory and learning (Jagdev and Barar 1983). Sublethal doses of lead did not hamper acquisition of memory in weaning rats but such an exposure limited the scope for further learning (Venkatakrishna-Bhatt 1984).

Motor disorders

Tremorine and oxotremorine induced experimental motor disorders involving a supraspinal genesis have been extensively studied by Ganguly and colleagues. The presynaptic effect of oxotremorine at extra- and intrafusal myoneural junction may affect motor performances independent of the effect of oxotremorine on the higher centres of CNS (Vedasiromani and Ganguly 1976; Das and Ganguly 1977; Das et al 1978). An imbalance between motor output and recurrent inhibition mediated through Renshaw cells was involved in the genesis of tremor and rigidity (Ganguly et al 1976,1978). The mechanism of action of a new tremorogen (LON-954 was also investigated by them in detail (Ganguly et al 1984; Vedasiromani and Ganguly 1984). Selective inhibition of somatic reflexes by glycine (Dhawan et al 1972) and facilitation by intrathecal administration of catecholamines in cats (Dhawan and Sharma 1970) have been reported. Dhawan and

Sharma were among the first investigators to demonstrate the involvement of alpha-adrenoceptors in a central mechanism.

Pharmacology of blood brain barrier

Noradrenaline was able to cross the blood brain barrier (BBB) in dogs when infused intravenously in a solution containing ascorbic acid (Haranath et al 1976). The inhibition of synthesis of prostaglandins (Sharma and Dey 1979; Dey et al 1980; Mohanty et al 1980) and increase in brain 5-HT level (Sharma and Dey 1978,1981) have been reported to increase the permeability of the barrier. Gulati et al (1984) in a more exhaustive investigation found no evidence of involvement of serotonergic mechanism in the regulation of BBB. An involvement of H2-histamine receptors in mediating histamine induced increase in permeability of the barrier has been reported (Gulati et al 1985c). A number of alcohols and hypertonic saline solution had profound effect on the permeability of the BBB (Gulati et al 1981,1985a,b). Awasthi et al (1981) and Gulati et al (1986) also studied the status of the permeability of BBB in several convulsive disorders. Gulati et al (1985b) have demonstrated a transitory opening of BBB by intravenous bolus of hypertonic saline and suggested that this may be used for delivering drugs to the CNS.

Thermoregulation

The mechanism of control of body temperature has been studied in a number of animals. Various neurotransmitters and modulators in thermoregulation are involved.

Rat. Noradrenaline or 5-HT in the brain had little effect on normal body temperature in the rat. Inhibition of dopamine activity induced hypothermia (Singh et al 1978c). GABA acting centrally altered body temperature by modifying the release of prostaglandin and noradrenaline in the brain(Dhumal et al 1976). The involvement of histaminergic pathways in the CNS was also shown (Dey and Mukhopadhyay 1986; Mukhopadhyay and Dey 1986).

Guinea-pig. ICV administration of noradrenaline, adrenaline, 5-HT and histamine reduced body temperature while prostaglandin increased the normal body temperature in guinea pigs (Gupta and Chawla 1977). The study indicates that prostaglandin is the ultimate neurotransmitter and the hypothalamus is the thermoregulatory site. The involvement of adrenergic mechanism in thermoregulation is also reported by Khan and Gupta (1981).

Pigeon. Dopamine and noradrenaline induced hypothermia in pigeons seems to be finally mediated via alpha adrenoceptors (Dhawan and Srimal 1976). Srimal et al (1980a) demonstrated the involvement of two types of

dopamine receptors in thermoregulation. The role of serotonergic and histaminergic mechanisms in hypothermia has been analysed by Shukla et al (1981a,1982b). The importance of a constant Na+ and K+ ion ratio in CSF is essential for the maintenance of normal body temperature (Saxena 1976).

Mastomys natalensis. In the desert rat a number of neurotransmitters seems to play important roles in thermoregulation and their concentration in the CSF also appears to be important. Adrenergic, histaminergic, dopaminergic, serotonergic and mu-opiate receptors were found to be involved in causation of both hypothermic and hyperthermic responses (Shukla et al 1980,1981a-e 1982a,b,1986,1988).

Other species. In poultry too, a hypothermic role of catecholaines is evident (Alam et al 1981; Yadava et al 1979). Evidence for the presence of central alpha adrenoceptors in the thermoregulatory mechanism in rabbits was shown by Dhawan and Dua (1971) and these findings have subsequently confirmed by several investigators internationally.

Kulkarni (1980a) postulated the involvement of 5-HT in hyperthermia in man.

Studies on stress

Bio-chemical changes in tissues have been analysed in cold and heat induced physiological stress in animals (Dandiya et al 1967; Varma et al 1968; Menon and Dandiya 1969). Chlorpromazine and reserpine protected against the changes induced by heat stress, suggesting an involvement of biogenic amines. This is supported by the observation that mescaline and LSD-25 modified biochemical changes induced by heat stress. Barbiturates, glucocorticoids and chlorpromazine prevented the effect of centrifugal stress on rat adrenals (Pohujani et al 1969a,b).

Analgesia: Endogenous opioids, adrenohypophysial activation, sympathetic and cholinergic input were shown to be responsible for stress induced autoanalgesia (Kulkarni 1980b,1983). Involvement of endogenous opioids in shock and stress induced by swimming has been shown by Sharma et al (1979). Lowering the levels of 5-HT and prostaglandin (Bhattacharya et al 1978c) reduced the intensity of analgesia induced by immobilization stress. The stress induced anti-inflammatory effect was studied by Bhattacharya and Das (1987). Recently Kulkarni (1988) has shown that naloxone, an opioid antagonist, and reserpine, a monoamine depletor, evoked hyperalgesia in mice.

Gastric ulcer: The role of central neurotransmitters in stress induced gastric ulceration was evaluated by Bhargava et al (1980). Involvement of central benzodiazepine and GABA receptors has been shown by Kunchandy and

Kulkarni (1987a,b). Gupta et al (1986) and Bhargava et al (1985,1986) demonstrated an inhibitory role of central and peripheral opioid receptors in gastric ulceration induced by stress. The facilitatory role of central 5-HT was described by Gupta et al (1983).

Drug tolerance

The major agents investigated have been cannabis, methaqualone and the opioids. Singh and Das (1977) have shown the development of tolerance to hypnotic, analgesic, anticonvulsant and hypothermic responses of cannabis in animals. Methaqualone administered along with diphenhydramine produced lasting and more severe tolerance than the effect of methaqualone alone (Singh et al 1980c). Rapid development of tolerance to morphine induced catalepsy has been reported in rats (Bose et al 1979). Striatal acetylcholine and cholinesterase were progressively reversed with the development of tolerance. An inherent role of brain 5-HT and cAMP was observed in the tolerance to tremorine-induced analgesia (Naik et al 1977).

Sharma et al (1980b), while assessing the mechanism of analgesia, noticed that both physostigmine and morphine produced autotolerance. Cross tolerance was seen to physostigmine in morphine tolerant animals but not to morphine in mice treated with physostigmine.

Opiate receptors were partly involved in the morphine induced analgesic tolerance (Ramaswamy et al 1981c). A high degree of supersensitivity to acetylcholine was observed during naloxone precipitated withdrawal syndrome (Ramaswamy et al 1981a). Pretreatment with clonidine attenuated the acute tolerance to morphine analgesia (Ramaswamy et al 1981b).

Other studies: The EEG studies by Bhargava (1976) provided a hypothesis of synaptic action of strychnine, curare, alloferine, atropine and hemicholinium in the rat cerebral cortex by selective blockade of cholinergic pathways.

Effect of some centrally acting drugs on handwriting was analysed by Dhawan et al (1969).

Bhattacharya and coworkers have extensively investigated the role of central neurotransmitters in the modulation of peripheral inflammation (Bhattacharya and Das 1987; Bhattacharya and Sarkar 1986; Das and Bhattacharya 1985).

The binding sites on blood platelet with high affinity for serotonin and dopamine have been characterized by Khanna and Seth (1987). Blood platelets could serve as a useful model for central 5-HT and dopamine binding.

CNS dysfunction following chronic administration of manganese (Ali et al 1983a,b, 1985) and cadmium (Chandra et al 1985) has been studied.

Studies on drugs known to be active in the CNS

Hypnotics and related CNS depressants

On the basis of changes in the serum LH-RH content, Shah and Sheth (1979) concluded that the hypothalamic effects of pentobarbitone are produced at subhypnotic levels of the drug and the pituitary is affected only at hypnotic doses. Rao et al (1980) suggested that pentobarbitone induced hypothermia in mice was dependent on ambient temperature. However, the relationship between the sleeping time and the ambient temperature was controversial (Sabir and Raviprakash 1977). The SAR of some phenothiazine derivatives for potentiating pento-barbitone induced hypnosis was reported by Jindal et al (1960).

In malnourished rats turnover of 5-HT was found to be decreased initially followed by an increase. The effect of pentobarbitone, which is 5-HT mediated, was also affected accordingly (Chakravarti et al 1985). Chatterji and Ghosh (1961) and Ghosh et al (1962) compared the anaesthetic activity and the margin of safety of a number of volatile anaesthetics. Chlordiazepoxide potentiated the hypnotic effect of ethanol and pentobarbitone (Madan et al 1962).

Delta-9-tetrahydrocannabinol (THC)

Ghosh and coworkers (Sarkar and Ghosh 1975a,b, 1976; Podar et al 1975,1978; Biswas and Ghosh 1975; Podar and Ghosh 1976; Banerjee et al 1977) studied the mechanism of the central action of THC by using various biochemical parameters. Single intraperitoneal injection of THC in rats increased levels of dopamine and 5-HT in the brain and decreased the level of noradrenaline. Chronic administration produced little alteration in the level or turnover of biogenic amines even though both chronic and acute administration of the drug affected the synaptosomes structurally as well as functionally.

Bhattacharya et al (1988c) showed that the anti-inflammatory activity of THC involves the hypothalamo-pituitary-adrenocortical and sympathoadreno-medullary axis. THC enhanced the prostaglandin E2 and F2 levels in rat brain (Bhattacharya 1986). The role of prostaglandins has been further investigated by Bhattacharya (1986) in potentiation of hexobarbitone hypnosis, anticonvulsant, antinociceptive and cataleptic actions induced by THC.

Psychotropic drugs

Employing specific enzyme inhibitors, Dandiya and coworkers studied the

role of catecholamines and 5-HT in the action of some psychotropic drugs (Menon et al 1987a,b; Bapna and Dandiya 1970,1972; Menon and Dandiya 1967a,b; Chopra and Dandiya 1969). The beneficial effect of MAO inhibitory and other antidepressants in drug induced Parkinson like syndrome in mice and rats were also demonstrated (Dandiya and Bhargava 1968; Patni and Dandiya 1972). Evidence for imipramine-like-activity of fenfuramine was provided by Srimal et al (1970)

Phenothiazines. Chloropromazine was the most potent protective agent against emesis induced by emetine and digitalis in pigeons (Gujral et al 1956a). It also protected against emesis in dogs (Ahmad 1957) and pecking in pigeons induced by apomorphine(Dhawan et al 1961). The other CNS effects of chlorpromazine were evaluated by Gujral et al (1956b-g) and Ahmad and Goswami (1956). If failed to inhibit the hypothalamic antidiuretic effect of nicotine in rats (Das Gupta and Hausler 1955). The biochemical mode of action has been studied by a number of workers (Das Gupta 1957, Das Gupta et al 1956, Das Gupta and Mukherjee 1956).

Das Gupta and coworkers did extensive studies with chlorpromazine soon after it became available. The drug caused suppression of sham rage (Das Gupta et al 1954b). It also suppressed excitability of hypothalamic and medullary pressor areas in diencephalic cats (Das Gupta and Werner 1954). Pethidine had an opposite effect on medullary areas (Das Gupta and Werner 1954a). Chlorpromazine also blocked spinal interneurones and brain stem reticular formation (Das Gupta and Werner 1955) and interfered with the conditioned reflex (Das Gupta et al 1954). Its behavioural effects have been studied in rhesus monkeys. It had no antagonistic effect on stress induced lymphocytopenia (Das Gupta 1957). It produced calmness and lethargy in animals and potentiated barbiturate hypnosis (Ahmad and Goswami 1956). Bhargava and Chandra (1963) correlated structure and antiemetic activity in a number of phenothiazines. Dua and Dhawan (1971) observed that carphenazine showed potent tranquillizing and antiemetic activity at subsedative dose levels.

Rauwolfia alkaloids. David et al (1977a) studied the effect of various drugs on the striatal syndrome of reserpine. Apomorphine and clonidine were able to suppress the effects of reserpine presumably through central dopaminergic and adrenergic activation. Catatonia induced by reserpine was reversed by amantadine, apomorphine, atropine, clonidine and l-dopa (David et al 1979). Motor depression induced by reserpine was reversed by icv administration of noradrenaline and dopamine (Kulkarni and Dandiya 1975). A selective depression of CT zone for vomiting by reserpine was proven by Malhotra and Siddhu (1956).

The central effects of nicotine in rabbits were markedly antagonized by reserpine, isonicotinic acid hydrazide and poorly antagonized by chlorpromazine (Malhotra and Mehta 1957).

Bose and his colleagues (1959) were among the earliest group of neuropharmacologists to initiate neurochemical studies with drugs and showed that tranquillizers like reserpine, serpentine, chlorpromazine and promethazine inhibit tissue respiration and markedly depress the succinic dehydrogenase system in the brain, whereas non-tranquilliser ajmaline produced the opposite effect (Bose and Vijayvargiya (1957). Reserpine increased the oxygen uptake of brain homogenates by stimulating the amino acid oxidases (Bose and Vijayvargiya 1960a,b) and inhibiting MAO. Benactyzine, diphenhydramine and rescinnamine also inhibited MAO but to a lesser extent than reserpine Mephenesin and meprobamate had no inhibitory effect. A spectrohotometric method for estimation of reserpine was developed by them for these studies (Bose and Vijayvargiya 1959).

Ajmaline produced reflex inhibition of central vasomotor activity most effectively when parts of the rhinencephalon remained intact after ablation of the neo-cortex (Das Gupta and Werner 1954c).

Gupta and Dhawan (1960a,b) investigated in detail reserpine induced emesis in pigeons. They showed that it could be prevented by LSD-25, caffeine, iproniazid, methamphetamine, morphine, rouwolscine and yohimbine. The drug that blocked emesis also showed a parallel antagonism towards the other effect of reserpine. Chlorpromazine also markedly blocked the emetic effect of reserpine (Ahmad 1957).

The effect of reserpine on lymphocytopenia following emotional stress was studied by Das Gupta and Mazumdar (1962). Stimulation of the hypothalamus was seen in rabbits.

Reserpine increases the acetylcholine content in all areas of brain except the hippocampus where it was reduced (Malhotra and Pandalik 1959). 70% release of catecholamine was noted in the brain(Chatterjee and De 1960).

Haloperidol: Withdrawal of chronic haloperidol administration produced marked increase in motor activity (Kumar et al 1981). This could be attributed to hypersensitivity of dopaminergic neuronal system.

Diazepam: Diazepam caused significant increase in acetylcholine content of rat brain. Electric shock produced an opposite effect (Singh et al 1980a). Imipramine and desimipramine counteracted the diazepam -induced changes of ATPase and cholinesterase in human foetal brain (Das et al 1981). A significant increase in brain monoamines was observed during diazepam withdrawal (Kunchandy et al 1987). Cimetidine increased the effect of diazepam significantly whereas ranitidine failed to do so (Shah et al 1983). This indicates non-involvement of specific histamine H2 receptors in the action of diazepam. The work of Hemnani et al (1983) indicates a synergistic anticonvulsant effect of diazepam and diphenylhydantion. Diazepam produced an increase in the beta and alpha

frequencies and decrease in theta and delta frequencies in the EEG recordings of the various cortical areas of conscious rabbits. The changes were reversed by RO 15-1788, an imidazobenzodiazepine derivative (Singh et al 1986).

LSD-25: Dhawan and coworkers (Dawan 1960; Dhawan and Gupta 1959,1960; Dhawan and Saxena 1960; Dhawan et al 1961) investigated the interaction of LSD-25 with various drugs. Morphine and related drugs antagonized effect of LSD-25 such as pyrexia and hypotension whereas morphine analgesia was antagonised by LSD-25. The pyrexia in rabbits was found to be potentiated by methamphetamine, whereas chlorpromazine and alpha adrenergic blocking agents antagonised it. LSD-25 was shown to have a potent antiemetic activity. Bapat et al (1970) reported that LSD-25 caused pyrexia by liberating catecholamines in the CNS.

Anticonvulsants

The work of Arora and Kapila (1959) lent further support to the unitarian concept of nerve-muscle impulse when they found anticonvulsant activity in several antiarrhythmic drugs. The nature of anticonvulsant action of bromides was correlated by Mukherjee and Chakravarthy (1956) to the intracellular concentration of electrolytes. Anticonvulsants reduced serum albumin and raised serum globulins (Bose et al 1960). Gujral and Dhawan (1957) studied the effect of some antiepileptic drugs on the anticonvulsant activity of primidone and showed that antagonism or synergism also depended on the relative proportion of the drugs being combined.

Saxena et al (1969) evaluated the anticonvulsant activity of 21 antihistaminic drugs. Sixteen compounds possessed antielectroshock activity. The structural requirements for anticonvulsant property in these compounds were discussed.

Various sulfonamides have been shown to potentiate the anticonvulsant effect of diphenylhydantoin in rats (Sharma et al 1978b). This may have an imporant clinical implication. Similarly thiabendazol also showed a potent antimetrazol and anti-electroshock activity in rats (Shashindran et al 1977),

The antitremorine and anti-acetylcholine activity of a number of antiParkinson drugs could be correlated (Ahmad and Marshall 1962).

Beta-adrenergic blockers

Propranolol is the most widely studied drug in this group. It showed anticonvulsant and CNS depressant activity. It also potentiated barbiturate

hypnosis in rats (Iyer et al 1975). Dashputra et al (1985) showed antiepileptic activity in pronethelol and propranolol. Propranolol affected the biosynthesis of catecholamine in the brain (Srivastava and Kapur 1983). The anti-convulsant activity has been correlated with effects on beta-receptor or cholinesterase (Khanna et al 1987). Beta blockers have also been shown to possess cholinesterase inhibitory property and they modify oxotremorine induced tremors (Alkondon et al 1983,1984,1985,1986). Antitremorine activity in some beta-blocking agents in mice was shown by Sharma and Dhawan (1971) and Sharma et al (1971) and SAR correlation has been established.

Labetalol produced ptosis, hypothermia, reduction in SMA and potentiation of pentobarbitone induced hypnosis in mice and rats but had no anticonvulsant activity (Dadhich et al 1979).

Morphine

Several effects of morphine involving the CNS have been investigated in detail. Mechanism of morphine and meperidine induced analgesia was investigated by Sethy et al (1970a,b). The activity of meperidine was reduced in mice pretreated with reserpine or PCPA. Morphine released dopamine in the CNS which stimulated the central dopaminergic receptors (Dhasmana et al 1972).

Involvement of different neurohumors in the analgesia induced by morphine has been discussed earlier. Effect of protoveratrine and ganglion blocking agents (Gupta and Dhawan 1960) and potentiation by mecamylamine on morphine induced analgesia (Gupta and Dhawan 1961) was also studied and supported involvement of a cholinergic mechanism. Raina (1975) has shown that morphine modified sensitivity to pain stimuli by influencing the brain 5-HT and dopamine levels in rats. Involvement of adrenergic mechanisms in its analgesic action has been shown by Khanna et al (1978) and Shukla et al (1985a,b). Dopaminergic mechanisms have been described by Singh et al (1986). Involvement of prostaglandins in the antinociceptive action is suggested by the results of Jain et al (1983). The effect of testosterone on morphine analgesia has been investigated by Rao and Saifi (1985a,b). Ray and Dey (1979,1980) located the central site of analgesic effect of morphine. Structures on the ventral surface of the brainstem caudal to the fossa interpeduncularis appeared to be the most sensitive site for its analgesic action.

Prakash and Dey (1980,1981) showed a cholinergic mechanism in the hyperthermic response of morphine. Morphine was shown to antagonise LSD-25 induced pyrexia (Dhawan 1960) and this is non-cholinergic.

Morphine modified the convulsion pattern in mice (Tripathi and Singh 1978).

Morphine induced dopamine release in brain facilitates vagal tone leading to bradycardia (Jain et al 1980). Central cardiovascular effects of microinjection of opioids were studied to elucidate the nature and role of opioid receptors in cardiovascular regulation (Tangri et al 1985). The release of dopamine also accounted for the Straub-tail phenomenon (Srivastava and Jaju 1987). Activation of spinal opioid receptors may be correlated to the antiarrhythmic action of morphine (Pant et al 1983a, 1984). Central cholinergic and histamine H2 receptors mediate its effect on spontaneous motor activity (Pant et al 1983b). Mohankumar and Sood (1983,1985,1986a,b) and Sood and Mohankumar (1985a,b,c) developed in mice a model of physical dependence to morphine, characterized the narcotic tolerance and dependence and various biochemical changes involved during the processes. Gujral and Khanna (1957) compared the analgesic activity of five narcotic analgesics. Certain classes of autonomic drugs like neostigmine, ephedrine and amphetamine (Saxena and Gupta 1957a,b) potentiated the analgesia induced by morphine.

Two aminoacids l-isoleucine and dl-isoleucine administered orally possessed significant analgesic activity (Saxena et al 1984).

Clonidine Dhawan et al (1975a,b), Srimal and Dhawan (1985), Srimal et al (1977) and Raghubir et al (1985) evaluated the central cardiovascular effects of clonidine. The drug inhibited the hypothalamic, medullary and spinal vasomotor loci in cat. This could be responsible for the bradycardia and hypotension produced by clonidine. The main site of action is located on the ventral medullary surface. A cholinergic link in the central cardiovascular effects is further evident. Clonidine has also been shown to decrease the total and free acetylcholine content of the whole brain (Phadke et al 1981).

A wide variety of other central effects of clonidine has been studied. It produced profound analgesia like morphine and the PA2 values indicate a link between analgesia and alpha2-adrenoceptors (Parale and Kulkarni 1985). Antidepressants antagonized the behavioural despair and EEG changes induced by clonidine (Parale and Kulkarni 1986a; Kulkarni et al 1986). The mechanism of interaction needs further evaluation. Alcohol abstinence was potentiated by clonidine and other alpha2-agonists (Parale and Kulkarni 1986b, Kunchandy and Kulkarni 1986a). This activity should be further exploited for clinical usefulness. Activation of central alpha-adrenoceptors was also shown to be responsible for the hypothermic action of clonidine in a number of laboratory animals (Saxena 1981, Rao and Saifi 1981). Clonidine has also been shown to block the amphetamine induced stereotypy in rats (Valame and Gupta 1981).

Histamine H2 receptors were shown to be involved in the clonidine induced pinna reflex in mice (Singh et al 1983a,1984,1985).

Clonidine increased the intake of food, antagonized chemically and electrically induced convulsions and counteracted catatonia induced by perphenazine in mice (Kulkarni 1981).

The clonidine induced automutilation effect was studied in detail by Bhattacharya and colleagues (Bhattacharya et al 1987a,b). It seems that the central serotonergic and GABAergic systems inhibit automutilation and the peptidergic system facilitates the behaviour.

Clonidine has thus shown a wide range of pharmacological activities in the CNS. The work done in India indicates that apart from the activity at the established alpha-adrenoceptor the drug may be interacting with other neurotransmitter receptors as well.

Behavioural and autonomic effects of centrally administered drugs

The technique of central administration of drugs developed by Feldberg has been extensively employed by Indian investigators specially in late 1950s. The drugs have been administered intracerebrally or intracerebroventricularly (icv) in various species of animals.

LSD-25 Intracerebral administration of LSD-25 in conscious dogs and cats produced profound activation of autonomic nervous system as evident by salivation, retching, emesis, micturition mydriasis and fear complex. Cats were, in addition, hyperreflexic to external stimuli. Ataxia was also seen in dogs(Haley and Das Gupta 1958).

Emetics Bhargava et al (1961) showed that apomorphine and emetine administered icv in very low dose (0.2-0.5 mg/kg) induced vomiting in dogs. The site of action, the medullary chemoreceptor trigger zone, was confirmed by ablation studies. This was also the site of action of iv sodium salicylate(Bhargava 1959).

Histamine administered icv increased the secretion of gastric acid (Bhawe 1957).

5-HT on icv injection caused hypotension in dogs (Bhargava and Tangri 1959). The mechanism appeared to be central as the carotid artery occlusion pressor response and the central vagal stimulation depressor response were inhibited. Dhawan et al (1967) analysed the nature of 5-HT receptor in the central vasomotor loci and found them to be neither of M nor of D type but to be undifferen-tiated. ICV administration of 5-HT produced a significant dipsogenic effect which was antagonized by cyproheptadine suggesting the role of central serotonergic receptors in the hyperdipsic behaviour (Kumar et al 1980).

Hypotensives Bhargava and coworkers studied the action of a variety of

hypotensive drugs by using the spinal compression- vasomotor response technique. Among these, certain ganglion blockers showed vasomotor stimulant activity (Bhargava 1960, Bhargava and Kulshreshtha 1959,1960). The central vasomotor effects of adrenergic neurone blocking agent was analysed by Bapat et al (1969). The central mechanism of hypotensive action of guanethedine was evaluated by Bhargava et al (1966). The effect seems to be through release of catecholamine in medulla oblongata. Hydralazine and chlorpromazine showed central vasodepressor action (Tangri and Bhargava 1960a,b). The action of chlorpromazine seemed to be on the hypothalamic region. Iontophoretical application of acetylcholine and noradrenaline to vasoactive neurones on ventral medullary surface in cat indicated that both cholinergic and adrenergic neurones found in this area may play a role in regulation of blood pressure (Raghubir et al 1988).

Role of various drugs and neurochemicals administered icv in characterizing central receptors for thermoregulation (Tangri et al 1976) and aggressive behaviour (Ammiraju et al 1976) has also been described. Effect of centrally administered agents are also described at other parts of this review.

Development of new drugs acting on the CNS

Several new drugs have been introduced. The major systematic effort in this direction has been made by the Central Drug Research Institute, Lucknow (CDRI). The first new drug was, however, introduced by the King George Medical College, Lucknow and Regional Research Laboratory, Hyderabad. A new antidepressant has been developed by Ciba-Geigy Research Centre, Bombay. A number of academic institutions have synthesised new compounds.

Hypnotics

Gujral et al (1955a) had tested a new series of 2,3-disubstituted quinazolones acting on the CNS in various ways. Nine such compounds showed significant hypnotic activity. Some of them also had anticonvulsant and antipyretic properties (Gujral et al 1957; Sethna and Nagar 1960). The best compound was 2-methyl-3-orthotolyl-4-quinazolone. It was more potent than phenobarbitone and showed a dependable hypnotic activity in preliminary clinical trials (Gujral et al 1956h). It was subsequently marketed in several countries as methaqualone and has been withdrawn only a few years earlier due to its marked addictive properties. While studying the SAR of various derivatives of quinazolone-4-ones, Sarin et al (1959) suggested that 3-phenyl-quinazolone-4-one moiety is essential for CNS depressant activity.

Kapil et al (1961) synthesized and screened a series of phenyl propionic

acid esters and corresponding alcohols for CNS depressant activity. 2-piperidyl-(1)-3-phenyl propanol was found to be the most promising. The pharmacology of trimeglamide, a new synthetic CNS depressant, was investigated by Sharma and Dandiya (1962).

Tranquillizers

Centbutindole, a 2-substituted pyrazinopyridoindole, has been developed at the CDRI as a haloperidol-like neuroleptic drug with a novel chemical structure and a slightly different profile of activity (Dua et al 1977; Nityanand et al 1976; Raghubir et al 1977; Singh et al 1977; Kar et al 1986; Dhawan et al 1988). Preclinical and clinical evaluation indicated that centbutindole possessed all the qualities of a good neuroleptic agent with few side effects. It can control patients on a low dosage (twice daily). The drug has been approved for marketing.

Centazolone, 3-aminobenzo-6,7-quinazoline-4-one, exhibited potent tranquillo-sedative activity in various laboratory animals (Bhaduri and Khanna 1977; Prasad et al 1977b,c; Sharma et al 1977; Sethi et al 1979; Laxmi et al 1980, 1984). The drug has been developed by the CDRI. It is effective clinically.

Centpyraquin, 3- (p-fluorobenzoyl propyl)-2,3,4,4a,5,6-hexahydro-1-(H)-pyrazinol(1,2-a) quinoline hydrochloride, primarily a hypotensive agent, developed at the CDRI, showed promising tranquillising activity in various laboratory animals (Singh et al 1978a,b). The compound merits use in hypertensive patients with associated anxiety.

Anticonvulsants

A CDRI compound, 3-p-chlorophenoxy-1-N-(3,4-dimethoxyphenyl) pyperazino-propanol-2, showed promising anticonvulsant activity, comparable to diphenylhydantoin, in various laboratory models (Dua and Chatterjee 1981) and has been found safe in subacute toxicity studies in the rat (Personal communication).

A marine cyclic ether, isolaureatin, possessed promising anticonvulsant property in mice without pharmacological side effects (Kulkarni and Kurosawa 1981).

A number of newly synthesized quinazolones showed potent anticonvulsant activity in addition to their tranquillising and antidepressant activity (Singh et al 1983). Some of the newly synthesized dibenzotriazoniums also showed anticonvulsant property (Kulkarni et al 1986). A number of other new synthetic compounds exhibited varying degree of anticonvulsant activity along with other CNS effects (Kumar et al 1983a,b; Joshi et al 1984; Agarwal et al 1983; Sharma et al 1987). None of them were potent enough to be followed up.

Central muscle relaxants

Patnaik et al (1977,1979a,b) and Chawla et al (1970) synthesized and evaluated a number of propiophenone derivatives for various pharmacological activities at CDRI. One of them (compound CN) possessed a potent central skeletal muscle relaxant activity like mephenesin. The compound, unlike mephenesin, was free from haemolytic activity. Another compound developed at CDRI, delta-3-chromene-3-carboxamide also had a similar profile of activity (Patnaik et al 1981a). These compounds merit further preclinical development.

Sharma et al (1978a) reported central muscle relaxant activity in acetylacetone azine (MS-3). The compound needs detailed pharmacological evaluation. Sridhar et al (1984a,b,1985) reported promising muscle relaxant activity in compound IDPH-791 which was found to be twice as potent and safer than mephenesin.

A number of compounds, with varying chemical structures, have been found effective in the treatment of Parkinson's disease (Kumar et al 1983a,b,c, 1985; Srivastava et al 1985a,b).

Analgesics

In order to improve the analgesic activity of met-enkephalin and to obtain a non-addictive analgesic agent a large number of new enkephalin analogues has been synthesized and evaluated for biological activity at CDRI. Some of them were found to be several fold more potent than metenkephalin, active on systemic administration, exhibit less respiratory depressant activity and have delta-selective opiate receptor activity (Raghubir et al 1979,1982,1985,1988a; Mathur et al 1979,1988). The compound d-ala2-(me)phe4-gly-isopropylamide was found to be most promising. It had less respiratory depressant effect and was devoid of cardiovascular effects. It was 625 times more potent as an analgesic than morphine by icv route and about twice as potent as morphine by systemic administration.

Sridhar et al (1984a,b, 1985) reported potent analgesic, antipyretic and anti-inflammatory activity in a novel compound IDPH-8261. Some newer acetazoline and azetidinones also possessed potent analgesic and acetipyretic activities (Tandon et al 1983a,b).

Epidural opioids for relief of pain and increase in blood flow in patients with peripheral vascular disease.An important practical application of the discovery of spinal opioid receptor is the epidural administration of opioids for relief from pain. Bapat, Kshirsagar et al (Bapat AR, Kshirsagar NA, Bapat RD 1979,1980, 1980) reported on the efficacy of epidural morphine and pethidine in the treatment of chronic pain. Epidural morphine also

increased blood flow and improved healing of wounds in patients with peripheral vascular disease (Bapat AR et al 1980). Since morphine, free from preservative, is not easily available, buprenorphine - a u receptor agonist - was tried. It too improved blood flow and the healing of wounds. U receptors thus appear to be involved in these centrally mediated vascular effects. Since surgery and hitherto available drugs have not proved effective in the management of peripheral vascular disease, the observed effects of epidural morphine and buprenorphine form important advances in the treatment of patients with peripheral vascular disease.

CNS stimulants

Patnaik and coworkers have developed a number of potent CNS stimulants at CDRI. Compound 4-(4-morpholinyl)-2,3-penta-methylenequinoline possessed a potent analeptic activity (Patnaik and Dhawan 1981). The activity profile simulates pentylenetetrazol with twice its potency. Another compound **centphenaquin** a polymethylene-quinoline derivative also showed potent analeptic activity. It was more active and safer than nikethamide and pentylenetetrazol (Patnaik and Dhawan 1985, Patnaik et al 1985). Centhphenaquin merits clinical exploitation. Patnaik and colleagues also showed potent CNS stimulant activity in a number of newly synthesized compounds belonging to different chemical structures. Some of these also showed strychnine like activity (Patnaik et al 1981; Prasad et al 1977,1981a,b).

Antidepressants

A new dibenzoxazepin antidepressant compound **sintamil** possessed activity qualitatively similar to imipramine in laboratory animals (Nagarajan et al 1968,1975; David et al 1972,1974). The compound was more potent than imipramine and had less anticholinergic activity. The drug was quite safe and effective clinically. Sintamil is being marketed in India.

Study of plants showing CNS activity

Most plants producing CNS effects exhibit varying degree of CNS depressant activity. Gupta et al (1960) have isolated osthol from the roots of Prangos pabularia. The compound produced powerful respiratory stimulation along with a rise in blood pressure (Jamwal et al 1962). It antagonized respiratory depression induced by a variety of narcotics. The effect was comparable to nikethamide and pentylenetetrazol. It produced CNS stimulation in conscious animals as well. The analeptic effect of osthol is promising but the compound is not soluble and no suitable dosage form could be developed.

Strictamine, an indole alkaloid isolated from the flowers of *Alstonia*

scholaris, showed monoamine oxidase inhibitory and antidepressant activity (Bhattacharya et al 1979). **Alstovenine and venenatine**, the 4-methoxyindole alkaloids from Alstonia venenata, showed significant psychopharmacological properties (Bhattacharya et al 1975c). The plant is known to be beneficial in the treatment of mental disorders in the ancient Indian system of medicine. Another alkaloid (**echitovendine**) has been isolated from the fruits of the same plant.

The first reports on the central effects of Rauwolfia were published from India. The alcoholic extract and total alkaloid from the roots of **Rauwolfia serpentina** were shown to possess hypnotic and sedative properties by Chopra et al (1933,1943a,b). **Neoajmaline** and **isoajmaline** also produced mild CNS stimulation followed by depression (Bhatia and Kapur 1944).

Two other plants produced significant CNS stimulation. The oil of *Artemesia aberinthium* produced unconsciousness and epileptic convulsion in animals (Krishna and Varma 1933). The oil of *Celastrus peniculatus* was found to stimulate the occipital area as evidenced by the EEG studies (Razdan and Das 1958). No further work seems to have been done on either of these plants.

The active principle of Acorus calamus were isolated and identified as the trans-and cis-2,4,5-trimethoxy-1-propenylbenzene (alpha-and beta-asarone) respectively (Baxter et al 1960). The detailed pharmacological study of **asarone** showed that it possessed marked CNS depressant activity in a number of laboratory animals including monkeys (Menon and Dandiya 1967; Sharma and Dandiya 1961, 1962; Dandiya and Menon 1963,1964,1965; Dandiya and Sharma 1962; Chak and Sharma 1965). It has a quick onset of action. Unlike reserpine it did not deplete the brain 5-HT or noradrenaline. In iproniazid treated mice its effects resembled chlorpromazine. Though a part of its chemical structure resembles reserpine, it does not appear to act on the same receptors. In a search for a better and less toxic asarone analogue a large number of derivatives were synthesized and their SAR was studied by Dandiya and coworkers (Dandiya et al 1962, 1966; Sheth et al 1969; Menon and Dandiya 1963; Sogani and Dandiya 1965; Sogani et al 1965; Sharma et al 1964, 1965; Hemanani et al 1966; Chaturvedi et al 1972; Petigara et al 1969; Chandra et al 1969; Mishra 1971; Dandiya 1970). No clinically useful product has, as yet, resulted from these studies.

Hersaponin (*Herpestis monniera*) produced sedation in mice and potentiated barbiturate and ethanol induced hypnosis. The potentiation was prevented by LSD-25. It had no anticonvulsant effect but had antiamphetamine activity (Malhotra et al 1960). The effects resembled chlorpromazine. Like reserpine, hersaponin and the oil of *Acorus calamusa* depleted 5-HT and noradrenaline from the rat brain and their effect was antagonized by dibenzyline (Malhotra et al 1961a). Dhalla et al (1961a,b)

showed that the alkaloidal fraction and the total extract of *H.monniera* and essential oil of *A.calamus* inhibited cellular respiration as studied by the oxygen uptake of rat brain homogenate. The alcoholic extract of *Bacopa monniera* showed improvement in learning as well as memory in rats in several test models. The activity has been attributed to the presence of two saponins, **bacosides A and B** (Singh and Dhawan 1978,1982,1985; Singh et al 1988). Detailed preclinical development of the bacosides is in progress (Personal communication). A related plant *Hydrocotyle asiatica* (also called Brahmi) had week sedative activity (Malhotra et al 1961b) only.

Jatamansone isolated from the essential oil of *Nardostachys jatamansi* showed tranquillizing and antiarrhythmic activities (Arora et al 1958,1966,1967) with a good therapeutic index (Arora 1960). The essential oil of *A.calamus* also showed similar activities in addition to anticonvulsant property (Madan et al 1960). The results provide a rationale use of these agents in traditional systems of medicine.

The ethanol extract of grain husk of *Paspalum scrobiculatum* and its alkaloid also showed tranquillizing activity in animals and human volunteers (Bhide and Aiman 1959). The detailed pharmacology was evaluated by Bhide (1962).

Marked tranquillizing and weak analgesic effect in rats was noticed in the essential oil obtained from the leaves of *Cymbopogon citratus* (Seth et al 1976).

A wide variety of CNS activity, chloropromazine like neuroleptic activity in particular, was observed from the seeds of *Fumaria indica* (Bhattacharya et al 1976c). Psychopharmacological effects were also seen with **l-nuciferine** and its derivative **atherospermine** isolated from the leaves of *Nelumbo nucifera* (Bhattacharya et al 1978b).

Angelecin isolated from *Selinum vaginatum* showed marked tranquillizing, anticonvulsant and muscle relaxant activities like chlorpromazine (Chandoke and Ray Ghatak 1975).

Details on the study on THC have been reviewed in the previous section. The neuropharmacological properties of the plant, the resin in particular, have been studied widely in various laboratory animals for over 40 years. The total extract and alkali insoluble fractions of *Cannabis indica* were reported to have narcotic properties by Bose and Mukherjee (1945) while the alkali soluble fraction was inactive. The alkali insoluble portion seems to contain some optical isomers of THC. The resin produced depression, hypothermia, analgesia, inhibited conditioned avoidance response, caused reduction in spontaneous motor activity and had a tranquillizing activity. The mechanism of action involving interaction with various neurotransmitters and effect on several biochemical parameters in the

brain is also well documented (Sharma et al 1975; Singh and Das 1976,1978a; Singh et al 1978d, 1980b; Ghosh and Bhattacharya 1978, 1979a,b, 1980a,b; Ghosh et al 1980a; Sethi et al 1986). The interaction between cannabis and copper was studied by Singh and Das (1978b). Their results indicated that copper sulphate enhanced the barbiturate potentiating property of cannabis in mice and rats. This supports the potentiating effect of copper observed in human being.

Weak CNS depressant activity has been reported for several other plants. The essential oil of *Curcuma zedoaria* and *Angelica archangelicer*, alkaloidal fraction (V-22) of *vinca rosea* and semisynthetic alkaloid **arboricine** obtained from *Glycosmis* produced varying degree of CNS depression in animals (Chopra et al 1954). The total alkaloidal fraction of *Withania somnifera*, **ashwagandholine** and **bacoside** A and B possessed weak CNS depressant activity (Malhotra et al 1965). The effect of bacosides on memory has been reviewed above.

Gujral et al (1955b) evaluated the antipyretic activity of some indigenous drugs and showed that *Wrightia tinctoria and Woodfordia floribunda* were more potent than acetylsalicylic acid. The alcoholic extract of *Cyperus rotundus* prevented apomorphine induced emesis in dogs (Singh et al 1970).

A large number of other plants has been reported to have CNS effects but detailed studies are lacking. Recent work on plants having potent CNS activity has been reviewed in several publications (Satyavati 1984; Dhawan 1986; Patnaik and Dhawan 1989). Some of the important plants included in these reviews are:

Azadirachta indica	(Singh et al 1987)
Bacopa monnieri	(Singh and Dhawan 1985)
Canavalia virosa	(Mukhopadhyaya et al 1986)
Cissampelous pareira	(Aswal et al 1984a)
Corchorus tridens	(Vohora et al 1983)
Cuscuta chinensis	(Akbar et al 1985)
Desmodium pseudotriquetrum	(Aswal et al 1984a)
Erinocarpus nomonil	(Abraham et al 1986)
Fumaria indica	(Kumar et al 1986)
Hippophae rhamnoides	(Abraham et al 1986)
Kalanchoe integra	(Varma et al 1986)
Morus indica	(Pal et al 1983)
Pseudosorghum	(Mehta et al 1983)
Saccharum officinarum	(Aswal et al 1984a)
Salvia haematodes	(Akbar et al 1984)
Scrophularia koelzii	(Aswal et al 1984a)
Solanum melongena	(Vohora et al 1984a)
Syzygium cumini	(Chakarborty et al 1986)
Trianthema portulacastrum	(Vohora et al 1984b)

Tribulus terrestris	(Prakash et al 1985)
Vigna mungo	(Sood et al 1985)
Vigna radiata	(Sood et al 1985)
Vigna sinensis	(Sood et al 1985)
Vitex negundo	(Ravishankar et al 1985)
Zingiber roseum	(Aswal et al 1984b)

Concluding remarks

As pointed out in the introduction, several laboratories in India have made significant contributions to growth of neuropharmacology as a discipline. Unfortunately, many of these have not concentrated on a specific problem and therefore much of work is of an exploratory nature failing to attract world attention. There have, however, been significant contributions in analysing thermoregulation and central cardiovascular control and these contributions are internationally quoted.

In the area of new drugs **methaqualone** has been the most outstanding contribution and more recently the work on enkephalin analogues has lead to synthesis of compounds with extraordinarily high potency, unsurpassed anywhere else. In the area of medicinal plants, even though work on Rauwolfia started early the lead was soon taken by Western investigators and the same is true of work on cannabis compounds. In the coming years it will be necessary to develop more centres of excellence if India is to make major contributions in this field. We should be able to exploit better the facilities already available here (facilities for primate work, investigations on carefully selected plants from traditional systems of medicine and on agents abused in India). There is also an urgent need for collaborative programmes with other neuroscientists so that various aspects of priority problems can be expeditiously tackled.

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Neurotoxicology

U.K. Misra

Ancient Indian neurotoxicology

Ayurveda consists of eight branches: kaya chikitsa (medicine), shalya chikitsa (surgery), kumar bhartya (pediatrics, obstetrics and embryology), shalakya chikitsa (ophthalmology and otorhinolaryngology), bhut vidya (demonology and psychiatry), rasayana (rejuvenation and geriatrics), vajikarana (virilisation and use of aphrodisiacs and agadhatantra (toxicology) (Keswani 1974).

Two major groups of poisons (vegetable and animal) were specified in the Charaka Samhita (Sharma 1983). A third group of synthetic poisons was added by Bhav Mishra (15th century). Poisoning due to vatsanebha, kalkuta (species of aconite) opium etc. has been reported. Amongst the animal poisons; snake, scorpion, frog, rat, insect, leeches, and lizards have been described. To take one example, the types of poisonous snakes, clinical manifestations of snake venom poisoning and prognostic factors after snake bite are detailed. Incision of the skin, suction of snake venom from the wound and application of tourniquet were advised in the Charaka Samhita (ch 23:38). Stages of intoxication by various kinds of wines in different types of persons have been explained (ch. 24:1-106). The syndrome of alcohol withdrawal and its management by giving small quantities of alcohol was known to ancient physicians (ch 14:109). In Kautilya's Arthashastra the use of neurotoxic poisons was advocated to produce madness, blindness, fainting and even death in enemies. Formulae for raising toxic fumes (war gas) and measures for detoxification have also been mentioned in this work (Garola 1962).

The detection of poison in food and drink was highly refined and used to protect the king from his enemies. The poisoner could be recognised by his suspicious or abnormal behaviour. The poisoned food, when put in fire produced an abnormally coloured flame, a bad smell and heavy smoke (ch 23:109). The alcoholic extract of such food was seen to acquire a blue tint (ch 23:112). These tests anticipate flame photometry and examination of alcoholic extracts under ultraviolet and other lights. The principle of biological testing of toxins was also well known to our ancients. Animals, insects and birds were offered suspect food and used to alert the observer to possible food poisoning.

In Unani medicine too, toxicology was given an important place. The poisons (sammiyat) were classified according to nature (khilquat). The subgroups of poisons include vegetable (sumoone nabati), animals (sumoone haivani), chemicals and minerals (sumoone keemyavi). The neurotoxic poisons were called Asabi poisons and subclassified into cerebral (dimagi) and spinal (sulabi). Amongst thecerebral poisons were listed opium, alcohol, ether, cannabis, belladona. In the spinal group were listed strychnine and other vegetable poisons (Jafri 1975 and Usmani 1967).

Modern neurotoxicology

Limitations of space disallow a review of all the neurotoxicology studies carried out in India. The most significant have been grouped as follows:

Chemicals (natural and synthetic): metals, solvents, pesticides, minerals, and miscellaneous compounds.
Plants : lathyrism, cycads, cannabis.
Animals : snake.

Chemicals (natural and synthetic)

Metals: The major Indian contributions on neurotoxicity produced by metals are with reference to manganese, copper, arsenic and lead.

Manganese: Poisoning as an occupational hazard in manganese miners was reported for the first time by Niyogi (1957). 1132 miners were studied. 28 cases of definite and 9 cases of possible manganese poisoning were described. The clinical features included maniacal behaviour, labile affect and Parkinsonism. Certain additional features were mentioned in the report of enquiry committee on manganese poisoning published by the government of India (1960). Wadia (1964) described spinal cord involvement in manganese miners for the first time the manifestations being similar to those in primary lateral sclerosis. Occurrence of the latter cases in areas where lathyrism in endemic and the clinical resemblance of the spinal form of manganese poisoning to lathyrism suggested an etiological relationship between manganese toxicity and lathyrism. Wadia (1964) postulated that the Parkinsonian form of manganese poisoning was due to inhalation of the metal and the spinal form due to oral ingestion of manganese. Manghani et al (1969) and Dastur et al (1971) have studied the effect of manganese loading using isotopic manganese.

In another study on occupational manganese poisoning Chandra et al (1984) suggested estimation of serum calcium in detecting early manganese poisoning. Adenosine diaminase levels were helpful in patients with established poisoning.

Experimental studies on manganese toxicity by Chandra et al (1978)

showed cerebral and cerebellar cortical degeneration. Singh et al (1974) showed the disturbance of oxidative phosphorylation to form the biochemical mechanism of manganese toxicity. Chandra and Shukla (1981) reported an increased turnover of neurotransmitters like dopamine and norepinephrine and increased concentration of striatal HVA in those exposed to manganese over long periods. Abnormal oxidative phosphorylation and energy synthesis was also seen in such persons (Chandra 1983). Greater susceptibility of immature brain to manganese toxicity was reported by Husain et al (1976) and Seth et al (1977). Studies on manganese carriers, tissue binding protein and the interaction of manganese with other metals have been reported by Chandra et al (1984).

Lead: Lead is known to produce central and peripheral neurotoxicity. There are a number of studies by the chief adviser to factories on workers in India exposed to lead (1953). A family exposed to lead fumes during extraction of gold and silver from jeweller's waste has been investigated. Here, the children developed gastrointestinal symptoms, respiratory infection and encephalopathy whilst the adults developed weakness and gastrointestinal disturbances (Getrude et al 1971). In another study on 16 workers employed in refiring silver there was clinical evidence of lead toxicity but the clinical evidence of neurotoxicity was present in just one person. Neurophysiological abnormalities such as decay in compound action potential, sensory nerve conduction velocity, H reflex and F response were, however, observed in many (Misra et al 1987).

Copper: Neurotoxicity is seen in the form of brain damage in Wilson's disease produced by abnormal copper metabolism. The first Indian report on Wilson's disease is that by Wadia and Dastur (1964).

Wilson's disease has an earlier age of onset in India than in the west (Dastur 1969). A third of Dastur's cases were of the osseomuscular form - probably due to a genetic variant. Murthy et al (1987) have reported on Wilson's disease in south India and the role of oral zinc therapy.

Arsenic: Arsenic neuropathy has been reported by Chuttani and Chopra (1979) following the use of indigenous drugs, illicit liquor and smuggled opium. Neuropathy has developed 2 hours to 2 years after ingestion of arsenic suggesting variation in individual susceptibility. Symmetrical sensorimotor neuropathy is the commonest. Pure sensory neuropathy has been reported but pure motor involvement is rare (Chuttani et al 1967). Chopra et al, in an unpublished study of 20 patients with arsenic neuropathy, found peroneal motor nerve conduction velocity to be unrecordable in 10, significantly slowed in 8 and normal in one. Electromyography showed denervation in the muscles of upper and lower limbs. Sural nerve biopsy in 22 patients with arsenic neuropathy showed severe loss of myelin in 10, moderate loss in 8 and mild to moderate loss in 4. Axonal loss was moderate in 4 and mild in 11. No axonal loss was found in 7 patients. Variable degree of thickening of the perineurium and

increase in collagen in and around the nerve fascicles was seen. In single nerve fibre preparations varying degrees of segmental demyelination and remyelination was noted. Ultrastructural changes have been reported by Chopra et al (1977).The use of British Anti-Lewisite (BAL) in the management of arsenic neuropathy was reported by Malhotra (1951). Chuttani et al (1967) felt that BAL therapy shortened the period of recovery.

Gold: Neuropathy following injection of gold for the treatment of rheumatoid arthritis was reported by Katrak et al (1980). The clinical picture included symmetrical progressive polyneuropathy, focal or generalised myokimia and a tendency for initial deterioration followed by improvement after cessation of chrysotherapy. Sural nerve biopsy showed axonal degeneration and segmental demyelination. Similar changes were seen in the peripheral nerves in animal experiments. The severity of neuropathy was related to the dose of gold.

Trace metals in the aetiopathogenesis of motor neurone disease: K. Sood and Devika Nag have studied the clinical spectrum of motor neurone disease in 43 patients and 30 age and sex matched controls in north India. The concentrations of manganese, mercury, selenium, aluminium, cobalt, calcium, magnesium, copper and zinc in the blood, plasma and cerebrospinal fluid of patient and controls were studied. The following observations followed: a) Motor neurone disease was eight times commoner in males. b) No definite risk factors or antecedent life events contributing to the development of motor neurone disease could be identified. c) A positive family history of motor neurone disease was obtained in 2 patients (4.6%). d) Blood and plasma levels of lead were significantly higher in patients with motor neurone disease than in controls. e) Patients with progressive bulbar palsy had significantly higher aluminium concentrations in the cerebrospinal fluid than did patients with amyolateral sclerosis, progressive muscular atrophy and controls. f) No significant difference was noted in blood, plasma and cerebrospinal fluid concentrations of manganese, cobalt, zinc, chromium and copper in patients with motor neurone disease and controls. They concluded that there is an abnormal turnover of lead in motor neurone disease. Excessive concentrations of lead in the plasma makes the heavy metal available for uptake by tissues. Harmful effects may be due to a complex interaction of many trace elements. A raised concentration of lead may lead to impairment of homeostasis of manganese and cobalt. These mechanisms may form the basis of motor neurone disease. (Personal communication.)

Solvents and alcohol: Petroleum distillates - (diesel, kerosene, gasoline, paint thinners) are central nervous system depressants and produce cell damage by dissolving cellular lipids. To study the effect of occupational exposure in those operating petrol pumps, 94 of them were examined by Pandya et al (1975). Alteration in immediate recall and remote memory,

poor psychomotor skills and learning abilities and high concentrations of phenol in the urine were the striking findings. A study of solvent toxicity by Rao et al (1975) showed that 25 hexane diol (HD)[a metabolite of hexane, isomax and gasoline] increased the cerebral MAO content in rats. Agarwal et al (1985) reported increase in dopamine receptor binding following exposure to HD and suggested the involvement of the dopaminergic system in the neurotoxicity of 2,5, HD. Bhatt et al (1988) felt that the reduction in cholesterol, ubiquinane concentrations and alteration of lipid profile seen in the brain of experimental rats were also possible mechanisms by which hexacarbons produced their toxic effects.

Methanol: The poor consume different kinds of illicitly brewed alcohol -khopadi in Maharashtra, hatata in Ahmedabad, kalakakkal in Madras and hooch in Delhi. Krishnamurti et al (1960) and Divekar et al (1976) reported clinical studies. The neuropathological findings in methanol poisoning included congestion, edema and petechial haemorrhages in the brain; toxic changes in Ammon's horns, midbrain and frontal lobe and oedema of optic nerve. Dastur et al (1977) have evaluated the effect of alcohol, malnutrition and deficiency of vitamin B complex on the peripheral nerves.

Pesticides: A large number of pesticides are extensively used in India. Organochlorine (DDT, BHC, endosulfan), organophosphate (malathion, fenthion, DDVP,) and carbamates account for more than 75% of the pesticides consumed annually in India. These pesticides are primarily neurotoxic. Easy availability and ignorance of the potential hazards have resulted in a high incidence of pesticide poisoning.

Accidental BHC poisoning resulting in neurotoxic manifestations (including epilepsy) has been reported by Gupta et al (1975), Nag et al (1977) and Khare et al (1977). Nag et al (1977) reported eight cases from the village of Sitapur, Uttar Pradesh (UP). These patients developed seizures after eating grains contaminated by BHC. Khare et al (1977) reported a large series of patients with acute poisoning by BHC from Lakhimpur Kheri district of UP. These patients presented with epilepsy, cranial nerve palsy, pyramidal signs and EEG abnormalities. Food and soil samples contained high concentrations of BHC. Organophosphorus compounds frequently cause acute poisoning. The clinical picture has been reported by Mutalik et al(1962), Gupta et al (1968) and Wadia et al(1974). Based on findings in 200 cases of organophosphate poisoning, Wadia et al (1974) classified the neurological changes thus: type I signs due to acetylcholinesterase inhibition, responded to atropine and were present at the time of admission; type II signs appeared later and included proximal limb weakness, cranial nerve palsy and areflexia. The neurophysiological changes in organophosphate poisoning were reported by Wadia et al(1987). In this study of 350 patients with Type II paralysis, motor nerve conduction velocity was slightly reduced. Decrement on repetitive nerve stimulation

was present at high rate of stimulation (30 HZ). Compound action potentials showed smaller amplitude and repetitive muscle activity. A syndrome like acute infective polyneuritis has been reported by Adlekha et al(1988). Delayed neurotoxic effects are produced by several organophosphates like triorthocresyl phosphate (TOCP), mapafox and leptophos. The predominant changes are seen in the distal large diameter fibres, the initial axonal damage being followed by myelin degeneration. These compounds inhibit neurotoxic esterase. Delayed neurotoxicity of organophosphates (TOCP) has been reported following contamination of edible oil by Vohra et al (1962)and Mehta et al (1975). Delayed neurotoxicity due to dichlorovos has been reported by Wadia et al (1985).

Aluminium phosphide is used for fumigation of stored grains. On contact with atmospheric moisture it releases highly toxic phosphine gas. By 1984, 94 cases of phosphine poisoning have been reported. Ingestion of aluminium phosphide tablets results in fatal phosphine poisoning. Since 1985, 52 such cases have been reported from India with a mortality rate of 56% (Misra et al 1988, Chopra et al 1987). Alteration of consciousness and delerium form the principal neurological features. A simple test for the diagnosis of aluminium phosphide poisoning was suggested by Chugh et al (1989).

Neurotoxicity from occupational exposure to pesticides: Acute poisoning by organochlorine pesticide (BHC), to produce toxic encephalopathy has been reported by Nag et al (1977) and Khare et al (1977). Based on the results of these reports, Misra et al (1984) studied cognitive functions in workers exposed to DDT for long periods. Impairment of visuomotor function was noted. 56% of these workers showed EEG abnormalities. Misra et al (1982) reported macular abnormalities in 19% of those exposed to fenthion, an organophosphorus pesticide. These changes were found to be due to toxic changes in pigment epithelium (Misra et al 1985). A subsequent experimental study from Japan (Imai et al 1983) also showed the toxic effects of fenthion on the retina. Neurophysiological techniques may help us detect these changes at an early stage. Monitoring serum cholinesterase to detect organophosphate toxicity appears insufficient. A combination of clinical and biochemical tests has been recommended by Misra et al (1985). In workers exposed to organophosphate over long periods, subtle neurophysiological changes including prolonged terminal motor latency, F and H latency and repetitive muscle activity have been noted. These changes were significantly altered in the followup study. Workers engaged in fumigation of grains (and consequently exposed to phosphine) were studied by Misra et al (1988). Moderate and reversible symptoms were noted. Nerve conduction studies were normal.

Experimental pesticide neurotoxicity: Studies at Indian Toxicology Research Centre, Lucknow and Brain Research Centre, Aligarh have focussed on the experimental studies on pesticide neurotoxicity. The mechanism of DDT neurotoxicity, cerebral neurotransmitters and mechanism of action of

anticonvulsants in DDT induced epilepsy have been reported (Matin and Kar 1976; Main, Jaffery and Siddiqui 1981). Neurobehavioural and EEG changes in endosulfan toxicity have been reported by Anand et al (1980). An increase in 3H serotonin binding in rats was felt to be responsible for endosulfan induced aggressive behaviour (Agarwal et al 1984). Organophosphate induced epilepsy and its relation to neurotransmitter (GABA) abnormalities was reported by Matin and Kar (1973). Involvement of striatal dopamine was suggested as a mechanism in the production of delayed neurotoxicity by certain organophosphates (Fareed et al 1976). Abnormal concentration of acetyl choline in the brain in dermalfenitrothion toxicity was reported by Kar and Matin (1971) and Anand et al (1977). Accumulation of acetyl choline was reported in cerebrum and cerebellum by Gupta et al (1976). Organophosphate (dichlorovos) increases lipid peroxidation in different regions of brain.(Hasan and Ali 1980). DDVP was shown to increase the regional lipid and cholesterol in different regions of brain (Tayyaba and Hasan 1981). Metasystox, another organophosphate compound has been reported to produce regional alterations in the concentrations of DNA and RNAse in the brain (Tayyaba et al 1981). Metasystox also inhibits lipid levels in discrete areas of brain by activating lipase and lipid peroxidation (Islam et al 1983).

Neurological involvement in endemic fluorosis: Fluorosis is endemic in many parts of India: Andhra Pradesh, Punjab, Rajasthan, Tamil Nadu, Haryana, Uttar Pradesh, Karnataka, Gujerat, Kerala and Madhya Pradesh. Neurological involvement by fluorosis is mainly mechanical-compression of spinal cord, nerve roots by hypertrophied bone or calcified ligaments or both. Shrott et al (1937) were the first to recognise the neurological involvement in fluorosis. In the available literature 214 cases of fluorosis with neurological manifestations were found from India as opposed to the very small number from other countries (Misra et al 1988). The largest series was reported by Jolly (1976). Nerve deafness following compression of VIII cranial nerve (Siddiqui 1973) and meralgia paresthetica from compression of lateral femoral cutaneous nerve have been reported (Chuttani et al 1962). Kaul and Susheela (1976) have reported myopathy in association with fluorosis. Electromyography in patients with fluorosis has shown evidence of neurogenic atrophy without any myopathic changes (Reddy et al 1978). Abnormalities in F response and H reflex with normal nerve conduction have been reported in fluorosis (Murthy et al 1986). These findings were suggestive of root involvement. Krishnamurthi et al (1981) in their studies on muscle biopsy in fluorosis reported neurogenic changes without any dystrophic changes. Rao et al (1981) in a study of sural nerve biopsy in fluorosis reported reduction in mean fibre density of myelinated fibres and decrease in the number of fibres of small size. There was poor correlation between internodal diameters, suggesting a process of demyelination and remyelination.

Fluoride content of the drinking water is the most important determinant

of skeletal involvement. In the western literature a concentration of 1 mg fluoride per liter of drinking water is recommended. Fluorosis results when there is a concentration of 4 mg/L or more (Royal College of Physicians 1976). In India fluorosis has been reported at much lower concentrations of fluoride in the water. Neurological complications have been reported even at flouride concentrations of 1.2-1.35 ppm (Siddiqui 1970). A long duration of exposure to high fluoride level, sex (males have higher incidence),occupation (high incidence in manual labourers), nutritional status and climate are said to contribute to severe fluorosis with neurological involvement in India (Jolly 1976).

There is no specific treatment for fluorosis. A naturally occurring mineral, serpentine reduced the concentration of fluoride in the body. Rao et al (1975) reported enhanced urinary and fecal excretion in the patients of fluorosis on serpentine treatment. In the management of compressive myelopathy due to fluorosis, decompressive laminectomy may be necessary (Gulati 1969, Jolly et al 1970,Reddy et al 1987 and Misra et al 1988).

Miscellaneous studies

SMON (subacute myelo-optico-neuropathy is a neurotoxic reaction to halogenated hydroxyquinolines and has been reported mainly from Japan. Two hundred and twenty cases of SMON have been reported outside Japan (Baumgartner et al 1979). Nine cases have been reported from India- 6 had myelopathy, 2 optico-myelopathy and one myelo-neuropathy. None had the full blown syndrome (Wadia 1977).

Methyl-iso-cyanate (MIC) neurotoxicity: On second and third December 1984, in one of the biggest industrial accidents at Bhopal, central India, a highly toxic gas leaked from the Union Carbide Plant. Many lives were lost. Many more suffer permanent disability. Bharucha and Bharucha (1987) studied 129 adults and 47 children affected by the accident. CNS involvement was seen in 3 of the adults (stroke, cerebellar ataxia and encephalopathy) and the neuromuscular syndrome in 10. Among the children, 24 had become comatose. 3 each had convulsions and regression of speech. In another study by Misra et al (1988), fainting (55%), pyramidal signs (15%), myoclonic jerk (3%), muscle weakness and hyporeflexia (6%) were reported following toxic gas exposure at Bhopal. Long term followup studies are under way.

Styrene and acrylamide are two important industrial chemicals with well known neurotoxic effects. Studies on the effect of styrene on brain glutathion-S transferase have been reported by Das et al (1981) and Agarwal et al (1982). Styrene increased the sensitivity of dopamine (DA) receptor. Styrene oxide increased the level of norepinephrine in midbrain and cerebellum and decreased monoaminooxidase (MAO) (Hussain et al 1984). Decrease in DA, norepinephrine and increase in MAO and cathepsin

D enzyme in different areas of brain has followed acrylamide enhanced DA receptor activity. Pretreatment with hepatic mixed function oxidase (SKF 525A) or methyl mercury chloride prevented acrylamide induced striatal spiroperiodol binding. These biochemical and behavioural findings suggest involvement of DA receptor in acrylamide neurotoxicity (Dixit et al 1981).

Vegetable Poisons

Lathyrism: Lathyrism is a type of spastic paraplegia in which the predominant lesion appears to be distal degeneration of corticospinal tract. It is produced by consumption of certain legumes like Lathyrus Sativa. This disease has been mentioned in the ancient Ayurvedic treatise - Bhav Prakash. General Sleeman described, in 1848, the association of L.Sativa and outbreak of epidemic lathyrism. Acute paraplegia in lathyrism, first noted by General Sleeman, was confirmed by others. Ganapathy (1960) noted that paraplegia was precipitated by exercise or cold. Lathyrism is reported to be endemic in UP, Bihar and Madhya Pradesh (Patwardhan 1952). Its prevalence figures range between 0.3% - 2.5% (Gopalan et al 1983). Impotence, disturbance of micturition and defeacation have also been reported in lathyrism. In 1975-76, subclinical lathyrism was reported by ITRC (1976) during an epidemic in the Unnao district of UP. Of 159 asymptomatic individuals examined in this district, 37 had no weakness. The knee and ankle reflexes were brisk and plantar responses extensor. All of them were found to be consuming lathyrus sativus. Despite cautioning them of the dangers of continued intake of this seed, 15 could not avoid eating it and later developed full blown lathyrism. The others, who had excluded lathyrus seeds from their diet, showed no progression of their neurological findings.

Extracts of L.Sativa and BOAA (BN-oxalyl-amino-L-alanine) produce various types of limb paralysis in animal models (Rao et al 1967,Mani et al 1971). Several compounds extracted from the various species of the lathyrus plant have been proposed as human lathyrogen. One of them is beta aminopropionitrite (BAPN). It causes vasospasm in animals and may be responsible for osteolathyrism (Dastur 1962). BAPN is not a component of L. Sativa. BOAA is implicated in human lathyrism. The complexities of identification of various toxic aminoacids and their derivatives from lathyrus plant have been investigated by Roy (1981). Rao and Sarma (1967) noted that young animals were susceptible and mature refractory to BOAA. However, the latter also became susceptible to BOAA when treated with drugs causing acidosis. This observation suggests the existence of a blood brain barrier for BOAA. Rao et al (1978) have questioned this hypothesis. Mehta et al (1979) failed to produce spastic paraparesis by feeding BOAA orally but produced flaccid or spastic paraplegia after intrathecal administration. The acute neurotoxic properties of BOAA suggest its etiological role in human lathyrism but administration of purified BOAA

in animals has not succeeded in producing lathyrism consistently (Roy et al 1963,Rao et al 1967). The role of vasospasm in the pathogenesis of lathyrism has been suggested (Acton and Chopra 1922). The pathogenesis of neurolathyrism is still unclear and further studies in this direction are needed.

Manganese may play a part in the genesis of lathyrism. A concentration of 5-15mg of manganese /100mg dry seed has been reported in L. Sativa seeds (Sadashivan et al 1960). In the village of Unnao, UP, where neurolathyrism was reported, the manganese content of drinking water is upto 42 times higher than the permitted level (ITRC 1975). Neurolathyrism is still a challenge. The difficulty in producing a satisfactory animal model, lack of autopsy studies (only three autopsies published so far) and paucity of neurophysiological studies have been the major hurdles in our understanding of this disease. Studies on lathyrism may provide a unique model for understanding motor neurone disease.

Cycads: The interest in the neurotoxicity of cycads has been stimulated by the high incidence of amyotrophic lateral sclerosis in Guam and Mariana islands. Nuts of cycus circinalis had been consumed in Guamanian food. Dastur (1964) studied the effect of orally administered cycads in monkeys. A quantitative chromatographic method for estimation of cycasin content of cycus circinalis was reported by Palekar and Dastur (1965).

Cannabis: Abusage of cannabis has registered a steep rise. Sethi et al (1984) reported normal nerve conduction and EEG studies in cannabis addicts. They did not find significant cognitive deficits.

Cerebra odollum is an intensely poisonous plant found in the coastal swamps of India. Its fruit is an important homicidal poison in Kerala. Kuruvilla (Vellore) found its effect on the conducting system of heart somewhat similar to that of digoxin (personal communication).

Animal Poisons

Snake bite. Of the animal poisons snake venom is the commonest and most serious source of poisoning. There are five main varieties of poisonous snakes: colubridae, elapidae, hydropidae, vipridae and crotalidae.The cobra and kraits (of the elapidae) are the commonest in India. Sanford (1963) estimated world mortality around 3000-4000 per annum. Banerji and Bhattacharya (1972) estimate that about 15000 people in India die of snake bite every year. The neurotoxicity of snake poison depends upon its paralytic action on the neuromuscular junction. This was first reported by Kallaway and Holder (1932). A number of studies on the isolation and pharmacological characterisation of the neurotoxin from cobra venom have been conducted by Indian scientists (Gangoly and Malkana 1936, Ghosh and De 1938, Ghosh and De 1941). The neuromuscular action of the toxin

at the endplate is like that of curare. The endplate is not depolarised but the depolarising action of acetylcholine at the endplate is abolished. The snake neurotoxin differs from curare in the slower and more persistent onset of action. The block cannot be removed by washing the endplate and is sustained for several hours after toxic exposure. The neurotoxic block is reversible only as long as it is partial. Once fully established, it is not affected by anticholinesterase (Meldrum 1965).

The role of artificial ventilation in the management of neuromuscular block in experimental cobra poisoning in dogs was shown by Gode et al (1968). Ghosh and Mandal (1964), Naphade and Shetti (1977) reported neuromuscular weakness following snake bite and suggested the usefulness of anticholinesterase therapy. Banerji et al (1972) in a study on 12 patients with neuromuscular weakness following snake bite reported significant therapeutic role of neostigmine and atropine. All the six cases survived under this regimen and recovered rapidly while in the group which did not receive neostigmine and atropine, only 60% survived. The authors stressed that neostigmine should be continued till the complete recovery is ensured.

Conclusion

Neurotoxicology has held an important place in India since antiquity. In the recent past lathyrism and fluorosis were studied intensively. Currently, with increasing industrialisation and environmental pollution by an ever increasing list of chemicals with neurotoxic potentials the neurotoxicological problems are increasing in diversity and magnitude.

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Neuropathology

Sarala Das and S.K. Shankar

History

When neurosurgery, as a speciality, was started in India, the histological diagnosis of tumours of the brain and spine was made by the pioneer neurosurgeons - Jacob Chandy, B. Ramamurthi and Ram G. Ginde -themselves. This was possible as they had received extensive training in neuropathology under Wilder Penfield in Montreal. As the departments evolved, neuropathology grew as a separate discipline at various centres.

In 1949, the Indian Council of Medical Research (ICMR) started a Neuropathology Unit at the Tata Memorial Hospital, Bombay. Khanolkar was the Director of Laboratories at Tata Memorial Hospital then and his work on the pathology of cancer and leprosy was recognised internationally. C.G.S. Iyer, who had just completed his M.D. in Medicine, was selected for training in neuropathology under L. Krainer,a neuropathologist and a Viennese refugee in India. On completion of his training, Iyer joined the neuropathology unit and worked on poliomyelitis which had assumed epidemic proportions in Bombay. In September 1950, D.K. Dastur, then a postgraduate student in medicine, was selected to join the neuropathology unit as Assistant Research Officer. Initially, this unit functioned as a part of the poliomyelitis unit under Professor Gharpure at the Grant Medical College. A little later, Iyer left for USA to study neurology and neuropathology at Harvard under Professors Derek Denny Brown and Raymond D. Adams respectively. He returned to India in 1952.

During the initial phases, studies were undertaken by Dastur and Khanolkar in the field of experimental poliomyelitis in monkeys. However, as Khanolkar had by then completed his work on the histology of early lesions in leprosy, stressing the neural involvement in the disease, Dastur started working on neural lesions in leprosy with special reference to correlations between cutaneous sensibility and intra-dermal neural histology in different types of leprosy. Using the method of intravital staining developed by Weddell in Oxford, Dastur demonstrated that the cutaneous innervation in normal hairy skin of man consisted only of the perifollicular nerve baskets, the interfollicular nerve nests and their freely ending axons (1955). Increasing degrees of sensory loss in the leprous skin

lesions were accompanied by decreasing density of intradermal nerves, the impairment of thermal and pain modalities being earlier and associated with loss of finer freely ending fibres and nerve nets. By this time Dastur had carried out his other study of vital staining of the terminal motor innervation in leprosy i.e. of the changes in myoneural endings and intramuscular nerves, in correlation with muscle histology and motor power (Dastur 1956).

The ICMR neuropathology unit was started in 1950 with the triple objectives of (1) conducting neurological research (2) giving diagnostic neuropathology service and (3) teaching neuropathology. Thus Bombay was in a unique position, not only in India, but perhaps in the world, of having a neuropathology service well before the neurologists and neurosurgeons got on the scene.'(D.K. Dastur -personal communication) Iyer and Dastur were able to establish a reference centre for neuropathology by collecting material from the different hospitals in Bombay. They undertook studies on Japanese encephalitis, Kyasanur forest disease, lathyrism, nutritional neuropathy and neurological disorders secondary to altered metabolism. Histological diagnosis of tumors, brain biopsies, muscle biopsies and other specimens also formed a part of their activities.

On Iyer's return, he tried to develop a department of neuropathology at the Seth G. S. Medical College and K.E.M. Hospital, Bombay. This plan did not materialise. In 1962, Anil Desai, then assistant professor of neurology at these institutions, wrote to Professor Ludo van Bogaert, requesting him to depute someone to train neuro-pathologists at these institutions. Bogaert, in turn, wrote to Abner Wolf in New York and 15 directors of neuropathology in the USA. Professor Feigin of New York University recommended his young colleague Ilona Bubelis. She accepted the invitation and set up the department in 1964-65. She took D. H. Deshpande under her wing and was able to state on January 4, 1965 that 'My successor, D. H. Deshpande is rapidly acquiring knowledge in neuropathology.' By the time she left India, she and Deshpande had completed an impressive amount of work and prepared 12 publications on subjects such as lathyrism, reticulosis, infantile Jacob-Creutzfeldt disease, gargoylism and the effects of hypothermia on the central nervous system. D. H. Deshpande then took over the reins of the department till his departure for Bangalore in 1974 when A.P. Desai became the head of the neuropathology unit. This department has focussed attention on tuberculous and fungal infections of the central nervous system, neuromuscular disorders, immunohistochemistry and ultrastructural study of brain tumors.

In 1961, Iyer was asked by the Government of India to establish the laboratories of the Central Leprosy Teaching and Research Institute at Chingleput, where he continued as the Head of the Division of Laboratories. From 1966 to 1979 he was the Director of the Institute and subsequently

an emeritus medical scientist of ICMR. This institute is an important centre for study of leprosy.

The neuropathology unit of the Grant Medical College and J.J. Hospital at Bombay started in June 1962 when Dastur and his colleagues moved over from the Tata Cancer Research Centre. Daya Manghani joined them in 1962 and worked on Wilson's disease and manganese poisoning. V.S. Lalitha joined them in 1964. They studied the prevalence and pathology of intracranial space occupying lesions, the many facets of neuro-tuberculosis and other commonly encountered problems.

At the All India Institute of Mental Health - now National Institute of Mental Health and Neuro Sciences (NIMHANS)- the department of neurosurgery had started in the year 1958, under R.M. Verma and the department of neurology under K.S. Mani. In 1959, S. Sriramachari started the department of neuropathology. In November 1962 he left to join the ICMR at New Delhi as Deputy Director. From 1962 to 1974, the department of neuropathology did not function satisfactorily. D.H. Deshpande, earlier Professor of Neuropathology at Seth G. S. Medical College and K. E. M. Hospital, Bombay joined the department in 1974. Sarala Das took over as Professor of Neuropathology in 1982. Research is being carried out at NIMHANS on Japanese encephalitis, neurotuberculosis, neurocysticercosis, neuromuscular disorders, stroke in young, degenerative disorders and developmental neurobiology.

During the early sixties, the department of pathology at K.G. Medical College, Lucknow, was fortunate in having one of the faculty members, Krishna N. Wahal, trained in neuropathology by John A Wagner at the University of Maryland School of Medicine, USA. He had worked on brain changes in mice in experimental hepatic encephalopathy and experimental brain tumors. The neuropathology service continued in the college as a part of department of pathology. Diagnostic service and teaching of postgraduate students of neurosciences have since been undertaken in addition to some research activities in this centre.

In 1965 S. Sriramachari moved on to the Indian Registry of Pathology (IRP), founded by the ICMR at the department of pathology, Safdarjung Hospital, New Delhi. Although the registry was meant for analysis and documentation of all pathological material, his interest and training in neuropathology prompted Sriramachari to initiate research activities in neuropathology. At that time there was no qualified neuropathologist at the All India Institute of Medical Sciences (AIIMS),Delhi. Sriramachari was appointed Honorary Professor of Pathology, AIIMS, from 1966-1968. He conducted brain cutting sessions for students of neurosurgery and neurology. Two research scholars of ICMR joined IRP with the aim of taking up neuropathology as a career. Sarala Das worked on biophysical and enzyme histo-chemical aspects of brain tumors and Balani, a veterinary

pathologist, worked on experimental brain oedema in monkeys. A study was also undertaken on enzyme histochemical aspects of muscle in human muscular dystrophy and experimental myopathy in chick. This was one of the few centres in India where work-up on neuromuscular disorders was conducted during the late sixties.

A separate department of neuropathology was started at Madras by V. C. Anguli. She had been sent to Canada under the Colombo plan for training under Penfield in neuropathology. On her transfer elsewhere three years later, C. G. S. Iyer (then posted at Chingleput) served as honorary neuropathologist. Sarasa Bharati joined the department in 1971 and worked on experimental brain tumors and produced neoplasms in brain of rats belonging to Madras Native Albino strain (MNA). Diagnostic service, teaching and research in neuro-pathology were thus established at the Institute of Neurology, Madras. She is also working on toxic changes in brain caused by oleander, organophosphorus compounds, ethyl alcohol, ultrastructural study of brain in protein calorie malnutrition and diabetic neuropathies.

Neuropathology as a discipline was started in the department of pathology at All India Institute of Medical Sciences (AIIMS), New Delhi in 1971 by Subimal Roy. For a few years, diagnostic neuropathology constituted bulk of the work. Over the years, teaching and research activities have increased. This centre is engaged mainly in the study of pituitary tumors. Localisation of hormones in the cells of pituitary tumors by immunohistochemistry and immunoelectronmicroscopy is the major area developed by Roy and his colleagues. In neuro-oncology they have concentrated on cell kinetics and cerebral edema associated with neoplasms. Other fields of work include the effects of undernutrition on development of brain and peripheral nervous system and infections of the central nervous system.

By this time there were several centres in India having neurosurgical and neurological services. However, in many of these pathologists working in morbid anatomy or histopathology rendered neuropathological diagnostic service.

In the late sixties, the need for neuropathology was increasingly felt at the Postgraduate Institute of Medical Education and Research (PGIMER),Chandigarh. A.K. Banerjee, trained in neuropathology at Queen's Square, London (1967-70) joined the department of pathology in 1971. His studies include the pattern of cerebrovascular disease (Banerjee 1973, 1989), paralytic rabies (Banerjee 1974, Chopra et al 1980), histology in the 'wasted leg syndrome (Chopra et al 1984, Prabhakar et al 1981), neuropathological findings in subarachnoid hemorrhage (Banerjee 1987), cerebral venous thrombosis (Chopra et al: in press), central neurofibromatosis (Banerjee 1982),

After completion of training and Ph.D at IRP, New Delhi, Sarala Das returned to S.C.B. Medical College, Cuttack in 1971 to start the discipline of neuropathology in the department of pathology so as to provide services to the departments of neurology and neurosurgery,teach postgraduates and conduct research in some aspects of myopathies and neuropathies. However, neuropathology as a distinct discipline, could not be established in the centre. The same situation prevails in many other centres in India where there are active units of neurosurgery and neurology. Diagnostic neuropathology is being provided by members of the department of pathology but the speciality has not got established. Either the pathologist is not trained adequately to develop it or there are administrative hurdles.

Neuropathology as a speciality was initiated and developed by Radhakrishnan at the Sri Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST), Trivandrum in 1978. The research areas here include infectious diseases of CNS, especially fungal infections and tuberculosis and experimental brain tumors.

Research in the field of neuropathology is also being carried out in Indian Cancer Research Centre (ICRC) at Bombay where V. S. Lalitha works on human and experimental tumors of nervous system and neurogenic teratocarcinoma. Preparation of antisera against glial fibrillary acid protein (GFAP) and neurofilament proteins have been undertaken successfully.

The Medical Research Centre of Bombay Hospital Trust has a department of neuropathology and applied biology established by D. K. Dastur after his retirement from the Grant Medical College and J. J. Hospital.

In our country much energy and time are spent in fighting infections. Most of the work in the speciality was and is directed towards understanding infections of the nervous system. Attention has also been paid to other disorders like neoplasms, cerebrovascular accidents, degenerative disorders, nutritional disorders, neuromuscular diseases and other diseases of nervous system. Some of the important contributions are highlighted below.

Infections of Nervous System

Neurotuberculosis

Tuberculous infection of the central nervous system is a common disease in India. Clinicopathological studies have been undertaken in several centres of India (Chandnani et al 1957, Ramamurthi et al 1961, Deshpande et al 1969). Detailed pathological studies on the disorder have also been done during the last 3 decades (Dastur and Udani 1966d, Dastur and Lalitha 1973). The different types of lesions seen in brain and spinal cord in tuberculous infection, **basal meningitis** which is thick and plaque-

like resulting in **arteritis** and infarction (one of the important parenchymal lesions in the disease), border zone encephalitis involving cerebrum and brainstem, granular ependymitis and presence of small tubercles in tuberculous meningitis have been discussed in detail. Association of diffuse cerebral oedema producing diffuse **tuberculous encephalopathy** was described. Delayed hypersensitivity i.e. cell-mediated immunity to tuberculoprotein was shown to play a role in the pathogenesis of tuberculous encephalopathy. (Dastur and Udani 1966) In a proportion of the cases hypersensitivity to the brain's own myelin-protein may be of importance (Dastur 1986a). Earlier Dastur and Wadia (1969) had elaborated the pathology and pathogenesis of **tuberculous spinal meningitis** with myeloradiculopathy.

Tuberculomas of brain are common intracranial space occupying lesions and had drawn the attention of most neurosurgeons in our country (Chandnani et al 1957, Ramamurthi et al 1961, Sinh et al 1968, Dastur HM 1972, Lalitha and Dastur 1980). Ultrastructural features of vasculopathy in and around brain tuberculoma showed vascular proliferation, vasculitis and affection of venules (Lalitha and Dastur 1974, Dastur and Dave 1977b). The altered basement membrane in the vessel wall was felt to be antigenic and responsible for perpetuating the necrotic vascular and perivascular reactions in tuberculous meningitis and tuberculoma.

An attempt was made to produce an **experimental model** of human tuberculoma in monkeys to get some informations on natural history, effect of antituberculous drugs on the lesion and relationship of tuberculoma to tuberculous meningitis (Tandon et al 1970,1974). Well circumscribed focal abscesses were produced, morphologically different from the classical tuberculomas. No further study in this direction is on record.

Hydrocephalus in children is one of the common complications of TBM (Dastur HM et al 1974). Shankar and Das (1984), studied pathological changes in pre and post shunted brains in post infective hydrocephalus. They saw no significant structural restitution of cortical mantle after operation. Emphasis is being placed on early diagnosis of neurotuberculosis so as to prevent the untreatable complications.

In an attempt to localise the tuberculous antigen in tissues and to identify the cells involved in antigen processing and storage, an immunohistochemical study was undertaken at NIMHANS, Bangalore using a battery of monoclonal antibodies directed to different components of the mycobacteria. IgM and IgG antibody secreting clones directed against lipoarabinomanin-B, a polysaccharide component of the bacillus stained specifically the giant cells and epitheliungal infectionsoid cells. In addition the endothelial cells and the smooth muscle cells of vessel walls were also stained indicating their role in antigen localisation and processing. The

antibodies to the protein component of bacillus localised the antigen on the vessel walls in the necrosed zone. The different components of the antigen appear to mediate the immune response at different sites to produce the end result.

Neural Leprosy

Leprosy is an interesting disease entity for the neuropathologist. Since a sizeable proportion (about 30%) of the global population of leprosy patients belong to India, leprosy constitutes a national health problem. The morbidity of the disease is in no small measure referable to the nerve damage. As early as in 1936, Muir and Chatterji suggested that cutaneous neurovascular plexuses provide the **route for mycobacterium leprae to infect nerves.** They further showed that leprous exudate was predominantly around intradermal nerve twigs. Based on their seminal studies of leprosy contacts, Khanolkar (1951,1955,1964) concluded that affected or healthy skin is the portal of entry for bacilli and their spread. He postulated that axons provided channels for bacillary dissemination. Dastur (1967a) terms leprosy **a model of peripheral neuro-pathology.** The Schwann cell is the target cell for leprosy bacilli (Dastur 1956, Dastur et al 1973b, Job and Verghese 1975). Job (1970) demonstrated mycobacterium leprae in Schwann cells and axons by electron microscopy. Ultrastructural studies by Dastur et al (1973b) led them to report that the major bacillary spread was contained within the Schwann cells associated with unmyelinated fibres to be followed by intraneural vascular endothelial cells, which swell and may rupture into the lumen, thereby producing bacillemia in lepromatous leprosy. The fine structure of nerves, including changes in Schwann and perineurial cells and infiltrating macrophages in untreated and long treated cases was elaborated by Dastur and Porwal (1979a,1982a) and the role of lysosomal enzymes in the digestion of M. leprae shown by Dastur et al (1982a). Vaidya et al (1970) have reported presence of bacilli in the central nervous system (probably in leptomeninges or blood vessels) in experimental animals, an unusual feature in man. In five autopsied cases where almost all the nerves of the upper limbs and cervical cord were dissected out at autopsy, Dastur (1978,1983) found the most proximal extent of M. leprae in the capsule cells of the ganglia (homologues of the Schwann cells). No organisms were seen in the ganglion cells, anterior or posterior horn cells.

Histopathological studies on peripheral nerves in leprosy have been carried out by many investigators (Iyer 1965, Job and Desikan 1968, Iyer and Desikan 1968) and have been reviewed by Dastur (1977,1978,1983). Srinivasan et al (1982) have noted the discrepancy in the histopathological features of leprosy lesions in the skin and peripheral nerves. Electron microscopic studies by those already cited, by Antia et al (1975) and Jacob et al (1987) have been fruitful in elucidating pathological changes in nerves. Nerve damage in relation to the immunological status of the patient has

also been investigated both in human (Dastur et al 1972 and 1982a, Job et al 1972, Job 1973 and 1988, Anthony et al 1979, Antia et al 1980) and in experimental leprosy (Mehta and Antia 1984, Chandi and Chacko 1986). Studies on nerve regeneration in leprosy have also been carried out in human subjects (Dastur and Razzak 1971, Dastur et al 1973b) and in experimental animals (Shetty and Antia 1981). Mathur et al (1971) have compared cutaneous and somatic nervous function in the lesions of leprosy and showed damage to both types of nerve fibres. Antia et al (1970) have shown the selective damage at certain sites in many nerves in leprosy.

Leprous myositis occurring due to bacillary invasion or nerve damage has been studied by Job et al (1969) and Koranne et al (1978) by light and electron microscopy. A detailed histological, histochemical and fine structural study of skeletal muscle was carried out by Daver et al (1980) and Dastur and Daver (1980). While occasional bacilli were found in intramuscular neurovascular bundles, Dastur and Daver found a bacillus within a muscle fibre only once.

Electrophysiological techniques have been applied as an aid in the diagnosis of leprosy and to determine the nature and extent of nerve degeneration in human and experimental leprosy by a number of workers (Dastur et al 1966, Antia et al 1970, Karat and Pichandy 1973, Pandya and Chulawala 1981, Gourie-Devi and Taliath 1981, Dhand et al 1988).

In order to facilitate early detection of leprosy, the suitability of branches of dermal cutaneous nerve for electrophysiological and histopathological investigation in patients with minimal neurological deficits has been stressed.(Dastur 1978, Gourie-Devi and Taliath 1981, Jacob and Mathai 1988) In an effort at understanding the biological basis of affinity of mycobacterium leprae to peripheral nerves and other related aspects, tissue culture studies have been undertaken by several investigators (Lalitha et al 1977, Mukherjee et al 1980). Lalitha et al showed the phagocytic capability of **Schwann cells** cultured from intracranial Schwannomas and spinal neurofibromas and suggested these cells as **'a possible model substrate for cultivation of M. leprae'.** Mukherjee and Antia (1985) have attempted to use nerve tissue culture as a model for the study of nerve damage in Hansen's disease.

It is evident that the extensive nerve damage produced by leprous neuropathy is unlikely to be repaired by drugs. An effective **vaccine** for prevention is being developed in several centres in India.

At the ICRC, Bombay, Bapat and Deo developed a vaccine against leprosy using the ICRC bacillus maintained in their laboratory for a long time. Administration of the vaccine has produced conversion of 60% of lepromin negative lepromatous patients to high immune lepromin positive state, verified histologically. As it has shown promise of improving the immune

status of leprosy patients and contacts, field trials have been initiated. Results are awaited. Similar efforts are also being made at the National Institute of Immunology, New Delhi and the Central Drug Research Institute, Lucknow.

Fungal infections of CNS

Cryptococcal meningitis has been reported from many centres (Sriramachari et al 1961, Devadiga et al 1968, Rao et al 1968, Icchaporia et al 1970, Sahoo et al 1974). The role of hyaluronidase has been tested in experimental animals having cryptococcal infection by Radhakrishnan et al (1982). Infection of CNS by other fungi is also documented (Dastur HM et al 1966c, Desai SC et al 1966, Kak et al 1972, Deshpande et al 1975, Deshpande et al 1976, Banerjee et al 1977, Sandhyamani et al 1981). Fungal granulomas of brain are not uncommon.

Fungal infections of CNS are usually associated with suppressed immunity as after prolonged chemotherapy for cancer and corticosteroid therapy. Asha et al (1986) have observed that 17 out of 25 of their patients, with fungal infections of CNS proven on culture, were immunologically uncompromised hosts. This is a common observation at other centres as well. In view of the fact that reports in western literature correlate AIDS with fungal infection of CNS, it is important to conduct a prospective study in our country on this aspect and test patients having proven fungal infections of CNS for AIDS.

Parasitic diseases

Amongst the parasitic diseases of CNS, neurocysticercosis and hydatid cysts of brain and spinal cord are the commonest lesions seen in our country. Earlier reports stressed the clinicopathological aspects of the disease (Singh et al 1963, Showramma et al 1963, Dinakar et al 1970, Ahuja et al 1978, Sawhney et al 1976, Srinivas et al 1980, Wani et al 1981). Tandon (1983) highlighted the clinico-pathological differences between the disease as seen in India and in other parts of the world. During the past decade, techniques for early detection of the disease, study of immune mechanisms involved and the production of vaccine are being pursued at centres set up by the ICMR and other organizations like ASTRA Research Centre,Bangalore. In human neurocysticercosis the dominant antigen responsible for various allergic and encephalitic reactions has been localised to the glycocalyx on the surface of the parasite by immunohistochemical techniques. High levels of antibodies to these glycoprotein-antigens are recognised in CSF following drug therapy. Further work is in progress at ASTRA Research Centre, Bangalore in collaboration with departments of microbiology and neuro-pathology, NIMHANS, Bangalore to identify the cellular system involved in the synthesis and secretion/excretion of these antigens from the parasites into the host.

Two asymptomatic but rare, provocative and microscopic lesions have been reported from India: a microfilarial granuloma in the brain (Dastur 1954) and encysted sarcocysts packed with larvae of Sarcocysts or Sarcosporidia in muscle fibres (Dastur and Iyer 1955).

Virus diseases

Poliomyelitis, rabies, subacute sclerosing pan encephalitis (SSPE) and Japanese encephalitis are some of the commonly encountered and widely distributed viral disorders in India.

Iyer and Dastur undertook experimental work on **poliomyelitis** in monkeys in 1950. A rare and interesting poliomyelitis like illness was seen in and around Bombay in patients with acute haemorrhagic conjunctivitis in 1980-1981. (See paper by Wadia in this volume for details.) Haemorrhagic myelitis was seen in 3 patients coming to autopsy at the J. J. Hospital, Bombay. Enterovirus 70 specific antigen was demonstrated in microglial cells and anterior horn neurons in these patients (Pal et al 1986).

There have been several reports on **rabies** and all the clinical forms have been documented (Banerjee et al 1974, Sandhyamani et al 1981). Histological features and ultrastructural characteristics have been studied in detail. Sandhyamani et al showed three forms of inclusion bodies in the cytoplasm of neurons. These observations were made in 6 patients surviving for more than 14 days after the onset of symptoms. Since rabies is a frequent malady in stray dogs in India, antirabies vaccine is extensively used following dog bite. Neurological complications due to B-propiolactone (BPL)-inactivated antirabies vaccination are encountered in most hospitals. Swamy et al (1984) have reported a detailed study of 76 such patients, 14 of whom died. Autopsy on 6 showed evidence of myeloradiculopathy, variable encephalitic involvement and necrotising myelopathy of immune type. Manghani et al (1986) studied the Negri body of rabies in human and experimentally inoculated mouse brain and showed, perhaps for the first time, neucleocapsid virions emerging from and accumulating around tubular or bullet shaped structures generally considered to be the viral material in Negri bodies.

Subacute sclerosing panenencephalitis (SSPE) is often seen in India. Reports on clinical and histopathological aspects are available (Mehta et al 1959, Mani et al 1964). In 1966, a year before the special meeting at the National Institutes of Health, Bethesda, USA, which recommended the use of the term SSPE, D. K. Dastur, in his presidential address to the Neurological Society of India had suggested the use of the term 'subacute gliosing panencephalitis' on the basis of his neuropathological studies on 15 patients with this illness at the J. J. Hospital, Bombay. Singhal et al (1974) reported on 39 cases with SSPE in 8 of whom the CSF showed

antimeasles antibodies. Shobha Broor and coworkers (1975,1979) have studied 79 cases with regards to detection of measles HAI antibodies in serum and CSF and discussed the significance in this condition. Nagraja et al (1985) have studied histopathology of brain from biopsied and autopsied specimens. Inclusion bodies are not seen in all the cases. (Nagraja et al 1985) Immunisation against measles has now been widely undertaken in India in the infant population to prevent this condition.

Since 1924, following an epidemic of encephalitis in Japan, many workers have reported neuropathological features in these patients. Biswas et al (1976) reported clinicopathological aspects of Japanese encephalitis(JE) epidemics encountered in Bankura. Comprehensive reports have been published in ICMR Bulletin (1980) and from National Institute of Virology (1980). Visceral larva migrans (of Toxocara canis) seems to potentiate sublethal infection of JE when mice are dually infected thus (Pavri et al 1975). Following an outbreak of epidemic at Kolar in the south Indian state of Karnataka, various aspects of this disease were studied and reported by Gourie-Devi et al (1981) and Shankar et al (1983a). Pathological features in autopsied brains included gliomesenchymal nodules and necrolytic lesions. This study is continuing and virological, immunological and immunohistochemical characterisations are being undertaken at NIMHANS. A significant association between J.E. and neuro-cysticercosis was also observed in this study. A national conference on J.E. was held at ICMR, New Delhi in 1982. The conclusions and recommendations regarding current status of J.E. in India, clinical aspects of management, laboratory diagnosis and control measures have been documented and published in the proceedings of the conference (1984). Recently a clinical picture like that of the Guillain-Barre syndrome following JE has been recognised at NIMHANS.

The single neuropathological study on the epizootic in monkeys in Kyasanur forest in south India, was reported by C G S Iyer et al in 1960. Twenty-two monkeys found dead in the forest were autopsied. Tick borne encephalitis was clearly shown in two. Three others showed some changes. Autopsy studies on humans succumbing to the disease have not yet been reported. Neuro-OncologyAs noted above, Jacob Chandy, B. Ramamurthi and Ram G. Ginde pioneered neuro-oncological studies at their respective centres.

Initial studies by neuropathologists centred around documentation of tumors seen at different centres and comparing them with those noted in the west. (Dastur and Iyer 1966a, Dastur and Lalitha 1980, Wahal et al 1981). The small differences noted at the different centres could be attributed to the aggressive approach of the neurosurgical team at some centres and the bias in selection of operable and inoperable cases. Two centres, one from Bombay (Dastur and Lalitha 1969, Lalitha 1975) and the other from Madras, have large series of brain tumors, well documented

for a meaningful comparison with foreign statistics. A compilation of national data is available in the proceedings of the National Seminar on Neuro-oncology conducted in Bangalore in 1979.

The application of ultrastructural studies in the pathogenesis and differentiation of tumors, has been taken up in Delhi, Bombay, Madras and Bangalore.

Most workers use the classical stains for delineation of various mesenchymal and neuroectodermal elements in tumors of the nervous system.Sarala Das and Sriramchari from Indian Registry of Pathology (ICMR), New Delhi, used for the first time, the bio-optical properties of the glial filaments, reticulin and collagen for better delineation and diagnosis of intracranial tumors. This has provided insight into intracellular fibrous proteins and intermediate filaments. Unfortunately, there is no further follow up of the work. Special attention has been paid to the study of ultra-structural and endocrinological features of pituitary adenomas applying immunohistochemical techniques at the Department of Pathology, AIIMS, New Delhi. They have noted many chromophobe adenomas producing acromegaly and shown these to be functional on ultrastructural study in contrast to the other nonfunctional chromophobe adenomas (Roy 1977, Roy 1983). Their studies were backed by the estimation of hormonal profile by RIA. In addition, this group has demonstrated the ultrastructural characteristics of the microvasculature and the oncocytic adenomas of the pituitary (Roy 1978, Roy 1979, Chowdhury et al 1986).

With the advent of **immunochemical techniques,** and commercial availability of the antibodies, work is in progress in most laboratories for better delineation of the various cellular elements in tumors. The application of immunohistochemistry has provided better understanding of the histogenesis of CNS tumors.(Sarkar et al 1988, Sarkar et al - in press) Multifarious antigenic expression of tumour cells, hitherto considered a homogenous population, has been noted. The demonstration of the differentiating potential in medulloblastomas and the evolution of the poorly differentiated primitive neuroectodermal tumors probably from the gliomas has prompted study on the mechanisms for differentiation and dedifferentiation in brain tumors (Roy et al 1980).

M. Mahadevan, Usha Ramasubban and colleagues in the department of pathology at the Dr. A. L. Mudaliar Postgraduate Institute of Basic Medical Sciences, Taramani, Madras subjected 100 tumours obtained from the central nervous system to **immunohistology** using seven tumour markers: GFAP, NFP, vimentin, F VIII R Ag, VEA-1 lectin, S100 protein and EMA. They concluded:1. GFAP is positive in all types of astrocytomas, more so in benign tumours. GFAP expression was also found in 8 oligodendrogliomas, 2 ependymomas and one malignant ependymoma.

GFAP helped not only in grading malignancy but also in differentiating tumours of astrocytic, oligodendroglial and ependymal origin and in distinguishing them from tumours of non-glial origin. 2. Tumours of the PNET group could be subclassified with respect to their expression of glial or neuronal origin by immunostaining with GFAP and NFP - a specific marker of neuronal cells. 3. Marker study with FVIIIRAg and VEA-1 lectin is essential for neoplasms of vascular origin and to rule out co-existing angiosarcoma in specified cases of gliosarcomas. They could also help in studying the elusive stromal cells of haemangioblastoma. 4. Vimentin is helpful in diagnosis of meningioma and gliosarcomas with a mesenchymal component. 5. Marker study with S 100 protein is helpful in diagnosis of peripheral nerve sheath tumours where all other markers are unhelpful. 6. EMA was not helpful in the study of meningiomas and craniopharyngiomas. (Personal communication.)

The centres at Bangalore and AIIMS have conducted limited studies to evaluate the **host immune response to the origin and evolution of the glial tumors,** both by conventional histopathology and immunohistochemical study with equivocal inferences. A detailed evaluation in this direction is called for.

The ICRC and the neuropathology department headed by Dastur in Bombay have used **tissue culture for studies on cell biology of CNS neoplasms.** They have demonstrated the phagocytic potential of the glial neoplasm. As noted above, Lalitha et al (1977) showed the phagocytic function of Schwann cells cultured from intracranial schwannomas and spinal neurofibromas. In vitro cultivation of the glial neoplasms is used at AIIMS,, New Delhi, for drug sensitivity and kinetic studies. In the field of **experimental neurooncogenesis,** the neuropathologists from Lucknow and Sarasa Bharati at Madras have developed the technique of intracerebral implantation of polycyclic hydrocarbons (Wahal and Ansari 1968). They have succeeded in producing sarcomas in the mesenchymal elements of the meninges and vascular wall. The development of glial tumors and the cell of origin were unpredictable. Sarasa Bharati has observed 'C' type virus particle in tumour cells next to the carcinogenic chemical implanted in the brain and has recorded the shortest time for the gross appearance of tumors in the Madras native albino mice.

Transplacental carcinogenesis using nitrosourea derivates, early neoplastic proliferations leading to glial neoplasms were evaluated at Bangalore and Bombay. Lalitha and her team from the ICRC (Hasgekar et al 1986) could modulate the incidence of the tumour by X-radiation of the animals, prior to injection of carcinogen. They achieved significant success in developing tumors with relatively predictable frequency. They developed transplantable teratocarcinomas in mice by implantation of embryo in the renal capsule of the rodent (Thakre and Lalitha 1988). One such tumor turned exclusively neurogenic with highly primitive neuro-

epithelial cells providing an animal model for primitive neuroectodermal tumors.

A few **animal and human glioma cell lines** developed indigenously are available. Further impetus to this is provided by the 'Cell Line Inventory' started at Poona by the Indian National Science Academy and more recently by the creation of a National Facility for Animal Tissue and Cell Culture at Pune by Department of Biotechnology.

Modifiers and modulators of radiation response of human brain tumors

This is a border zone between the pathology of the neural tumors and their therapy. Most brain tumors are virtually incurable by existing forms of therapy. These neoplasms are heterogenous and repair-efficient, hence sustain themselves and maintain their growth potential even after treatment. In addition to conventional radiotherapy, chemotherapy and combination therapy, attention is bestowed on modifiers and modulators of radiotherapy. Earlier studies in lower cellular systems have shown that 2-deoxy-glucose (2-DG), an inhibitor of glucose uptake and glycolysis, can differentially inhibit post-radiation repair in cells (like the cancer cells) with high glycolysis. Applying this analogy to cerebral gliomas, in vitro studies on human brain tumors were initiated at NIMHANS. Induction of micronuclei was used as a measure of the radiation damage as cells with micronuclei are known to be associated with reduced reproductive capacity.(Dwarakanath and Jain 1987a) The study has shown that 2DG in appropriate concentration can enhance radiation damage in brain tumours.(Dwarakanath and Jain 1985, Dwarakanath and Jain 1987b) In view of the heterogeneity of brain tumors, their proliferation kinetics and DNA repair mechanism, it is essential to select the cases for clinical trials by in vitro sensitivity tests. Phase I of clinical trials have started. Halogenated analogues of thymidine such as 5-bromodeoxyuridine (5-BUDR) and 5-iododeoxyuridine get incorporated into the DNA of proliferating cells leading to an increase in the cellular radiosensitivity. A combination of 5-BUDR and 2-DG has been found to act additively to increase the sensitivity of the tumors to radiation. The toxicity noted when BUDR is used alone at a high concentration is reduced when the combination is used. As the native cells of the brain are relatively amitotic and stable, while the neoplastic cells are in the growth phase, this combination therapy appears to have a specific role in modulating and optimizing therapy that may not be applicable in other areas of the body. (Kalia and Jain 1987, Kalia 1988)

Another line of investigation in the study of modulators is the role of photodynamic therapy (Jain 1987). Photo-sensitizing chemicals, in the presence of light, cause reduction in mitochondrial respiration and oxidative phosphorylation resulting in cellular energy deficit and necrosis. The tumor cells appear to respond differentially to these chemicals in

contrast to normal cells. Studies are in progress at NIMHANS, Bangalore.In brain tumors, the distinction between benign and malignant neoplasms, on the basis of histological features alone is often difficult and fallacious. It is desirable to complement the clinical and histological evaluation of the brain tumors with studies which provide quantitative and objective kinetic information on the biological behaviour of neoplasms. At NIMHANS, using the technique of flow cytometry of brain tumour cell suspension, the DNA index and percentage proliferation fraction were estimated.(Dwarakanath et al 1984) This showed multiple DNA indices in some cases, indicating the presence of different subpopulations of cells and a cell kinetic heterogeneity in histologically uniform tumors. This has helped in better delineation of the proliferating potential, the malignant nature and biological behaviour of tumors. At AIIMS, in vitro culture of tumors and autoradiographic studies are used for similar evaluation. Cytophotometric studies have been attempted but methodological difficulties in making accurate measurement on large sample of cells has limited the application of this technique. Currently, in vivo cell kinetics of brain tumours in man, using BUdR are in progress at the same institute.Some studies on mathematical modelling and computer aided calculations were attempted in the field of neurooncology.(Bhaumik et al 1984) These models may be used to examine consequences of certain assumptions on the behaviour of biological systems and also in meaningful and objective interpretation. A mechanistic study of cell division can also provide some insight into the morphogenesis of the growing organism (Sahay 1984).

Cerebrovascular diseases

Stroke in the young (patients below 40 years of age) is commoner in India than in the west (Bansal et al 1973, Dalal 1979, Chopra et al 1979, Srinivasan 1984). Cortical venous thrombosis is common in our country and forms a major cause of cerebrovascular disease. Reports on detailed pathological studies on brains from patients with stroke are lacking. Data concerning different clinical aspects of stroke have been published in Stroke Symposium based on discussions at 28th Annual Conference of Neurological Society of India held at Trivandrum in 1978. Studies from Madras and Bombay show that the occurrance of atherosclerosis in Indian population is not significantly different from that seen in the west. (Subramaniam and Kulangmra 1967, Dalal et al 1982) Biochemical and coagulation factors in cerebrovascular disease (CVD) have been worked out and correlations have been attempted to explain the pathogenesis of CVD on the basis of these changes.(Bansal et al 1978) Bansal and coworkers (1986) also detected familial hyperlipidaemia in young patients suffering from strokes.

Work on cerebrovascular disease in India during the past 35 years has been reviewed by Jain and Maheshwari (1986). The incidence of stroke

reported from India is less than that in the west. This may be a reflection of population at risk.

Reviewing the experience at the K. E. M. Hospital, Bombay, Nagpal (1983) reported a large number of patients with cerebral cortical, deep vein and venous sinus thrombosis. A striking feature in that series was the number of young males presenting with acute symptoms and signs and showing clinical, angiographic, computerised tomographic and pathological evidence of extensive venous thrombosis in the brain with hemorrhagic infarction. The only feature common to the majority of these young men was the fact that they were habitual consumers of illicit alcohol.

Studies on autopsy material have been undertaken at NIMHANS, Bangalore and at PGIMER, Chandigarh. Of 2017 autopsies conducted during 1976-1985 at NIMHANS, 430 were on patients with cerebrovascular disease. 178 of 430 were cases of stroke in the young. Hypertension and athero-sclerosis were major aetiological factors causing stroke in general while cortical venous thrombosis, both post partum and idiopathic, was the cause in 48% of stroke in young individuals. (Personal experience, presented at the 34th Annual Conference of NSI, 1984,Varanasi). Clinical and pathological studies conducted so far have not been able to pinpoint the cause for cortical venous thrombosis being so common in many parts of India.

Developmental defects

Though spinal dysraphism and the herniation of the meninges through spinal defects have been noted both by paediatric surgeons and neurosurgeons (Dinakar et al 1980), no systematic study has been conducted. In a limited study, Talwalkar and Dastur from Bombay (1970) proposed a new classification for better understanding of pathomorphological lesions. They suggested the term 'ectopic spinal cord' in the place of meningomyelocoele. They noted two main lesions: (1) the tethering of the lower end of spinal cord in some cases of meningocoeles and meningomyelocoeles (2) gross exposure of the cord they called 'ectopia'- a hall mark of meningomyelocoele. They reviewed neurological findings in 144 patients with 'meningoceles'. In 113, the stalk of the meningocele was connected to neural tissue. 52 patients had a lipoma tethering the spinal cord and 56 had a cystic mass with tethered spinal roots (Talwalkar and Dastur 1985). Dastur DK (1977a) compared neuropathological findings at autopsy in 16 infants and children with congenital aqueduct stenosis and 183 with tuberculous meningitis. 9 of the 16 had associated spinal meningocele, encephalocele or porencephalic cyst. Aqueductal findings included narrowing into a slit, perhaps by edema and gliosis.

Deshpande (1980), in collaboration with Vidyasagar, a neurosurgeon, has

made an original contribution on the histology of persistent embryonic veins in arteriovenous malformation of the brain (AVM). AVM in the brain represents a congenital vascular lesion, where a segment of the foetal vasculature has persisted to postnatal life, resulting in varied haemodynamic abnormalities. They established the histomorphological similarity between the normal human embryonic veins and veins present in the AVM.

The faculties of anatomy at AIIMS, New Delhi and Banaras Hindu University, Banaras, in collaboration with their departments of paediatric surgery have studied cranial and spinal defects in experimental animals. Many variants of congenital anomalies of the cranial, vertebral and neuroectodermal components have been seen both by the pathologists and veterinarians. No indepth study has followed. Individual cases continue to be recorded as anatomicopathological curiosities. Neuropathological findings in congenital atlantoaxial dislocations were reported by Dastur DK et al in 1965.

Dastur et al (1989) have suggested a myopathic pathogenesis for the rare condition where the bowel has normal autonomic plexuses but the infant suffers from Hirschsprung's disease. Findings on multiple enzyme histochemistry and electronmicroscopy of nerve cells, fibres and muscle fibres in the bowel in this disease have been described.

Using the technique of flow cytometry, Mishra et al from New Delhi (1983) have shown a reduction in the quantity of DNA per cell in the cerebellar external granular layer (EGL) of 'nervous mutant' mouse. This was accompanied by an increase in the DNA dispersion during 6-8 days of postnatal life. This loss of DNA was due to a partial degeneration of the cells of basal granular layer during the first week of postnatal life. The surviving cells were found later to achieve a DNA content equivalent to their bone marrow. DNA flow cytometry thus helped in early detection (almost 2 weeks before the clinical manifestation of the disease) of the homozygous nervous mutant.(Mishra et al 1983b) Unfortunately, this very powerful tool has not been applied to human material. Similar studies in microcephaly, macrocephaly, anen- cephaly and other teratological and developmental anomalies in aborted human embryos will yield very valuable and basic information on human neurobiology.

Malnutrition -brain pathology

The data on small-for-date human neonates(39-40 weeks duration) showed that the proportionate reduction in the brain was more marked in the cerebellum and medulla oblongata. The brain weight/body weight ratios showed that intrauterine undernutrition from maternal malnutrition causes greater abnormality in fetal body weight than in brain weight. Cerebellum and brainstem are more affected than cerebrum. The brain weight of under nourished children was found low for age than in controls.

Gopinath et al (1981, 1983) working with rat model showed that the type of nutritional deficiency,(either total or protein) is not as important as the time of nutritional insult to the developing brain. The types of cell damage also appear to be the same irrespective of the kind of undernutrition. The intensity and duration of malnutrition seem to determine the severity of the defect and their reversibility. The effect of undernutriton on the neuronal maturation of the pyramidal cells of the cortex and Purkinje cells of the cerebellum is reflected as reduced dendritic spines and synapses. (Chowdhury et al 1982) Almost complete reversibility of the induced changes could be noted when adequate nutrition was provided during early suckling period, while only slow and partial recovery was recorded when rehabilitation started at a later period (Gopinath et al 1983). In the peripheral nerve, a definite delay in the axonal and myelin growth was observed in rat, while in protein malnourished primate, Roy et al (1972) noted degenerative changes in myelin. Desiraju and coworkers from NIMHANS, using Golgi technique and quantitative morphometry have shown that even long periods of nutritional rehabilitation could not prevent the deviations in synaptic spine genesis caused by earlier malnutrition during growth spurt phase.(Gundappa and Desiraju 1988)

Deo et al from the department of pathology, AIIMS, New Delhi studied the cell cycle, and other kinetic parameters of the cells subjected to malnutrition. Prolongation of cell cycle was the key event in protein calorie malnutrition. The'S'phase was prolonged in all the organs, and 'G2'phase was affected in hair follicle, but not in the brain and intestine and 'G1' phase was shortened. The data on the developing cerebellum suggest that 40% of cells would be in the S phase in the 'fissura prima' in well fed animals and 70% in the S phase inundernourished animals (Kumudini Deo et al 1978). Tardy migration of the cells is another feature of protein calorie malnutrition and affects all organs including brain.

In the developing cerebellum, there is,normally, a programmed cell death in the external granular layer in which following mitosis the cell has the option to (a) continue to divide (b) die or (c) differentiate into a non-dividing functional cell. Using kinetic studies, X-radiation and autoradiographic techniques in control and malnourished animals, Deo et al showed the 'decision to die'a 'physiological death' was taken at the end of S phase and the cells were dying at the end of G2 phase. No significant difference was noted in the quantum of 'physiological cell death' in normal or undernourished animals. It was concluded that atrophy of tissues in malnutrition is due to reduction in acquisition of cells. Cell death is not affected (Kumudini Deo et al 1979).

Geriatric pathology, degenerative diseases, toxins, inborm errors of metabolism, demyelination and radiation damage

Geriatric neuropathology and the study of various genetically determined

degenerative diseases have received scant attention. Though the neuropathological hallmarks of ageing (neurofibrillary tangles and senile plaques) were said to be rare in Indian brains, this impression is not backed by a systematic study. Only one pathologically verified case of **Alzheimer's** disease has been reported recently from India (Shankar et al 1988), though the diagnosis of this condition is made frequently in psychiatric practice. A limited pathological evaluation of dementia was undertaken at NIMHANS.(Shankar et al 1982) Though Dastur had worked on pathophysiology and cerebral circulation in ageing and **dementia** at the National Institutes of Health (NIH),USA, the work could not be followed up in India (Dastur et al 1963). His recent review on cerebral blood flow and metabolism in normal human ageing and dementia is noteworthy.(Dastur 1985) His excellent historical review on pathology of **schizophrenia** (1959) again written from NIH was not followed up in India. Pyschiatric pathology has received scant attention from neuropathologists and psychiatrists.

As in other fields of neuropathology, a large series of **Creutzfeldt-Jakob** disease, a slow virus infection, was studied and documented from Bombay by Singhal and Dastur (1983). Recently, neuropathologists at NIMHANS made an attempt at registering all the cases noted in India. They collected 27 cases seen over a period of 18 years, 19 of them being pathologically verified. A study of various degenerative diseases is now being undertaken by them. The role of neurofilaments and other cytoskeletal filaments in the pathogenesis and evolution of Alzheimer's disease, motor neuron disease and neurotoxin induced axonopathies is being investigated.

In the field of *degenerative neurological disease,* many special variants are noted specifically in India : **heredofamilial spinocerebellar degeneration with slow eye movements** (Wadia from Bombay), **Madras pattern of motor neuron disease, monomelic amyotrophy** (single limb wasting syndrome). No indepth neuropathological studies to characterise them were undertaken though some attempts have been made (Jagannathan 1973, Gourie Devi et al 1984, Chopra et al 1984). Neuroscientists from Christian Medical College (CMC) Vellore and AIIMS, New Delhi, have conducted indepth studies into various clinical, electrophysiological and therapeutic aspects of epilepsy. K.S. Mani and others from NIMHANS described the entity 'Hot water epilepsy'-a variant of reflex epilepsy, specially noted in this part of the country.(Mani et al 1972, Satishchandra et al 1988) No significant work on neuropathological aspects of epilepsy was carried out at any centre, but for a small study from NIMHANS (unpublished).

Toxic and metabolic disease. **Neurolathyrism,** though recorded and described from India, has unfortunately received scant attention. The lead in pathogenic studies has been taken by scientists in the USA. Iyer and Dastur fed monkeys the seeds of Lathyrus sativus (in chapatis or pancakes)

over long periods. Neither neurologic signs nor neuropathologic changes (at autopsy) were noted. Other neurotoxins (cyanide or azide) given along with L. sativus produced expected effects but did not 'potentiate' the action of lathyrus (Dastur 1962). The neurotoxicity of lathyrus compounds in experimental animals was first demonstrated by Rao et al from NIMHANS (1967). In his global review of the neuropathology of lathyrism, Dastur could find only two autopsy studies, one by J. G. Greenfield on an Indian patient studied in England in 1921. Despite formal requests by Iyer and Dastur through the ICMR to over 10 hospitals in Madhya Pradesh and Uttar Pradesh (where lathyrism is common) never was brain or spinal cord of a patient sent to them.

The neurotoxic role of **cycad** was described in the rhesus monkey over two decades ago by Dastur (Dastur 1964a, Palekar and Dastur 1965) and is recently being confirmed in the USA. The neurotoxin in the cycad, b-methyl-amino-alanine (BMAA), like the neurotoxin of lathyrus (BOAA), is a glutamate agonist. A spurt of fundamental research, including molecular biology and trace element analysis has followed in the west.

India has caught up with the west in the social problems of alcoholism and drug abuse. Many studies describe hepatic injury by alcohol. Long term structural and pathological effects of alcoholism on nervous system have not received much attention. Recent studies at NIMHANS on changes in brain following abusage of alcohol showed cerebellar vermian atrophy, neuronal loss and gliosis in the anteromedial thalamus, mammillary bodies and periaqueductal gray. The features are similar to those recorded in the west, though the types of alcohol consumed are different. Indepth study is needed to evaluate the effect of toxins in the locally and illicitly made liquors and the synergistic effect of the psychotrophic drugs consumed by the addicts.

Neuropathological studies of the *inborn errors of metabolism* such as **Wilson's disease** are few, scattered in clinical journals, the histopathology being dealt with superficially (Wadia and Dastur 1963, Dastur et al 1963a, Manghani and Dastur 1968). Autosomal recessive mode of inheritance was demonstrated on a study of patients, parents and unaffected sibs (105 in all). 8 of 25 patients presented with a peculiar osseomuscular variant of Wilson's disease (osteoporosis, proximal muscle weakness without myopathy). Rubeanic acid-positive copper accumulation was seen in liver cells. Narang and Dutta from PGIMER (1983), Chandigarh, showed for the first time accumulation of arsenic in liver and brain and the possible role of this toxic element in the evolution of Wilson's disease.

Dastur has carried out ultrastructural studies of some of the **lysosomal storage disorders.** Neuropathologists at NIMHANS have studied nearly 50 brain biopsies over a period of 8 years, including conditions like Lafora body disease, Canavan disease, metachromatic leucodystrophy, Schilder's

disease, SSPE.(Nagaraja et al 1985) A case of Canavan's disease, diagnosed by brain biopsy was reported earlier from AIIMS. (Shankar et al 1979.)

Unlike in the west, **multiple sclerosis** (MS), a demyelinating disease is rare in India. Only a handful of pathologically verified cases have been documented (Dastur and Singhal 1973d, Banerjee et al 1977, Shankar et al 1984a). Dastur and Singhal (1976) have described, perhaps for the first time, the neuropathology in Eale's disease - venopathy with episodic demyelinating retino-encephalo-myelopathy as a hypersensitivity response to bacterial or viral infection. The unusual association of a glial neoplasm co-existing with the demyelinating lesion was recorded twice at NIMHANS.(Vasudev Rao et al 1986) The role of viral infection in the pathogenesis of MS, has not been studied in India. On the other hand, post infectious and post vaccination (especially post antirabies vaccine) demyelinating lesions are being described from various centres. Though antirabies vaccine derived from human diploid cell line is available, its high cost forces most to use B-propiolactone inactivated sheep brain vaccine and to a limited extent chick embryo vaccine. This explains the incidence of allergic encephalomyelitis in India (Swamy et al 1984).

Radiation damage. At present there is no direct evidence of radiation induced genetic disorders in human beings. The genetic risk evaluation is entirely based on extrapolation from results obtained in mice. On the basis of recent analysis of cases of mental retardation in children born to women exposed to radiation during pregnancy at Hiroshima and Nagasaki, it is now recognised that the CNS is highly radiosensitive during the first 8-15 weeks of pregnancy. Risks of mental retardation have been estimated to be 4 cases/1000 foetuses exposed to radiation during the critical period. Another study from AIIMS (Gopinath et al 1987) using low doses of radioisotopes of I121 and P32 showed that there was a minimal radiation dose (18 rads) above which only morphological changes were seen. Changes induced during the early postnatal period with higher doses (upto 26 rads) subsided gradually during the growth period of brain, without leaving any appreciable tissue loss.

There is an active interest in the utilisation of the radioactive energy as an alternative source of energy. Many scientists are involved in various research projects. Some of the geographic localities in South India are known to have high levels of Thorium in the soil. However, no concerted effort is being made to study radiation induced nervous damage, either at low or high levels of radiation.

Though it has been demonstrated that mouse brain retains bound tritium (^{3}H) for a longer period and in larger amounts than other organs after protracted tritiated water exposure (heavy water in nuclear plants), this radiation hazard of neurobiological concern has not been explored sufficiently. Scientists from Radiation Biology Laboratory in Rajasthan

have shown that continuous intrauterine exposure of Swiss albino mice foetuses from 16-21 days to tritiated water (HTO) at a dose of 203 KBQ, results in significant deficit in the cortical depth of frontal, temporal, visual and auditory areas by the second week postpartum. The visual area is most vulnerable while the frontal and auditory areas are relatively resistant. Low level of pre- and post-natal exposure to HTO at a dose of 11.1 KBQ/ml did not appear to result in significant alterations in adult behavioural performance, though morphometrical retardation was seen.

Indepth studies on the neurobiological effects of exposure to irradiation, high and low gravitational forces and other accelerating and decelerating stresses need to be conducted to keep pace with advances in atomic and space technology.

Disorders of muscle

Detailed pathological studies on disorders of muscle, have been undertaken at a few centres. Histological, biochemical, electrophysiological and clinical aspects of different neuromuscular disorders have been reported during the sixties (Iyer et al 1961, Desai et al 1966, Bharucha et al 1966, Dastur 1967b, Patel et al 1968, Reddy et al 1968, Desai et al 1969). Enzyme histochemical study of muscle biopsies of patients of Duchenne dystrophy was undertaken in 1966 by Janaki and Shusheela. They showed consistent change in lipase activity. Desai et al (1969) reported on changes in central nervous system in Duchenne dystrophy and suggested that the muscle and central nervous system manifestations are influenced by a genetic abnormality. An attempt has been made to produce experimental myopathy in chick by isonicotinic acid hydrazide and a comparative study with human dystrophy was conducted using histological and enzyme histochemical parameters (Narayanan et al 1970). Other clinicopathological aspects like neurogenic factors in muscular dystrophies (Dastur and Razzak 1973c), muscle changes in leprosy (Dastur and Daver 1980) and hypothyroid myopathy (Deshpande et al 1973) are also on record. A relatively benign myopathy with slow progress has been termed 'monomelic amyotrophy' and the report includes study on 23 patients with single limb atrophy (Gourie Devi et al 1984). Prabhakar et al (1981) had also reported similar cases and called it'wasted leg syndrome'. Studies on muscle in malnutrition were conducted by Krishnamurthy and his associates at Nutrition Research Laboratory, Hyderabad. Dastur (1982) has reviewed the work undertaken on neuromuscular and related changes in malnutrition. This includes the work conducted in different Indian centres in addition to research data obtained from centres abroad. Muscle changes in osteomalacia,(Dastur et al 1975) in human malnutrition,(Dastur et al 1979a) including fine studies and quantitative histology of muscle in protein calorie malnutrition are some aspects studied in our country. Roy et al (1972) have also made observations on ultrastructural changes in skeletal muscle and peripheral nerve in experimental protein deficiency in monkeys, correlating the findings with nerve conduction studies.

Enzyme histochemical and ultrastructural aspects of neuromuscular disorders are studied at NIMHANS with emphasis on congenital myopathies and floppy infants. Light and electronmicroscopic characteristics of muscle biopsies in congenital muscular dystrophies, centro-nuclear myopathies and mitochondrial myopathies have been made and the data presented (Annual Conferences of NSI, 1987, 1988). Ultrastructural studies of muscle in Werdnig Hoffman disease suggested a neurogenic mechanism in pathogenesis while associated dysmaturation of myofibres contributed to small 'foetal-like' fibres in the disease (Das et al 1986).

Peripheral neuropathies

Leprosy and nutritional deficiencies are the common causes of peripheral neuropathy in India. A few studies have been undertaken on pathological and pathogenetic aspects of peripheral neuropathies in conditions other than leprous neuropathy. Stray reports on histological changes in skin, cutaneous nerve and posterior root ganglia in radicular sensory neuropathy (Bhaktavaizian et al 1971), congenital sensory neuropathy (Wadia and Dastur 1960), pathological studies on vincristine neuropathy, (Bhan et al 1970) diabetic neuropathy (Vijayan et al 1971) and vascular neuropathy (Shankar et al 1983) are on record. Sehgal et al (1972) reported on diabetic neuropathy in experimental animal. A study on nutritional neuropathy by Dastur (1986) showed that in protein calorie malnutrition there is loss of myelinated fibres similar to that seen in experimental animals. The degenerative changes and loss of fibres were more marked in secondary protein calorie malnutrition than in primary protein calorie malnutrition. There were also fine structural changes of neurofilament accumulation in axons similar to those seen in INH toxicity and alcoholism suggesting the importance of vitamin deficiencies. In experimental animals Roy et al (1972) had observed ultrastructural changes in peripheral nerve in protein calorie malnutrition and correlated these findings with those on nerve conduction studies.

Studies in progress

In the field of neuro-oncology, Roy and his team at AIIMS, New Delhi, have proposed work on (a) immunoelectron microscopy and tissue culture of brain tumors with special reference to the pleurihormonal adenomas and non-functioning adenomas of pituitary, (b) cell kinetics, in-vivo and in-vitro in brain tumour to evaluate its prognostic significance, (c) mechanism of brain oedema in brain tumors. Sarasa Bharati and her coworkers at Madras have a continuing interest in brain neoplasms, both human and experimental, and are engaged in examining the different morphological aspects. At the cell pathology division of ICRC, Bombay, work on transplantable terato carcinomas induced in mice by Lalitha et al

continues. In future they plan to work on cell differentiation of these transplantable neural tumors and develop a nidus for working on biology of neural tumors. At NIMHANS the study of microvasculature in cerebral astrocytomas and developing human foetal brain relevant to the development of blood brain barrier is being pursued by Vasudev Rao. Cell kinetics in experimental gliomas is one of the aspects proposed to be studied at SCTIMST, Trivandrum.

As neurotuberculosis still poses important problems to clinicians and basic scientists, immunodiagnostic aspects of tuberculous meningitis are being studied at SCTIMST, Trivandrum and at NIMHANS, Bangalore. The departments of neuropathology and microbiology are working on evaluation and analysis of immune architecture of CNS tuberculomas to understand the immunopathology which may explain the variation and diversity in the response of patients with tuberculomas to antituberculous therapy. Electron microscopic aspects of tuberculous pathology in brain are being studied at Institute of Neurology, Madras. Different aspects of ageing and dementias need to be explored in our country. Study of changes in the ageing brain has been initiated in Madras. and at J.J. Hospital, Bombay. In the latter project Barodawala has plans to study neuronal and glial architecture by Golgi technique and examine blood vessels for evidence of amyloid angiopathy. At NIMHANS, Shankar and his associates have started a study of the morphological aspects of ageing brains and the role of neurofilaments and other cytoskeletal filaments in pathogenesis and evolution of Alzheimer's disease.

Alcoholism and drug abuse are two other major problems. Multidepartmental collaborative work at NIMHANS and PGI, Chandigarh are in progress concerning different aspects of the problem. Initially liver biopsies in alcoholics attending de-addiction clinic were studied before and after abstinence. A study of autopsied brains has been initiated to evaluate the permanent pathological changes seen in the nervous system from chronic alcoholism.

Pathological study on autopsy material of cerebrovascular disease is under progress at NIMHANS. As cortical venous thrombosis was found to be the major cause of fatal strokes in the young, there is a proposal to undertake a detailed haematological, clinical and epidemiological studies on this disorder.

Work on muscle changes in protein calorie malnutrition has been done at the neuropathology units in Bombay and New Delhi. At NIMHANS, Das and her colleagues are engaged in studying muscle changes in congenital myopathies. Based on light and electromicroscopic characteristics they propose a comparative study of the morphology of muscle in congenital myopathies and foetuses to understand some aspects of the pathogenesis of these disorders.

The visual system of frog, spider and drosophila are being analysed by Ramamohan and his team at NIMHANS and R N Singh et al at the Tata Institute of Fundamental Research, Bombay in an attempt to decipher how information processing, an important task performed by the brain, is carried out in such model system. This is to understand the underlying principle of organisation which in turn can permit molar relations to be established between form and function of the nervous system.

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Immunological aspects of brain tumours

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Patients with tumours within the central nervous system (CNS) are excellent subjects for the study of their immunologic status as these tumours rarely metastasise and do not affect the general condition of the patient. It is now realised that immunologic factors may be important in the development and growth of the CNS tumours. There is evidence that immunotherapy is helpful in control of some solid tumours but adequate knowledge of the immunobiology of glial tumours is not yet available.

Most workers (Mahaley 1972 and 1977, Brook et al 1972, Gerson 1974, Thomas et al 1975, Young et al 1976, Gerosa et al 1981, Ramchandran et al 1983, Sharma et al 1984, Nayak 1988) have reported that immunological activity, especially cellular immunity, is suppressed in patients with brain tumour.

Indian contributions:

The status of cell mediated and humoral immunity was studied in 120 patients with histologically verified intracranial tumours admitted to the neurosurgical unit, University Hospital, Banaras Hindu University, Varanasi. None had received steroids before the study. 43 of the intrinsic brain tumours were benign and 77 malignant. The study used the following parameters:

A) Cell mediated immunity:

1. Contact sensitization to 2:4 D.N.C.B. antigen.
2. Skin sensitivity to recall antigen PPD.
3. Skin sensitivity to recall antigen candida albicans.
4. Absolute lymphocyte count.
5. T-cell rosette count.

B) Humoral immunity: Estimation of levels of following immunoglobulins in the serum:
1. Serum IgG level.
2. Serum IgA level.
3. Serum IgM level.

C) In 20 cases of malignant brain tumours non specific immunopotentiation was achieved by levamizole. The effect on cell mediated immunity

in the patients with brain tumour was studied using the above mentioned parameters. Ramchandran et al(1983) found that absolute lymphocytecount, absolute T lymphocyte count (ALC) and percent E-rosette cells, were significantly low in patients with brain tumour Phytohaemagglutinin induced lymphocyte blastogenesis index was also low in the study group as compared to that in the control group.

Sharma et al (1984) found that delayed cutaneous hypersensitivity (DTH) to recall antigens PPD and candida was depressed in all patients with brain tumours. No difference was seen in the magnitude of depression between patients with benign and malignant tumours. Responsiveness to DNCB was not much different in patients with brain tumours and controls. ALC was found depressed in the former group without any difference on the basis of malignancy. E-rosette counts, however, were of value in discriminating between benign and malignant brain tumours.

Nayak (1988) found the cutaneous D.T.H. response to contact sensitizing agent 2:4 D.N.C.B., recall antigen PPD and candida; T-cell rosette count and peripheral blood absolute lymphocyte count were suppressed in patients with benign and malignant brain tumours when compared to controls.A detailed analysis of data in the subgroup with malignant tumours showed a highly significant suppression of all parameters in glioblastoma/anaplastic astrocytoma. Lesser suppression was seen in those with astrocytoma (grade I,II) and those with medulloblastoma. The least suppression was seen in the subgroup with other malignant tumours. Serum immuno-globulin profile showed that serum IgG level remained unaltered in patients with benign and malignant brain tumour as compared to controls, whereas serum IgA levels were significantly suppressed in patients with benign and malignant tumours. In the malignant sub-group, maximal changes were seen in patients with astrocytoma grade (I, II) and medulloblastoma. IgM levels were significantly raised both in benign and malignant tumour cases. Of the malignant subgroup, the maximum rise was seen in astrocytoma (grade I,II) and medulloblastoma.

Thus cell mediated immunity was depressed overall in patients with benign and malignant brain tumours, the depression being more marked with malignancy.

These findings suggest that defective immune surveillance may play an important role in the progression of brain tumours. In addition to attacking individual cancer cells by monoclonal antibodies it may be necessary to potentiate the general immune response in patients with brain tumour to achieve the best results.

Immunophenotyping

Immunophenotyping is useful in identifying cell lineages in brain tumours

and their cultures. Instead of relying on imported antisera, V. S. Lalitha at the Cancer Research Institute, Bombay has started raising polyclonal antisera in India. To start with, glial fibrillary acid protein (GFAP) and neurofilament protein (NFP) were isolated and antisera raised in rabbits. Sections of paraffin embedded human gliomas and medulloblastomas were immunostained with these antisera. The results are comparable to those obtained with imported kits. These antisera are now being used in diagnostic neuro-oncology (Lalitha-personal communication).

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Neuromicrobiology

A. Chandramukhi

Introduction

The term *neuromicrobiology* can be defined as an evolving neuroscience which deals with both community acquired and iatrogenic infections of the central nervous system (CNS) caused by a variety of microbes: bacteria, fungii, parasites and viruses.

It is only during the past four decades that the clinical neurosciences are being recognised as specialties in India. Neurology and neurosurgery were earlier part of medicine and surgery respectively. In some medical colleges and hospitals even now these two specialties are under the control of medical and surgical departments. Disciplines like neuropathology, neuroradiology, neuroanesthesia, neurophysiology, neuropharmacology, neuromicrobiology, neurovirology and neuroimmunology are recognised as sub-specialities of neurosciences. At present these paraclinical neurosciences are still part of parent paraclinical disciplines like pathology, radiology, biochemistry and pharmacology. The development of microbiology as an independent discipline itself, is of recent origin in India. Earlier, microbiology was part of general pathology. It is only in the 1960's that microbiology came to exist as a separate science and sub-courses were started including bacteriology, parasitology, mycology and virology.

For the first time in the country, the All India Institute of Mental Health was started in 1954 at Bangalore. It is now known as the National Institute of Mental Health and Neuro Sciences (NIMHANS). This Institute was started with an objective of development of specialties relating to the brain and the mind. Thus in the setting of a mental hospital, neurology, neurosurgery and neuroradiology were started in the year 1958. The department of neuropathology was commissioned in 1959. The institute took the help of the department of microbiology of the Bangalore Medical College until 1977. In 1977, an independent department of microbiology was started at NIMHANS. In this country this is the only department exclusively meant to aid neurology, neurosurgery and psychiatry in understanding and diagnosing the microbiological aspects of CNS infections.

There is a need to develop neuroimmunology along with neuromicrobiology

to extend better diagnosis for CNS infections along with their immune modulating disease entities.

Infections of the nervous system as prevalent in India can be broadly categorised into: (1) **acute infections** which include acute purulent or septic meningitis; the encephalitic syndrome which could be of viral, tuberculous and rarely cysticercal etiology; CNS manifestations of systemic infections by salmonella, Gram negative organisms and rarely Brucella (2) **sub-acute to near chronic infection** which includes pyogenic brain abscess; partially treated pyogenic meningitis, tuberculosis meningitis; neurocysticercosis; fungal infections and neurosyphilis (3) **chronic infections** namely tuberculous meningitis; neurocysticercosis; complications of systemic infections like salmonella; fungal infections and neurosyphilis (4) iatrogenic CNS infections following invasive diagnostic procedures or neurosurgical procedures.

Bacterial meningitis

Bacteria can cause acute infections of CNS by direct implantation, contiguous infection from a local septic focus or an infected foreign body, or by haematogenous dissemination. Acute infection may also occur due to the neurotoxin produced at a distant focus of infection and following systemic infection. Acute pyogenic meningitis of community-acquired-type is often due to Streptococcus pneumoniae in adults and due to Haemophilus influenzae in infants and children. In neonates a variety of Gram negative bacilli can cause meningitis as part of the generalised septicemia or along with brain abscess. Meningococcal meningitis, as studied from different reports, is usually of low prevalence except during epidemics (Deorari, 1987; Dubey, 1986; Prashad, 1985).

Subacute or chronic bacterial meningitis is often produced by tubercle bacilli in this country. At most centres the incidence of tuberculous meningitis (TBM) is greater than that of acute pyogenic meningitis (Fig. 1).

Murthy et al (1983) carried out a clinical study of pyogenic meningitis. Ayyagari et al (1979, 1980) from Post Graduate Institute of Medical Education and Research (PGI), Chandigarh characterised and standardised counter immuno-electrophoresis for the diagnosis of H.influenzae meningitis and pneumococcal meningitis with improved antigen detection rates. Her team has also carried out experimental studies on H.influenzae meningitis in animals (Ayyagari et al, 1981). Scientists at PGI have reported on sero type of pneumococcus as seen in CNS infections around Chandigarh,(Ayyagari et al, 1984) Salmonella CNS infections, (Ayyagari, 1985) Citobacter meningitis, (Jain et al, 1980) and Flavobacterium meningitis (Ayyagari et al, in press). Alka Gogate and Lina Deodar (1984) from Bombay have analysed the bacterial profile of pyogenic meningitis

in both community acquired and iatrogenic meningitis. They have found pneumococcus to be the predominant etiological microbe in community acquired meningitis. They have reported on salmonella meningitis (1982) and Listeria mono-cytogenes meningitis (1981). They have analysed the use of gas liquid chromatography (GLC) as an adjunct in the diagnosis of pyogenic meningitis (1984). Paediatric pyogenic meningitis have been analysed by Dhingara (1978), Ghosal (1978), Santhanakrishnan (1974), Reddy (1973) and Singh, J.V. (1979).

The experience with regard to acute pyogenic meningitis at the department of medical microbiology at NIMHANS has been as follows. Of the 461 cases of pyogenic meningitis studied from 1978 to June 1988, the causal microbe was identified on culture in 76.13%.(Fig. 2) The predominant organism was Streptococcus pneumoniae. Pneumococcus was isolated 123 times out of 351 cases (35%). The other organisms in community-acquired-pyogenic-meningitis were H.influenzae, Meningococci, Citobacter, Enterobacter, E.coli, Pseudomonas, Salmonella including S.typhi (Gokul et al, 1988), Proteus, Bacillus anthracis (Chandramukhi et al 1982; Neelam Khanna et al - in press), Morganella morganii, Klebsiella, haemolytic and non-haemolytic Streptococci, Flavobacterium meningosepticum (Gokul et al in press) Listeria monocytogenes and anaerobic bacteria (Chandramukhi et al 1982). Primary anthrax meningitis has been reported from time to time only from southern India - from Vellore and Bangalore (Chandramukhi et al, 1982; Koshy, 1981, Prema Bhat, 1983 and Neelam Khanna et al -in press). Unusual microbes like flavobacterium acinetobacter and anaerobes are reported from time to time (Sharma 1984; Sachdev 1980; Chandramukhi 1982).

Anaerobic meningitis was identified for the first time in India by Chandramukhi and Ramadevi (1982). In just over a decade the department of neuromicrobiology at NIMHANS has encountered 18 cases of anaerobic meningitis predominantly due to bacterioides fragilis. Often anaerobic meningitis is associated with middle ear infection, mastoiditis and brain abscess. Mollaret's meningitis, a rare type of meningitis, where the patient has recurrent polymorphonuclear pleocytosis in the cerebrospinal fluid and no organisms can be identified has been reported by Vishnu Bhat.(1978) Singh (1987), Vincent (1982), Kanudhinya (1979), Chowdhary (1986) and Ramji (1987), have contributed to the literature of pyogenic meningitis.

Clostridium rarely causes infection of the brain. Cases of cephalic tetanus have been reported by Vakil et al (1973) and Ahuja (1978). Occasional cases of meningitis due to clostridium have been reported by Gokul and Chandramukhi (1987). Treponemes involving CNS are usually those causing neurosyphilis (Rao, 1972; Srinivasan, 1977).

With respect to iatrogenic meningitis in neurological services, Mahapatra

et al (personal communications) from the All India Institute of Medical Sciences, New Delhi, (AIIMS) have studied 507 patients undergoing neurosurgery and found an over all incidence of wound infections in 4.7% and an incidence of iatrogenic meningitis in 2.3%. The incidence of post-operative meningitis at NIMHANS between 1978 and 1988, was 2.18%. The bacteria encountered were Staphylocccus epidermidis, Staphylococcus aureus, Gram negative bacilli ranging from E.coli, Klebsiella, Pseudomonas species, Enterobacter, Salmonella typhimurium, Proteus and non-fermenting Gram negative bacilli and rarely Pneumococci, non-haemolytic Streptococci, Haemophilus aphrophilus and Diptheroides. The percentage isolation of etiological microbes in post operative meningitis has been 94.03% (Fig. 3). Infection following cerebrospinal fluid (CSF) shunt has been reported by Upadhyaya (1985) and Bhatnagar (1983).

Ramamurthi (1974) from Madras has reported on post operative disc space infection. Chandramuki et al (1983) have reported haemophilus aphrophilus in a neurosurgical set up at NIMHANS.

Sub-acute to chronic meningitis resembling TBM can be caused by the higher bacteria termed as Nocardia (previously classified as fungus.) The species Nocardia asteroides has been the etiological agent in 4 cases of chronic meningitis at NIMHANS in the past decade (Chandramukhi et al, 1980). These cases were diagnosed as TBM and were resistant to antituberculous therapy. Switching to treatment by sulphonamides cured the meningitis.

The diagnostic modes applied to CSF from patients with pyogenic meningitis have varied from a simple technique such as Gram smear, culture to counter immuno-electrophoresis and immunological detection of minute quantities of bacterial antigens in CSF. Recently immune antigen detection kits are being marketed by pharmaceutical firms to detect nanograms of the antigen of etiological microbe. However, the cost is hindering routine use of these in most centres. The need to aid diagnosis by immediate and prompt Gram's stain and culture on appropriate media is essential. The role of C-reactive protein detection in the CSF of pyogenic meningitis has been stressed by Gokul et al (in press). This can be done only if the microbiology laboratory is geared predominantly for CNS infections. In most centres where the Microbiology laboratory is part of a general hospital, immediate optimal care in the processing of CSF on a 24 hour basis is often lacking. In this field the development of neuromicrobiology for neurological centres is imperative.

Brain abscess.

The management of brain abscess in all its aspects remains one of the highest tests of neurosurgical skill. Late diagnosis and inappropriate antibiotics are the principal causes of death in patients with brain

abscess. (*British Medical Journal, 1969*) A better understanding of microbial etiology (with appropriately tailored antibiotic therapy) is necessary for reduction in mortality.

Bhatia et al (1973), found 16 out of 55 brain abscesses sterile on culture. Anaerobic cultures were not attempted. Brain abscesses have been analysed and studied by various workers from time to time in India. Dharker et al (1978) from Gwalior have analysed 87 cases of brain abscess.

Rapid processing of the pus aspirated from the brain abscess has dispelled the myth of 'sterile brain abscess'.

The role of anaerobic infection in the production of brain abscess and the efficacy of metronidazole in chemotherapy were shown for the first time in India by Chandramukhi, Hegde and Narayana Reddy in the year 1979 (Chandramukhi et al, 1980). In an initial study of 50 brain abscesses, anaerobes were isolated in 62%. Subsequently, in 416 brain abscesses seen over the past decade, Gokul and Chandramukhi (1987) isolated microbes in over 85% of the cases - aerobes in 43%, aerobes and anaerobes in 35.2%, only anaerobes in 22% of the cases. The predominant anaerobic Gram negative bacilli were Bacteroides, Fusobacteria and anaerobic Gram positive cocci. Clostridia were seen in 11 post traumatic brain abscess. The establishment of a neuromicrobiology laboratory which caters exclusively for analysis of pus from brain abscess on a 24 hour basis has helped greatly. Gokul et al (1989) have shown microbial spectra in 454 cases of brain abscess.

Usha Gupta et al (1986) from All India Institute of Medical Sciences have done pioneering work on the role of GLC in rapid diagnosis of anaerobic brain abscess. Grace Koshy and Lalitha (1982) have also studied the incidence of anaerobes in patients with brain abscesses. Ayyagari et al (1983) have also reported anaerobic brain abscesses.

Out of 40 cases of brain abscess studied at the K E M Hospital, Bombay during the two years 1979-80, 12 had pure aerobic isolates, 8 had mixed isolates (aerobic and anaerobic) and 8 had pure anaerobic isolates. Thus the incidence of anaerobic brain abscesses was 40% (Mehta Ajita, Walimbe S, Goyal S K, Nagpal R D, Unpublished data). At the same hospital between 1984 and 1987, 235 cases of brain abscesses were studied. 97 of these had pure aerobic isolates, 16 had mixed aerobic and anaerobic isolates and 40 had pure anaerobic isolates. The incidence of anaerobic infection had thus come down to 23.8%. The most common isolate was Bacteroides melanogenicus (19 isolates) followed by Bacteroides fragilis (12 isolates). (Mehta Ajita, Nagpal R D, Karnam R R, Pinto Amala, Unpublished data).

Bhatia (1983) and Mahapatra et al (1984) studied brain abscess and

subdural empyema in children of age below 15 years. The commonest sources of infection for brain abscesses is middle ear infection and mastoiditis, followed by head injuries, congenital heart diseases (Bhatia et al, 1976) and haematogenous spread from distant foci. Intracranial abscess and subdural abscess due to Salmonella typhi have been reported by Bhatia and Mahapatra (1987), Chandramuki (1980) and Gokul (1988).

Spinal abscesses have been reported by Sushil Kumar and Gulati (1978). Intramedullary abscess presenting as acute transverse myelitis was reported by Sanjeev Gupta (1979) from Chandigarh. Subdural empyema in children have been studied by Mahapatra (1984). Analysis of intracranial abscesses has been done by Balakrishnan and Natarajan (1971). Tandon et al (1974), Panchal et al (1974) reported thalamic abscesses. Bhatia et al (1986) reported on 5 pyogenic abscess of basal ganglia and thalamus in a review of 21 cases of inflammatory lesions of that region. Nagpal (1988) (personal commumication) reports on the series seen at the department of neurosurgery, KEM Hospital, Bombay. Between 1957 to 1988, 156 cerebellar abscesses, 423 cerebral abscesses, 19 spinal abscesses, 95 subdural empyemas were encountered. Epidural abscess of the posterior fossa has been reported by Mathuriya and Khosla (1987) from PGI, Chandigarh. Subimal Roy (personal communication) of the All India Institute of Medical Sciences, New Delhi, reported on the histology of brain abscess in 272 cases seen over 18 years.

The diagnosis of brain abscess has been made easy with the advent of computerised tomography (CT) scan. Evolving 'real time microbiology' or rapid modes of microbial diagnosis will further speed up the isolation of the causal microbe.

Neurotuberculosis

Neurotuberculosis is one of the most common forms of extra pulmonary tuberculosis in the Indian sub-continent. Though tuberculosis meningitis (TBM) in children seems to be on the decline especially after implementation of BCG vaccination, there is an apparent increase in recognition of adult onset TBM. The diagnosis of tuberculomas and other forms of neurotuberculosis has been made easy with the availability of CT. TBM is the most important differential diagnosis of subacute and chronic meningitis in India. It is also the common form of neurotuberculosis in this country.

The other forms of neurotuberculosis encountered are intracranial tuberculomas, tuberculous encephalitis, tuberculous brain abscess and tuberculous radiculo-myelitis. These clinical forms have been described by neurosurgeons, neurologists, paediatricians and neuropathologists from different parts of the country since 1950. Indian neuroscientists and clinicians have made important contributions to the literature of

neurotuberculosis. (Dastur HM,1962,1965,1968,1972; Dastur DK, 1966-1986, Tandon PN, 1973,1978; Udani, 1946-1980). Udani et al (1980) have described multifaceted forms of neurotuberculosis in children in detail. Dastur, Dave, Lalitha (1974) and Udani have studied in depth etio-immunopathological aspects of various forms of neurotuberculosis (1966,1969,1970,1973, 977,1978,1980,1986). Tandon et at (1970) worked on experimental tuberculosis of the central nervous system in guinea pigs and monkeys. Clinicopathological studies of TBM have been carried out by Thomas et al (1977), Deshpande et al (1969), Benakappa et al (1983), Sathyagupta et al (1981), Gourie Devi et al (1981).

Rajagopal et al (1967) have carried out a comparative trial of 3 culture media and 2 homogenisation methods for primary isolation of mycobacterium tuberculosis. Identification and culture of tubercle bacilli from the CSF is often frustrating and non rewarding in most patients with clinically diagnosed TBM. Since TBM can be simulated by partially treated pyogenic meningitis, carcinomatous meningitis, mycotic meningitis, chronic meningitis due to neurocysticercosis a search for alternative modes of confirming the clinical diagnosis of TBM by immunodiagnosis and other methods continues.

Studies at NIMHANS over the last 10 years yielded between 5% and 23% positive yield of tubercle bacilli in patients suspected to have TBM. (figure 4) In many culture negative cases, the classical CSF profile of TBM is seen. They respond to antituberculous therapy. Such patients fall into the category of clinical TBM with negative cultures. Even on repeated attempts (4 to 6 times) cultures have been negative in autopsy proven TBMs. The detection of special epitheloid cells and floating tubercle on CSF cytology helps in the diagnosis of TBM (Chandramukhi et al, in press).

Neurotuberculosis may present in a variety of atypical clinical forms : stroke, infarction, demyelination, behavioural abnormalities, hemifacial spasm (Sandhya et al 1983), posterior fossa cystic arachnoiditis (Srivatsva et al 1982), posterior fossa syndrome (Dinakar 1977), neuro-ophthalmic syndrome (Misra 1985), acute myelopathy (Pamra et al 1969), Eale's disease (Vaishney et al 1978), tuberculosis of the vault of the skull (Gupta et al 1979), Guillian-Barre syndrome (Rama Rao et al 1983), atlanto axial dislocation due to tuberculosis (Pandya 1971), tuberculous abscess of the brain (Devadiga 1969, Ramamurthy 1981, Sandhya Mani et al 1981, Chandramukhi et al 1981), tuberculous radiculo-myelopathy (Ahuja et al 1978), cauda equina syndrome of tuberculous etiology (Prusty and Chandramouli 1987), tuberculosis of the intervertebral disc (Prusty and Sarla Das 1987.

Sinh G et al (1968), Bagchi (1965,1981), Kalyanaraman (1983) have reviewed literature on tuberculomas and tuberculous space occupying lesions. Space occupying lesions of tuberculous etiology have also been

reviewed by Ramamurthi et al (1956,1973), Mathai (1967), Chandrasoma (1976), Vimala and Dinakar (1979), Dinakar et al (1975), Bhagwati (1986). Rare cases of spinal dural tuberculous granuloma with abscess have been reported by Sushil Kumar (1985). Unusual presentation of tuberculomata has been stressed by Sinh G et al (1968), Narayana Reddy and Prusty (1983), congenital dermal sinus associated with tuberculous granulomas have been seen by Dinakar et al (1974). Dastur (1962) Dayananda Rao (1963), Sait and Kanaka (1980) have reported cystic tuberculoma. Dastur (1968), Natarajan (1974), Chandrasoma (1976) and Raja Reddy (1972) described intraspinal tuberculomas. Udani (1970) described the entity of tuberculous encephalopathy in children. This has been strongly supported on histopathological and etiopathological collaborative work by Dastur (1965). Kalyanaraman (1986) has described the CT scan appearances of tuberculous encephalitis.

Many attempts have been made to detect tubercle antigens and antibodies (Kadiwal, 1982,1986,1987; Subhashini P and Anna Oommen, 1987 Chandramukhi et al, 1985,1989). Bromide partition test in the diagnosis of TBM has been analysed by Rangan and Virmani (1972) and Ahuja et al (1983). Its routine use is cumbersome. Most workers are aiming at the fine tuning of immunodiagnosis of neurotuberculosis with a satisfactory specificity and sensitivity in a given endemic area. Molecular biological tools like DNA probes, monoclonal antibodies and a battery of purified mycobacterial antigens should help in accurate immunodiagnosis on a larger scale in the future.

The immunodiagnostic tool developed in 1983 at NIMHANS in collaboration with Juraj Ivanyi and his team at the Medical Research Council, U. K. has helped in the diagnosis of patients strongly suspected to have tuberculous meningitis but showing no tubercle bacilli in the CSF on routine examination or culture. Confirmation of diagnosis has been possible in about 80% of cases (Chandramukhi et al, 1985, 1988 - in press). When over 1500 CSF samples were studied for tubercle antigen and antibody using crude antigen, purified antigen and monoclonal antibody to the lipoarabinomannan (LAM) antigen, 55% - 85% sensitivity was noted (Chandramukhi et al, in press). Tubercle antigens were also localised in cells in the CSF and tuberculomas by immunochemistry. Shankar and Chandramukhi, in an attempt at localising the mycobacterial antigen in tuberculomas by immunohistochemical methods, using a panel of monoclonal antibodies ML-34, ML-02 and other monoclonals (provided by Dr. J Ivanyi and colleagues from the Medical Research Laboratory, UK) have shown lipoarabinomannan polysaccharide antigens and protein antigens within the epithelioid cells, giant cells, endothelial cells and occasionally in the glial and neuronal cells. Whilst studying processing and storage of mycobacterial antigens in neurotuberculosis it was observed that there existed a spectrum of architecture af antigen localisation and types in different patients. The role of these in response to therapy which is

different in different patients, antigen clearance, persistence, long time effects such as demyelination, myelitis and other allergic etiopathogenesis in many of the atypical neurotuberculosis is under study. In subacute or dormant neurotuberculosis immunodiagnosis is the only means of specific diagnosis as the CSF culture is negative. (Table I a-f)

Metabolites of mycobacterium tuberculosis in body fluids have also been looked for as diagnostic markers in neurotuberculosis. These tests, when perfected, will help in early diagnosis and in the diagnosis of atypical cases. There is a need for immune markers to be seen by immunodiagnostic methods and immune scans. Basic molecular biological work of mycobacteria towards application in immunodiagnosis is being carried out in many laboratories in the country (Katoch VM, Kumar S, Ganguli NK, Dhand R, Khuller GK, Bhattacharya A, Kaushik NK, Jagannath C, Talwar GP, Batra HV and Reddy P. - *Symposium on Recent Advances of Tuberculosis Research*, September 3-4, 1988, PGI, Chandigarh). The role of immunology as an aid in monitoring the recently advocated short course therapy has also to be looked into. The nature of the mycobacterial antigenicity and the varied host immune responses is apt to make neurotuberculosis a Immunodiagnostic challenge.

In 1987 the Fogarty International Center of the National Institutes of Health at Bethesda, Maryland, USA, held a workshop on research towards global control and prevention of tuberculosis with emphasis on the development of vaccine. Immune mechanisms and the pathogenesis of tuberculosis, animal model studies of pathogenesis, genetic control and susceptibility to mycobacterial infection, DNA cloning in mycobacteriology and its role in diagnosis were some of the topics discussed. In depth study of mycobacterial antigens with the recently available molecular biological tools and the in vitro analysis of cellular mechanisms involved in immunity to tuberculosis appear promising. To carry out such studies it is essential that there be an interplay between basic scientists and clinicians both by the patient's bedside and in the laboratory.

Neurocysticercosis

The larval form of taenia solium-cysticercosis cellulosae- is capable of causing severe morbidity in man especially in the form of neurocysticercosis.(NCC) 'Cerebral cysticercosis (or neurocysticercosis) is an abominable disease that is found predominantly in the third world and is synonymous with ignorance, poverty, lack of hygiene, deficient public health services - all the products of apathy, corruption and political irresponsibility.'(Daniel Gonzalez of the Neurological Institute, Mexico. 1987). NCC is one of the most pleomorphic of neurological disorders. The most common form of cysticercosis in man is NCC. The commonest parasitic disease of CNS in this country is cysticercosis.

Table 1: The incidence of MY4-antigen (RPHA) or antibody (SPRIA)-positive CSF from patients with tuberculous meningitis and control subjects

Group	*Origin*	*Clinical diagnosis*	Number of specimens that gave the indicated result for								*Percentage of specimens positive for*	
			MY 4 – Antigen (RPHA)				*Antibody (SPRIA)*					
			Tested	2*	2–8	16	Tested	2+	2–20	20	MY4 antigen	SPRIA antibody
IA	S.India	Tuberculous meningitis culture positive	25	3	11	11	23	6	10	7	88	74
IB	S.India	Tuberculous meningitis	64	17	22	25	56	19	32	5	73	66
IIA	S.India	Pyogenic meningitis	19	15	0	4	19	12	5	2	21	37
IIB	S.India	Head trauma; mental retardation	13	12	1	0	13	11	2	0	8	18
IIIA	U.K.	Aseptic (viral) meningitis; neurosyphilis	13	13	0	0	4	4	0	0	0	0
IIIB	U.K.	Multiples sclerosis; demyelination	82	82	0	1	29	29	0	0	1	0

* Antigen titre measured by RPHA

\+ Antibody titre expressed as ABT 50 [see methods is Detection of Mycobacterial antigen and antibodies in the cerebrospinal fluid of patients with Tuberculous meningitis: A. Chandramukhi et al, J. Med. Microbiol. – Vol. 20 (1985) 239–247].

Table 2: Incidence of Lipoarabinomanan-B antigen in CSF of TBM and control cases by RPHA test (1985 to 1986 NIMHANS (n=516)

Clinical types of cases	*No. tested*	*No. positive*	*% positive*	*No. negative*	*% negative*
I. CLINICAL TBM	355	320	90.14	35	9.86
a) Culture positive TBM	29	27	93.10	2	6.90
b) Culture negative TBM	326	293	89.87	33	10.13
II. CONTROL CASES (NON TBM)					
a) Pyogenic meningitis	27	3	11.11	24	88.88
b) Viral meningitis	27	3	11.11	24	88.88
c) ?SOL	22	12	54.54	10	45.46
d) Beningn intracranial tension	26	19	73.07	7	26.93
e) Cord compression	34	29	85.29	5	14.71
f) Miscellaneous CNS diseases	25	0	—	25	100.00
	161	66	40.90	95	59.10

Table 3: Incidence of LAM-B antigen (Tandom ELISA ML 34) and simultaneous MTSE antibody in CSF of TBM and control cases (NIMHANS 1987/1 year study) (n=138)

Clinical types	*No. tested*	*No. positive*	*% positive*	*No. negative*	*% negative*
I. TBM					
a) Total AG	49	38	77.55	11	22.45
b) AG only	49	9	18.36	40	81.64
c) AG and AB	49	29	59.18	20	40.82
d) AG and IgG only	49	12			
e) AG and IgM	49	2			
f) AG and IgG and IgM	49	15			
g) Antibody only (IgG/ IgM/both)	49	8	16.32	41	83.67
h) AG only/AB only/both (combined assay)	49	46	93.87	3	2.11
II. Control (non TBM)	89	9*	10.11	80	89.89

* 1 case Cong hydrocephalus, 2 cases stroke in young, 2 cases of CT shadow, 2 cases of ICT, 1 case of pyogenic meningitis. 1 case of SOL.

Table 4: Incidence of total antimycobacterial IgG antibody assay by ELISA in CSF of TBM and control (non TBM cases) (NIMHANS 1987 – October to May 1988) (n=824)

Clinical types	*No. tested*	*No. positive*	*% positive*	*No. negative*	*% negative*
I. TBM	224	175	79.25	49	21.87
II. Control cases (non TBM cases)*	600	86	14.33	514	85.66

* Includes all CSFs submitted to department of Microbiology and Immunology, NIMHANS-pyogenic meningitis, neurosyphilis, epilepsy, neurocysticercosis, demyelinating diseases, multiple sclerosis, motorneurone disease, cortical venous thrombosis. SSPE, GBS, optic atrophy, dementia, organic brain syndrome, myelopathies, radiculopathy, stroke in young, BIH, NPH. cong. hydrocephalus, etc.

Table 4a: Diagnosis of non-TBM cases wherein anti MTSE AB is shown

(October 1987 to May 1988)

Pyogenic meningitis	14 (No tested 69)	20.28%
Cord Compressions	21 (No tested 39)	53.84%
Myeloradiculopathy	6 (No tested 25)	24.00%
Seizures/fits/epilepsy	7 (No tested 42)	16.66%
Guliien barrie syndromes	5 (No tested 36)	13.88%

(other 33 cases include–headache hydrocephalus (3), catatonia (2), GPI, cerebral abscess (3), demyelin disease, dementia (3), NCC (2), MND, Amyotrophy, post fossa mass, MS, brach neuroitis, MDP (2), disc 1, cladosporium granuloma, tabes dorsalis, carc. meningitis, organic brain syncrome, cranial NN palsy (2), optic atrophy).

Table 5: Incidence of anti MTSE antibody in CSF of spinal anaesthesia CSF (India) normal CSF (Sweden) MS (Sweden)

	Test	*Number Positive*	*Percentage Positivity*	*Percentage Negative*
Spinal anaesthesia CSF (S.India)	25	3	12%	88%
Sweden (normal CSF)	18	Nil	—	100%
Sweden (MS CSF)	13	Nil	—	100%
UK (CNS Inf. CSF)	13	Nil	—	100%
UK (MS and Demyelin. CSF)	89	Nil	—	100%

Improved diagnostic imaging and immunology of NCC has brought more cases to light. Variations in pathogenesis can result in granulomas, calcifications, residual fibrosis and a variety of other lesions. Ramamurthi and Balasubramaniam (1970) found the incidence of cysticercosis to be 1.25% of all intracranial space occupying lesion in south India. Mahajan and Chopra at the PGI, Chandigarh,(1974,1975,1981,1982) have reported the incidence of NCC to be 27% of all intracranial space occupying lesions. They found NCC in 17% of their epileptic patients. This team has also studied the incidence of sero positivity among hospital and slum population and found a percentage of 2-3 and 12-15 respectively. Tandon (1983), Wani et al (1981,1982) from AIIMS, New Delhi, have reported an incidence of 2.5% among space occupying lesions in the practice of neurosurgery. Several case reports of NCC have been added to the literature from time to time in this country by Dinakar and Mathai (1970), Natarajan et al (1970), Vijayan et al (1977), Ahuja et al (1985), Shadangi et al (1977), Mani et al (1974), Mehta et al (1971), Dinakar et al (1979), Raja Reddy et al (1986), Wani et al (1982), Subramaniam TK (1983) and Chopra et al (1981). These reports cover a wide range of NCC viz. intracerebral, intraspinal, epidural, subdural, subarachnoid space, intraocular (Malik 1968; 1978; Patnaik 1979) and rarely in muscles (Dinakar 1979).

Immunological testing of the CSF for anticysticeral antibodies has been established at the department of Medical Microbiology at NIMHANS over the past decade. The protean mainfestations of this disease as epilepsy, increased intracranial tension, chronic meningitis even at times mimicking tuberculosis, organic brain syndromes, dementia, radiculomyelitis, encephalitis, vascular strokes following infarctions, myopathy, etc., there is a need for routine CSF immunology for cysticercosis in neuropsychiatric illnesses in endemic areas (Chandramuki et al 1988-in press). Using the porcine cyst antigen, complement fixation test, passive haemagglutination assay and enzyme linked immunosorbent assay have been carried out on CSF of in-patients and out-patients attending NIMHANS with a variety of neurological illnesses. (Table II a-c) A percentage positivity between 9-15 was noted. Over all positivity was as follows: 25% in epileptic patients, 26% in patients with space occupying lesions and increased intracranial tension, 10 % among patients with chronic meningitis, 17 % among patients with behavioural disorders, 10% among patients with viral encephalitis, 42% in patients suspected to have NCC (on the basis of CT scan or soft tissue calcification, positive stool examination or subcutaneous nodules) and 14% among patients with radiculomyelitis (Chandramuki et al 1988).The recent introduction of immunoscans can localise the cyst prior to surgery.

Immunocytochemistry studies on human porcine cyst by Shanker and Chandramuki have localised the cysticercal antigens in glycocalyx layer of the bladder wall and subtegumental cells. Molecular biological research on porcine cyst with respect to characterisation and

Table II-a: Distribution of Anticysticercal Antibody in CSF of suspected Neurocysticercosis patients by Complement Fixation Test of Nieto using the Mexican Antigen-at NIMHANS, 1978 –1988.

Sl. No.	*Clinical DX*	*Total*	*Number Negative*	*Number Positive*	*Percentage Incidence*
1.	Epilepsy	257	227	36	14%
2.	Chronic Meningitis	224	188	36	16%
3.	SOL/BIH/IICT	188	148	40	21.27%
4.	Dementia	60	54	6	10%
5.	Organic Brain Syndrome	8	5	3	----
6.	Neurocysticercosis*	99	88	11	11.11%
7.	Viral Encephalitis	47	39	8	17.02%
8.	Radiculopathy	19	15	4	---
	Total	902	758	144	15.96%

Table II-b: Percentage Incidense of Anticysticercal Antibody in CSF by Passive Heamagglutination Test - a two year study 1985 – 1987.

Clinical Diagnosis	*Total No.*	*Negative No.*	*Positive No.*	*Percentage Positive*
Epilepsy	32	26	6	18.75%
SOL	30	26	4	13.33%
Chronic Meningitis	247	233	14	5.66%
Behavioural Disorders	30	25	5	16.66%
CH MEN & SOL	2	1	1	---
Seizure & SOL	1		1	---
Total	342	311	31	9.06%
Control B Cases				
CNS Infections	119	113	6	5.04%
NON INF CNS DIS	142	139	3	2.11%
Total	261	252	9	3.44%

Anticysticercal antibody profile of CSF of patients with various clinical syndromes as seen by Elisa test

Clinical DX	*Total No.*	*Negative No.*	*Positive No.*	*PO S %*
Epilepsy	24	18	6	25%
SOL/BIH	23	17	6	26.08%
CH MEN/TBM	341	305	36	10.55%
Behavioural Disorder	23	19	4	17.39%
Viral Encephalitis	48	43	5	10.41%
Neurocysticercosis	28	16	12	42.85%
Radiculopathy	28	24	4	14.28%
Total	515	442	73	14.17%
Control Case:				
CNS Infections	81	73	8	9.87%
Non/infection CNS DIS	216	208	8	3.70%
Total	297	281	16	5.38%

Note: Neurocysticercosis denotes those cases wherein there is additional evidense by CAT scan, Stool examination or histopathology.

purification for immunodominant fraction to be applied in immunodiagnostic tests is in progress both at NIMHANS and at Astra Research Centre India, Bangalore. More research is needed in this country on this disease entity of NCC which still needs definition and perfection with special regards to clinical suspicion, specific diagnosis and specific therapy.

Shankar, Deshpande and Vasudev Rao from NIMHANS (1978) showed the coexistence of cysticercal cyst and Japanese encephalitis in patients studied at autopsy. Srinivas, Vasudev Rao and Deshpande described the encephalitic variant of cysticercosis (1980). Virendra Kumar and Gourie-Devi (1986) have analysed the clinico-pathological correlation of neurocysticercosis in a retrospective analysis of neurological case records (1986).

Other parasitic disorders seen in India

Amoeba, the malarial plasmodium, echinococcus, visceral larva migrans have been reported in the CNS. Raja Reddy et all (1972,1984,1986) found 1% of intracranial space occupying lesions in India to be parasitic. They described 5 patients with hydatid cysts (3 cerebral, 2 intradiploic cranial) and 6 cases of cysticercosis. Spinal hydatid disease was encountered by Ashok et al (1987), Suresh Narain et al (1987). Sushma Kapoor et al (1976) have described encephalopathy due to visceral larva migrans.

Bhatia et al (1971) have reported menigoencephalitis due to soil amoeba. Vasudev Rao et al (1988) have reported primary amoebic cerebellar abscess. Alka Gogate reported primary amoebic meningoencephalitis and isolated Naegleria fowleri from swimming pools in Bombay which could be potential cause of amoebic meningoencephalitis (1984,1985).

Guinea worm infestation of tuberculoma has been reported by Dinakar et al (1977), encephalopathy in association with ascariasis by Basu et al (1979), toxoplasmosis of the brain by Sanathanarath et al (1986), polyneuropathy in kalazar by Vijayan et al (1981).

Fungal infections of the central nervous system

A variety of fungal agents have been associated with CNS lesions, the most common being cryptococci, aspergillus, mucor, candida and cladosporium. Nocardial lesions are still being classified as fungal by many workers though the organism has now been categorised under higher bacteria.

Reports of fungal infections have come from different parts of India. Ramamurthi et al (1954) have also reported on cryptococcal fungal granuloma in neurosurgery. Dastur described his experiences at the department of neurosurgery,K.E.M.Hospital, Bombay with cerebral

chromoblastomycosis due to cladosporium trichoides in 1966. Raja Reddy (1971) documented a case of cryptococcal brain abscess. Vasudeva Devadiga (1968) has reported a case of cerebellar cryptococcal granuloma. Rama Rao et al (1968) and Singhal et al (1974) have reported cases of cryptococcal meningitis. Balaparameshwara Rao et al (1970) have reported a rare case of spinal extra dural granuloma. Balasubramaniam et at (1971) have reported on fungal granuloma. Deshpande and Desai (1975,1976) have reported on aspergillosis and mucor mycosis of central nervous system. Banerjee et al (1975) from Chandigarh have reported on 11 patients with fungal intracranial space occupying lesions seen over 8 years. Abayankar et al (1986) have reviewed the literature on cerebral mucormycosis. Talwar and Meera Sharma (1986) studied the incidence and diagnostic aspects of cryptococcosis in Chandigarh. Radhakrishnan et al (1983) from Sri Chitra Tirunal Institute, Trivandrum have studied cryptococcal infection in animal models, the role of hyaluronidase in in vitro phagocytosis of encapsulated yeasts of cryptococcus neoformans and circulating cryptococcal capsular polysaccharide titres (Annamma Mathai and Radhakrishnan, 1983). Subimal Roy of the department of neuropathology, AIIMS, has described the histopathology of fungal infections of the brain in 33 cases seen over 18 years (Personal communication). Mohandas et al (1978) from the otorhinolaryngology department of the same institute have described four cases of aspergillosis of the central nervous system.

At NIMHANS over the past decade, we encountered 40 patients with fungal infections of different types. 23 were of cryptococcal etiology, 4 cases of cladosporium trichoides infection, 7 cases due to aspergillus fungi and 5 cases of zygomycosis. Cryptococcal granulomas were encountered in 4 cases. Chronic cryptococcal meningitis resembling TBM was seen in 20 cases. Cladosporiosis presented as brain abscess in 2 cases as cerebral infarction in 2 others (Chandramukhi et al 1983). The lesions caused by aspergillus and zygomycetes-rizopus and mucor were granulomas. Most of the fungal infections encountered at this centre have proven fatal inspite of antifungal therapy. A history of diabetes was present in all cases of zygomycotic granulomas. In 4 of the 20 patients with cryptococcal meningitis, there was associated tuberculosis of the lung. India ink smears, CSF cytology by cytospin to recover the scant cryptococcal yeast and by carrying out 'more than routine' fungal cultures of CSF biopsy tissues a foolproof surveillance of fungal infections of the brain can be set up.

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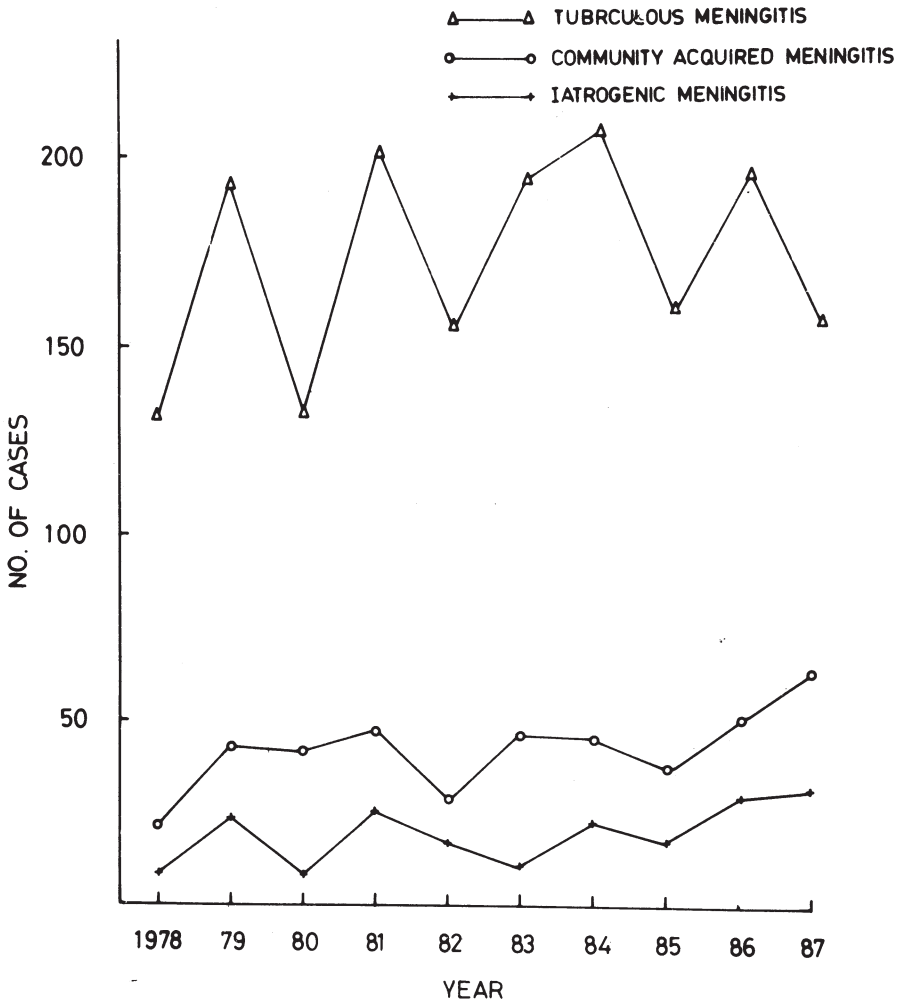
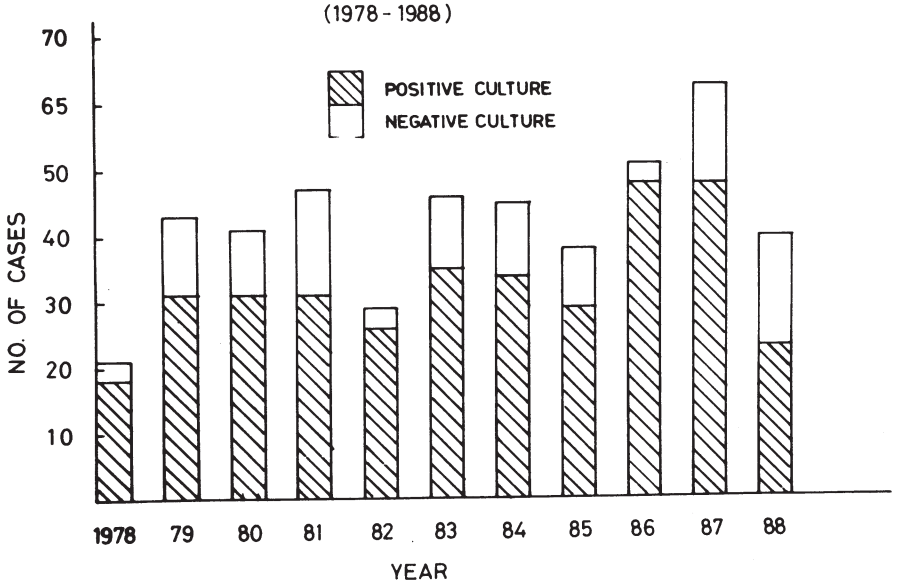
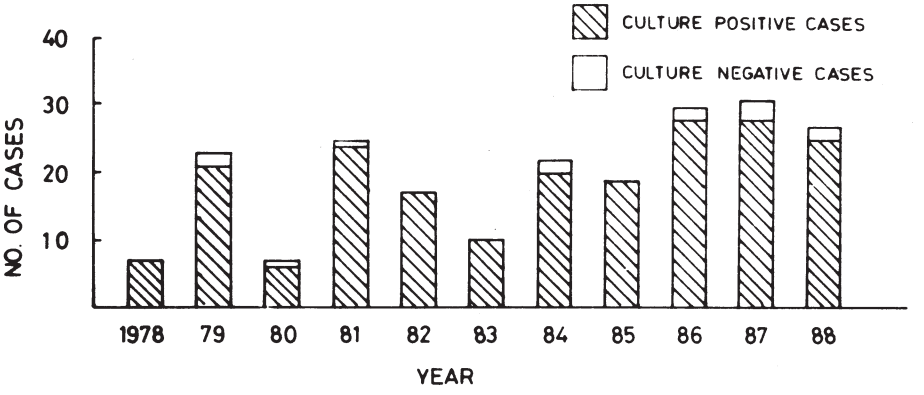
INCIDENCE OF TUBERCULOUS MENINGITIS, COMMUNITY ACQUIRED MENINGITIS & IATROGENIC MENINGITIS IN NIMHANS (1978-1987)



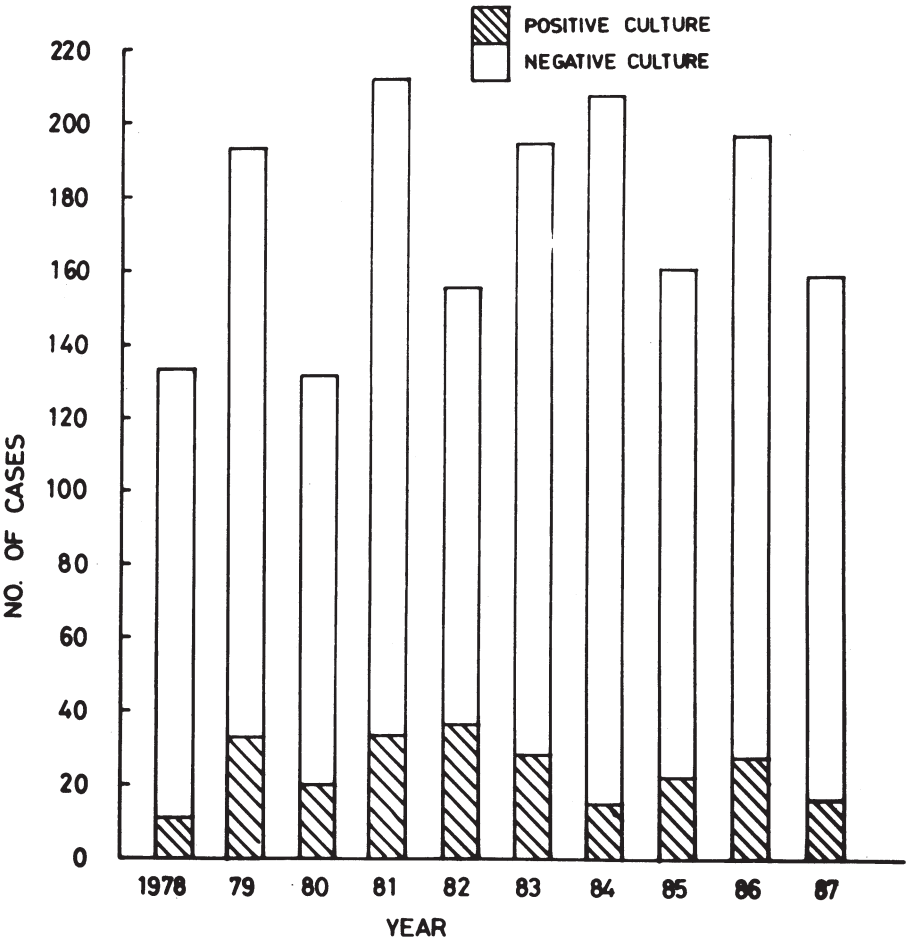
COMMUNITY ACQUIRED PYOGENIC MENINGITIS AT NIMHANS
(1978 - 1988)



IATROGENIC MENINGITIS IN NIMHANS
(1978-1988)



PERCENTAGE OF POSITIVE CULTURE IN TBM CASES
YEAR WISE INCIDENCE OF CLINICAL TBM



Clinical neurochemistry

B.S. Sridhara Rama Rao, Vijayalakshmi Ravindranath

Clinical neurochemistry has come to be recognised as a speciality by itself since basic knowledge concerning the chemistry and metabolic processes taking place in the brain, spinal cord, peripheral nerve and muscle has increased in a remarkable manner. The application of this knowledge has enabled us to gain an insight into the etiopathogenesis of several neurological and behavioural disorders.

In India work in clinical neurochemistry has been carried out in leading medical institutions. Mention could be made here of the studies reported from the ICMR Neuropathology Unit at the J J Group of Hospitals, King Edward Memorial and Jaslok hospitals, Bombay; Institute of Child Health and Postgraduate Institute of Medical Education and Research. Calcutta; Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh; All India Institute of Medical Sciences (AIIMS), New Delhi; Institute of Genetics and National Institute of Nutrition, Hyderabad; King George Medical College, Lucknow; Institute of Neurology, Madras; Christian Medical College, Vellore; Indian Institute of Sciences and National Institute of Mental Health and Neurological Sciences, Bangalore.

A number of workers have evinced interest in evaluating the role of nutrition in brain development. The effects of protein-calorie malnutrition on the development of the nervous system has been extensively investigated. The ICMR Neuropathology Unit at the J J Group of Hospitals in collaboration with the departments of neurology at that hospital and at the K E M Hospital in Bombay studied the role of vitamin B in malnutrition, alcoholism in adults and in collaboration with the department of pediatrics at the J J Hospital, studied protein-calories malnutrition in children. Some of the other major developments in this behalf have been reviewed in a publication of Indian National Science Academy (Tandon and Gopinath, 1984), where the following have reviewed their work: P N Tandon, Gomathy Gopinath, P S Sastry, P S Murthy, K N Agarwal, N Kochu Pillai and Saroj Mehta.

Saroj Mehta has established a clinic at PGIMER, Chandigarh in collaboration with the local branch of Indian Council of Child Welfare. She

has carried out a painstaking programme in the low socio-economic group for more than a decade (personal communication). She has observed the growth and development of infants and the utility of supplementary nutrition programmes for preschool children. She has completed a follow up study of new born babies from birth to 2 years of age with a view to observe feeding, growth pattern and morbidity. Studies on experimental animals, specially to see the changes in brain as a result of altered nutrition have also been done (Relan et al 1985). At the Institute of Medical Sciences, Banaras Hindu University, Agarwal has studied to understand the relationship of delayed development of mental function in children to their nutritional status (Agarwal et al 1987). He and his associates have also studied the effect of cereal and pulse diets and of latent iron deficiency on neurotransmitters and trace elements of the brain of fetal and weaning rat (Agarwal 1984, Taneja et al 1986, Shukla et al 1989 a,b). Agarwal (1984) has also studied the effect of nutritional status on brain growth and development in experimental animals.

At Hyderabad, Subba Rao has carried out work on the biochemical composition of developing human foetal brain and has shown that the accumulation of various biochemical constituents (in particular, DNA and RNA) occurs in two phases possibly representing neuronal and glial cell proliferation schedules. Studies on brains obtained at autopsy from Kwashiorkor subjects show reduction in cell size but no significant cell loss. In addition, the proportion of long chain fatty acids and polyenoic acid was also decreased. Studies using experimental animals have also been carried out (Sarma et al, 1983).

It is increasingly being realised that neonatal hypothyroidism is easily detectable and can be treated with gratifying results. Kochupillai's (AIIMS, New Delhi) is probably the only report from a developing country which has convincingly shown the need for screening for neonatal hypothyroidism in iodine deficient areas. He showed that 4-13% of newborns from areas where goitre is endemic in India are hypothyroid at birth. In areas without iodine deficiency, the incidence of neonatal hypothyroidism is one in 1000 births or less. Mass screening of newborn in advanced countries has shown that the prevalence of hypothyroidism is one per 3000 and that neonatal hypothyroidism is the most frequent cause of preventable mental retardation (Kochupillai et al, 1986).

Ahuja and coworkers from AIIMS, New Delhi have carried out systematic studies on etiopathogenesis in patients with myasthenia gravis. They have developed a simplified ELISA method for antireceptor antibodies in myasthenia gravis (Jailkhani et al, 1986). They have also reported on the reaction of myasthenic antibodies with heart and brain nicotinic acetylcholine receptors (Asthana et al, 1987).

From the Institute of Neurology, Madras; Valmikinathan has reported that it is possible to identify different types of motor neuron disease depending on the type of biochemical abnormality noted. These observations were based on the analysis of citrate, pyruvate, lactate and also on the effect of glucose load (Valmikinathan, 1987). Dastur, for the first time, reported the role of cycad in the production of amyotrophic lateral sclerosis in Guam and how cycad damages the central nervous system. (Dastur, 1964; Palekar and Dastur, 1965; Dastur and Palekar 1966). Subsequent work by Spencer and coworkers has confirmed these findings (Spencer et al, 1987).

Mohanty and coworkers from the Department of Neurosurgery at Institute of Medical Sciences, Banaras, have carried out systematic studies on alterations in biochemical constituents in patients with head injury. The analysis included plasma biogenic amines, serum LDH and serum choline esterase. Studies in experimental animals followed. The same group has studied alterations in biogenic amines in cerebral edema (Nayak et al, 1980; Mohanty et al, 1979). Alteration of biochemical constituents such as enzymes and isoenzymes in neurological diseases has been studied in CSF and serum. (Dave et al, 1986, Dave et al, 1987).

Mishra and Nag from Lucknow have been carrying out systematic studies in clinical neurotoxicology. Their work on subjects exposed to pesticides (DDT and organophosphorus compounds) has been documented. (Mishra et al, 1985; Siddiqui et al, 1981). The National Institute of Occupational Health (NICH), Ahmedabad has a team of dedicated workers who have carried out work on environmental pollutants. The annual reports of NICH are quoted in several of the WHO publications and their international collaborative work on lead is especially noteworthy. Extensive studies have been made on neurolathyrism (characterised by upper motor neuron dysfunction) induced by habitual consumption of the pulse lathyrus sativus. Workers at the National Institute of Nutrition (NIN), Hyderabad isolated the toxic principle and went on to devise a practical method of detoxification. (When it is realised that economic compulsions force farmers in the poorer districts to live on lathyrus sativus, the importance of this contribution becomes evident.) NIN has also established clearly that the outstanding nutritional problem in the country today is the correction of the widespread protein energy malnutrition that leads to physical and mental retardation and underdevelopment of so many of our children.

Several series of patients with inborn errors of metabolism have been reported from different centres in India. Kumta (Bombay) has reported cases of galactosemia and lipidosis. Verma (Delhi) has reported on cases of homocystinuria (Verma, 1978). Bacchawat and coworkers from Vellore showed for the first time that patients with metachromatic leucodystrophy were deficient in lysosomal arylsulfatase A. This is now used as a marker

for the diagnosis of this disease (Austin et al, 1963). Subsequent papers from Vellore describe a number of inborn errors of metabolism (involving glycoconjugates) leading to mental retardation (Jadhav et al, 1978).

Several cases of phenylketonuria (PKU) have been reported from the Institute of Genetics, Hyderabad. A new type of metabolic effect -threoninemia- has been described. (Verma, 1986).

The largest series of cases of PKU -representing nearly 80% of such cases reported from India - has come from NIMHANS. Bangalore. Other aminoacidurias, lipidoses and mucopolysaccharidoses associated with mental retardation have also been reported from NIMHANS, Bangalore (Verma, 1986). Patients with Maple syrup urine disease have been reported from Bombay, Madras and Bangalore (Dastur et al, 1986; Verma, 1986).

The largest series of cases of Wilson's disease have been reported by Dastur and coworkers. Clinical, biochemical, histopathological and other investigations have been extensively documented in these cases (Wadia and Dastur, 1963; Dastur et al, 1968; Manghani and Dastur, 1968).

Several centres in India (Vellore, Chandigarh and Bangalore) have been interested in epidemiological and risk factors associated with stroke. The article by Chopra (1972) is worthy of study.

Several Indian centres have been working in the area of biological psychiatry. These include King George Medical College, Lucknow; Christian Medical College, Vellore; PGIMER, Chandigarh; Madurai Medical College, Madurai and NIMHANS, Bangalore. Possible risk factors in the etiopathogenesis of major psychoses -viz. schizophrenia and affective disorders- have been studied. The importance of genetic factors in the development of these disorders has been established at all these centres. Suitable biochemical and genetic markers are being identified. Some of this work has been reviewed in the proceedings of the **Indo-US Symposium on Schizophrenia and Affective Disorders** held at NIMHANS, Bangalore during 1983-84 wherein investigators from different centres in India participated and presented their findings.(Venkoba Rao and Parvathi, 1987; Channabasavanna et al 1987)

Research in clinical neurochemistry is being carried out under very trying circumstances at most of the medical centres. The pressure of clinical work occupies workers fully. It is fortunate that at teaching hospitals trainees are stimulated and develop interest in this field. It is gratifying to note that many of them have either taken short term projects in this area or have initiated projects upon return to their alma mater.

This review of work done in the area of clinical neurochemistry in India has incorporated reports that were available to us. We are grateful to all those who responded to our request in this behalf.

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Clinical Neurophysiology

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Introduction

Clinical neurophysiology in India made a beginning in the early 1950s with the establishment of electroencephalo-graphy (EEG) laboratories at higher centres of learning at Calcutta, Vellore, Madras, Bombay, New Delhi and Bangalore. This was possible due to the pioneering work and untiring efforts of S. T. Narasimhan, T.K.Ghosh, Baldev Singh, Menino DeSouza, N.S.Vahia and E.P. Bharucha. Over the next two decades similar facilities became available in many teaching institutes, medical colleges and in the private sector. In late 1950s and early 1960s electromyography also took root in few centres notably at Bombay, Calcutta, New Delhi, Chandigarh and Bangalore. Currently EEG and EMG facilities are available in more than 50 centres to fulfil diagnostic, teaching and research needs. In many of these laboratories evoked potential studies are also being undertaken. Clinical neuro-physiology has not yet evolved as a separate discipline in India. With a few exceptions of full time clinical neurophysiologists, most of the work in this area is done by clinical neurologists. The growth, development and progress of clinical neurophysiology will be dealt under 3 sections: (1) electroencephalography (2) electroneuromyography and (3) evoked potentials.

Electroencephalography

Baldev Singh commenced electroencephalography on the small machine he had brought with him to India. On completion of his training at the Institute of Neurology, New York, S. T. Narasimhan returned to Madras with an EEG machine and set up a laboratory at a stage when there were no neurosurgery units in the country. Later, he lent the services of his EEG laboratory to the neurosurgery department at the Madras Medical College and Hospital.

After the establishment of EEG laboratories, studies were directed at understanding the rhythm of the brain and in assessing the value of EEG in primary generalised and focal epilepsies. A collaborative epidemiological

study on epilepsy with investigators from Bangalore, Bombay, Calcutta, Madras and New Delhi has provided a large data base. To enhance the diagnostic yield of EEG in epilepsy various activation procedures were introduced. Depth electrode studies provided valuable information in understanding epilepsy and behavioural disorders which logically led to better management. EEG as a diagnostic tool was applied to a variety of states of consciousness and disorders of nervous system. A brief resume of certain selected papers is reported.

Singh and Chandy (1955) in an exhaustive study of delta waves in 800 EEG records at Christian Medical College Hospital (CMCH), Vellore, found two main forms, those which occur in bursts and others which are irregular. The distribution of delta waves may be either focal or diffuse. They may occur in a variety of conditions. The localising value is more accurate if the lesion is on the convexity of the brain. They do not accurately predict the nature of the lesion. The genesis of delta activity is attributed to metabolic changes in the cortex, disturbances in the function of Magoun's area, abnormal discharges from the thalamus, cortical isolation from the brainstem reticular system and defective acetyl choline liberation. One or more of these factors may be operative in a specific situation. It was observed that 6 and 14 Hz. positive complexes were associated with pain (15), emotional changes particularly anger and aggression (10) and seizures (6) in the descending order of occurrence (Singh et al 1962). These EEG features were found in 35 out of 630 EEGs done for epilepsy and other paroxysmal phenomena. Experimental observations in cats indicated that the site of origin of these complexes is diencephalon.

Epilepsy

Two large series have focussed attention on interictal EEG abnormalities in various types of epilepsy. Mani (1973) analysed the interictal changes in 1447 EEG records of 621 subjects over a 2 year period to identify factors determining the occurrence of epileptiform activity. Definite seizure discharges were noted in 31.5% records. The following factors were identified : (1) earlier age at onset of symptoms (2) earlier age at the time of recording (3) greater duration of illness (4) greater total number of attacks prior to recording (5) earlier recording after a recent attack (6) no anticonvulsant therapy at the time of recording (7) greater duration of a record and finally (8) greater degree of relaxation. No association was observed between the frequency of attacks and a positive record nor between the subsequent attack and a positive record. This study having been based on the number of records and not on the number of patients did not highlight the positivity of EEGs in different types of epilepsies.

Sayeed et al (1975), analysed the EEG records of 410 patients done at the beginning of the study and after the fourth year and concluded that (a) initial normal EEG was seen in 9 to 30% of patients, the highest being

in major epilepsy, (b) in myoclonic seizures (10 patients) all patients had abnormal initial record, (c) the majority of patients (79%) with initial normal EEG continued to have normal record at the 4th year, (d) nine percent of patients of generalised epilepsy had purely focal abnormality, 36% of patients of TLE showed bilateral synchronous spikes or spike and wave discharges and only one of 12 patients with absence showed focal abnormality and (e) forty percent of patients with initial abnormal record showed a reversal to normal, at the end of 4th year with the exception of myoclonic seizures and absences where the EEG abnormality persisted.

In an analysis of EEG records of 61 cases who had recurrent paroxysmal brief attacks, symmetrical and synchronous spike and wave discharges of varying frequency (1-5 Hz) and rhythmicity were seen in 29 cases.

In 14 patients there were paroxysmal slow and sharp waves and in the remaining 18 cases no abnormality was observed (Mondkar et al 1975). In complex partial seizures, the localization of focal discharges and correlation with aura has been attempted.

Mani et al (1976) in a study of 248 subjects with temporal lobe epilepsy found definite focal spikes and/or sharp waves in 30% of EEGs. EEG foci were most frequently localised to anteromedial (69%) and less commonly to antero-lateral region. Abnormalities were uncommon in mid temporal and posterior temporal regions. The aura of dreamy state, automatism and lip smacking had the best correlation with EEG foci while vertigo, visual or auditory hallucinations had no correlation, contrary to the observations reported in literature of focus in the posterior temporal region. In a recent paper Bhaskar (1982), reported correlation of emotional aura and automatism to infero-medial and anterotemporal foci.

Mani et al (1968) are credited with the clear description of **hot water epilepsy,** a peculiar type of reflex epilepsy, predominantly seen in the state of Karnataka, South India. The first report described 42 patients from the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore (earlier known as All India Institute of Mental Health) and subsequently more cases were added to the literature from the same institute and by others (Mani et al 1972, Subramaniam 1972, Satischandra et al 1988). Generalised or focal seizure discharges during interictal period were observed in one third to two-thirds of patients. Despite all attempts to reproduce the attack with specific stimulus, for obvious technical reasons, ictal EEG recordings could not be obtained.

Photosensitive epilepsy has also been reported (Maheshwari 1978). In 2 patients with impulsive waving of the hand in sunlight, spike and slow wave discharges in frontotemporal and temporal region were seen. The hand waving has been considered part of the ictus. In another interesting type of reflex epilepsy, **eating epilepsy,** well defined temporal or

frontotemporal focus was seen and in a few, generalised spike and wave discharges were observed (Ahuja et al 1980, Chemburkar and Desai 1977, Nagaraja and Chand 1984). Of special interest were the patients in the series of Nagaraja and Chand (1984) who had normal EEG before, during and after eating. Rare epileptic phenomena including ictal hematemesis (Radhakrishnan et al 1982), paroxysmal episodes of blindness (Maheshwari 1982), episodic nystagmus (Chopra et al 1986) and paroxysmal running (Koul and Razdan 1988) have been associated with focal or generalised epileptic activity. Recognition of these rare forms of epilepsy aids in the proper management and avoids unnecessary investigations.

EEG abnormalities have been reported in migraine and consisted of synchronous bursts of spikes and or sharp waves in the resting record and induced by hyper-ventilation and photic stimulation. The EEG changes provided the basis for phenytoin as a prophylactic agent (Sridharan et al 1982).

Some of the problems in the drug therapy of epilepsy are the choice of anticonvulsant drug combination to be used and the final withdrawal of the drugs. Interictal EEG has been used as a guideline for arriving at a decision on these issues. Based on experimental data in animals the anticonvulsant drug combinations were chosen for treatment of grandmal epilepsy (Paul et al 1957). The effect of six different combinations of drugs (phenytoin, phenobarbitone and primidone) on EEGs of 88 cases was evaluated. The best improvement of interictal EEG was obtained with a combination of phenytoin and phenobabitone in a ratio of 3:1 or along with mysoline in 3:1:1 combination. Vahia et al (1956) found that there was no correlation between EEG and clinical improvement in a study of 23 cases of grandmal epilepsy who responded to treatment and another group of 23 patients who did not show satisfactory response over a period of 1 to 4 years. However, in the cases where there was no EEG improvement, recurrence of seizures occurred on withdrawal of medication.

Although EEG is a useful diagnostic tool in epilepsy, the yield from interictal scalp EEG records is 70 percent. To improve this further, various activation procedures have been in practice. In the early 1950s metrazol was used for activation. Desai and Vahia (1957) tested the combined use of metrazol and photic stimulation to identify the threshold of cerebral excitability on epileptics and hysteria and it was found that the average threshold was low in idiopathic epilepsy. Further studies with the use of cerebral stimulants such as bemegride and procyclidine showed that although these were useful activating agents, the untoward effects of precipitation of seizures in epileptics and activation of EEGs in normal individuals restrict their utility (Suri et al 1976). With better available activation procedures and pharmacological agents such as hyoscine, these early methods have become obsolete (Virmani et al 1975). Spontaneous whole night sleep records were found to be useful especially in patients

with epilepsy occurring in sleep (Chemburkar et al 1976). Epileptic discharges were observed in second and third stages of sleep. Interestingly no discharges were seen in stage IV in this study contrary to the observations reported in the literature. With methohexitone activation the normal records showed focal abnormalities and the pre-existing abnormalities were further exaggerated in 33 percent (Deshmukh et al 1972; Hansotia et al 1971). Mani and Varma (1960), using sphenoidal electrodes, were able to detect focal abnormalities in 35% of patients with temporal lobe epilepsy in contrast to the low positivity of only 4% with routine scalp EEG. With a combination of sphenoidal EEG and methohexitone activation there was a further improvement in the diagnostic yield (Mani et al 1972). Sphenoidal recording with pentothal activation was also found to yield a high positivity of 93 to 100% in temporal lobe epilepsy (Arjundas 1980, Arjundas and Ramamurthi 1967).

Depth electrode study supplements information obtained from scalp EEG in identifying the epileptogenic focus and also reveals foci not evident in scalp EEG records (Arjundas 1976, Ramamurthi et al 1976). Depth studies are also useful in understanding the propagation of epileptic discharges. Singh and Chandy (1954) observed that negative spikes in frontal, central, anterior temporal and occipital area spread as negative spike of low voltage to the homologus area. The phase of the spike is variable when the spread is to the other zones. It was concluded that conduction of spike with the negative or positive sign depends on the identity of the structures. If the two sides are homologous and symmetrical in structure the projection is negative although of lower voltage. On the other hand, if these conditions are not satisfied and the areas are interconnected, the projection is positive. Depth electrode study along with electrocorticography also provides precise localisation of the epileptic focus. This information is useful for planning appropriate surgery (Kanaka and Balasubramaniam 1980, Mathai 1985, Ramamurthi et al 1976). In a study by Mathai (1985) of 50 patients with epilepsy at CMCH, Vellore, depth recordings showed epileptiform abnormalities confined to anterior temporal region in 16, anterior temporal region in association with minor abnormalities in posterior temporal, frontal and parietal region in 18, discharges outside the anterior temporal region with minor changes in anterior temporal region in 12 cases and in amygdala alone in 4 cases. Following amygdalectomy there was a decrease but not a total absence of epileptiform abnormalities, showing that amygdalectomy is only palliative except under the rare situation where epileptiform activities are confined to amygdala.

A number of internal and external environmental factors are known to precipitate epileptic attacks. Venkataraman (1976) hypothesised that changes in the geomagnetic field and ionosphere may influence the clinical and EEG phenomena in epileptic individuals. A rare opportunity to study such effect arose during the solar eclipse on 16th February 1980 which was visualised in many parts of India. The incidence of seizures in 38

known epileptic patients and EEG changes in 15 subjects (11 patients and 4 normal) were studied at NIMHANS, Bangalore, and it was observed that there was no positive correlation between the occurrence of seizures, scalp EEG and geomagnetic variations (Srinivas et al 1981). In a similar study carried out simultaneously at New Delhi and Cuttack, Tandon et al (1983) observed that solar eclipse had no adverse effect on the clinical occurrence of seizures or EEG changes in 12 epileptic subjects.

EEG in altered states of consciousness:

EEG changes in physiological and pathological states of alteration of consciousness have been studied in considerable detail. Disturbance of sleep pattern may occur in behavioural disorders and epilepsy. In coma due to metabolic factors or structural lesions of the brain, EEG is often useful in diagnosis, assessment of severity and prognostication.

Sleep pattern may not differ with a given personality or intelligence but REM sleep is minimal in schizoid personality. In a given subject there is no consistent temporal sequence from night to night. The amount of time spent in each stage of sleep varied in an individual and even the number of sleep stage changes differed in subjects (Mamdani et al 1972). The effect of a sudden loud auditory stimulus, such as a bang, on the spindle stage of sleep was studied in 10 normal and 45 epileptic subjects by Singh (1958). In the normal individual the response consisted of sharp wave followed by high voltage slow waves of 0.2-0.3 seconds duration and later by 13-14 Hz activity. In petit mal the response consisted of high voltage sharp topped waves lasting for 0.1 sec. Singh et al (1959) analysed the significance of sleep humps and spindles in normal adult humans and patients with temporal lobe seizures. The study also included 18 animals (adult monkeys and cats). The presence of hump activity was considered to be due to pallidothalamic integration and the absence of such activity in cats and monkeys was attributed to immaturity of this integration. Sleep spindles and slow waves however have been found in animals as well, implying that functional inhibition at hippocampal, upper brain stem and possibly at thalamic level is present. Unilateral atrophy of hippocampal region in temporal lobe epilepsy produced asymmetry and asynchrony of sleep spindles.

EEG in 18 cases of **coma** of varied etiology were analysed using 4-5 stage clinical and EEG grading. The discrepancy between the clinical and EEG grades was attributed to the complicating metabolic factors and cerebral edema. In coma of grade I and II, lateralised and localised abnormalities were seen, but as the coma deepened to grades III and IV, the over-riding delta activity masked focal changes (Kohiyar 1965). Arjundas et al (1965) selected 9 patients of hepatic encephalopathy who were either conscious or drowsy. They observed disturbance of normal rhythm in all the patients which correlated with the degree of impairment of sensorium. This

observation is contradictory to the findings of Kohiyar (1965) (vide supra). This discrepancy is perhaps due to the difference in the severity of the disturbance of consciousness in the two studies. Triphasic waves were seen in 4 and seizure discharges in the form of sharp waves in 6 of the 9 patients. Only two of these 6 patients had fits. The slow activity was synchronous and fairly symmetrical, changing from theta to delta with increasing drowsiness. This slow activity was blocked with eye opening. Irrespective of the underlying disease of the liver, EEG changes were similar.

Although neurological disturbances have been well recognised in chronic pulmonary insufficiency there are very few reports on electroencephalographic changes. Nagendra and Kohiyar (1968) studied arterial blood gases, pH and EEGs of 16 patients with chronic pulmonary insufficiency. The EEG was abnormal in 4. In one, this abnormality was attributed to cerebrovascular disease and in the other 3 cases the changes could be attributed to disturbed gaseous exchange since there was no evidence of focal neurological deficit. The salient features were paucity of alpha rhythm and rhythmic theta activity in the background. In 2 of these 3 cases, there was periodic build up of theta/ delta potentials of high amplitude for short periods predominantly over the frontal region. Hyperventilation abolished this build up activity which however reappeared on cessation of hyperventilation. More effective gas exchange might be responsible for this effect. No direct correlation was found between the EEG abnormality and degree of oxygen saturation, CO2 or pH.

EEG changes in acute (23 patients) and chronic (22 patients) renal failure were studied by Sawhney et al (1975). Slowing of background activity and increased slow wave activity in theta range were the essential features. Paradoxical response to eye opening and photomyoclonic response, reported by others, were conspicuous by their absence. There was a deterioration in EEG findings in 18/30 cases following hemodialysis. However, clinical worsening was seen only in 3 patients indicating that there was no correlation between clinical and EEG status. Correlation between EEG changes and biochemical parameters was also not seen. Studies in patients with prolonged unconsciousness (35 records in 13 patients) and organic brain damage (99 records in 70 subjects) and analysis of sleep pattern led to the following conclusions: (a) a well formed sleep pattern may be observed in unconscious patients suggesting that neural substrates for sleep and consciousness are not identical although they may overlap (b) in patients with identical clinical stage sleep structures may be altered to a varying extent giving rise to different EEG patterns (c) absence of sleep like activity suggests brain stem damage and (d) preserved sleep activity indicates a favorable prognosis (Tandon et al 1972, Tandon et al 1976). Similar observations were made in cerebrovascular accident by Sumra et al (1972).

Alpha coma in 8 patients has been reported by Satischandra and Gourie-Devi (1986). Alpha was diffuse in all subjects and in 3 of them predominant alpha activity was seen in frontotemporal and central leads. Alpha was

found to be responsive in 4 subjects but in the rest, it was nonresponsive to a variety of stimuli. The cause of coma was subacute encephalitis in 3, drug overdosage in 4 and brainstem infarction in one patient. Only one patient with phenobarbitone overdosage recovered fully while the others died. Neither the distribution nor the behaviour of alpha in these comatose patients was useful in predicting the outcome. The authors reiterated the observations reported in the literature that alpha coma indicates a grave prognosis.

In a variety of disorders including encephalitis, space occupying lesions, cerebral venous thrombosis etc. EEG has been useful for accurate diagnosis, precise localisation and predicting the outcome. However in view of the complexity of the genesis of electrical rhythms and propagation of impulse activity, electroencephalo-graphers need to be alert to the fallacies.

Japanese encephalitis, a paradigm of acute encephalitis, has occurred in epidemic form in many parts of the country since the year 1973. EEG was consistently abnormal in the majority of patients. Slow waves in theta or delta range with asymmetrical electrical activity were seen. The abnormalities varied from mild disturbances of background rhythm to gross slowing. Although clinical seizures were common, spike activity or seizure discharge in EEG were rare. Burst suppression was observed in deeply comatose patients. On the whole the EEG changes reflected the severity of brain damage but did not necessarily provide a guide line to the final outcome (Gourie-Devi and Deshpande 1982). Hypsarrhythmia was a prominent feature in patients with mild to moderate coma in acute encephalitis presumably due to coxsackie virus (Padmavati et al 1958).

The EEG features of **subacute sclerosing panencephalitis** have been reported by a number of authors (Mani et al 1964, Singhal et al 1974). The characteristic features were disappearance of alpha activity with slowing of background, occurrence of high voltage slow wave periodic complexes and rarity of spike discharges. Simultaneous EMG recordings showed that the complexes and myoclonic jerks had 1:1 relationship. It has been suggested that these periodic complexes originate in the brain stem or cerebral cortex. In one patient with typical periodic complexes, Gupta and Sawhney (1969) demonstrated that right intracarotid injection of sodium amytal completely suppressed these complexes while left sided injection had no effect. Right frontal lobectomy had no influence. This prompted the authors to suggest that the site of origin of the periodic complexes may be the deep subcortical structures.

Intractable seizures, progressive dementia and a neurological deficit in the form of hemiplegia or quadriplegia were reported in 4 patients with **chronic persistent encephalitis** manifesting in the first decade of life (Gupta et al 1974). Focal spikes seen in 3 patients were abolished by

surgical ablation and the clinical seizures also were fully controlled or were considerably decreased in frequency. There was evidence of chronic concephalitis on histopathological examination of the brain tissue. In a patient with a clinical picture of diffuse meningo-encephalitis, the EEG showed interesting feature of periodic lateralised sharp and slow wave discharges. Autopsy revealed the surprising findings of extensive generalised **cerebral cysticercosis** (Vijayan et al 1977). It is of interest to note that periodic lateralised discharges have also been reported in a child of **acute pneumococcal meningitis** (Ahuja et al 1980). Atypical EEG changes were reported in two patients of **Creutzfeldt Jacob disease** by Srinivas et al (1982). There was a rapid transformation from short runs of symmetric slow wave discharges to periodic complexes within a few days and these complexes could be abolished by intravenous diazepam. Interestingly these complexes did not have clinical correlate of myoclonus.

Significance of EEG in the diagnosis of **space occupying** lesions had been assessed in 100 confirmed cases (Ghosh 1965). Lateralised EEG abnormality was seen in 73 of them and in 60 there were localised changes. Nonspecific changes in 18, normal record in 5 and false lateralisation in 4 were the other features. The percentage of lateralised abnormality was higher (83.5%) in a sub group of patients with hemispheric lesions (Ghosh 1965). Arjundas and Ramamurthi (1965) critically analysed the EEG abnormalities in 115 cases of confirmed supratentorial lesions. Abnormalities were seen in 97% and the most reliable feature was slow wave activity in delta and theta range. This abnormality was localised or lateralised in 68%. The next frequent change was disturbed normal rhythm (56%) and the least common was focal or lateralised epileptic discharges (41%). Although the EEG was a useful diagnostic aid and supplemented clinical examination, it did not provide a clue to the nature of the pathology. In yet another study on the value of EEG in brain tumors, Janaki (1968) observed that the commonest abnormality was localised delta focus which was particularly seen in tuberculoma, astrocytoma and abscess. In contrast, in highly malignant lesions like glioblastoma, generalised slow wave discharges were seen, indicating wide spread disturbances. She also found that accurate anatomical localisation was possible with tuberculoma and astrocytoma in temporal and frontal region.

Electroencephalographic features in 50 patients of postpartum **cerebral venous thrombosis** have been reported by Srinivasan (1983). Diffuse nonspecific changes were seen in 30 and focal lateralising slow and sharp waves in 10 patients of superficial cortical venous thrombosis and rhythmic anterior slow wave bursts in two patients with deep vein thrombosis. Eight patients had normal EEG. Serial EEGs done over a 3 week period showed improvement but the clinical recovery antedated improvement in EEG abnormality.

Infantile tremor syndrome, a clinical entity of interest to pediatricians and neurologists in India, has been studied intensively. EEG features were analysed in 22 children (Bajpai et al 1972). The abnormalities were slow background activity, unifocal or multifocal spikes, voltage asymmetry and lack of drug induced fast activity. In the pre-tremor phase the EEGs were normal, while in the tremor phase abnormalities were detected in 75% of cases, spike discharges being the commonest finding. In the post-tremor phase, the abnormalities persisted and bilateral slow wave activity was the predominant feature.

Clinical neuroscientists in India have also worked on **behavioural disorders.** Singh and Chandy (1956) in 18 subjects with schizophrenia reported data of scalp EEG and depth electrode studies of the frontal lobe before performing lobotomy. The characteristic *choppy activity* was found with a higher frequency in schizophrenia compared to other forms of psychosis and convulsive disorders. This choppy activity is considered to be a result of suppression of alpha activity. An interesting observation was the asymmetrical activity over the two hemispheres and this lack of coordination of the hemispheres was postulated to be responsible for derangement in conditioned reflexes and adjustment to the environment. The differences in the electrical activity observed over the superior convexity and orbital surface were attributed to strati-laminate histological structure in the frontal gray matter and the reverberating connection with thalamus and hypothalamus. Of special interest was the finding of multiple foci of activity in the substance of the frontal lobe, the discharges from these foci remaining isolated from each other. This electrophysiological failure of coordination might reflect the disturbance of normal function of frontal lobes. At the Institute of Neurology in Madras, the leading centre in stereotaxic surgery in India, electro-physiological studies were carried out in a large number of subjects with hyperkinesia and behavioural disorders (Balasubramaniam et al 1972). Depth EEG recording showed amygdala spindles, which are characteristic but were not as common as in the experimental animals. It is conjectured that in these patients the amygdala was altered electrically or chemically by the disease process. The finding that depth recording from amygdala changed after hypothalamotomy established their close interaction.

Electromyography and nerve conduction

Concentric needle electromyography (EMG) affords information about the presence or absence of muscle involvement from primary muscle disease or secondary to nerve or anterior horn cell disease. Further advances in technology allowed increase in the sensitivity of electromyography as a diagnostic tool. Motor and sensory nerve conduction studies of peripheral nerves have been widely applied in the study of nerve damage in a variety of diseases. Some of the cranial nerves are also amenable for such conduction studies. The late responses (F waves, H reflex) provide

information about the integrity of the proximal segment of nerves as well as the reflex arc. By a combination of all these techniques it is possible to localize the lesion to one or more sites in the neuromuscular apparatus with a fair degree of precision.

Myopathy in nutritional osteomalacia has been studied by a number of workers (Irani 1976, Singhal 1966, Skaria et al 1975, Wadia and Swamy 1970). The EMG characteristically showed low voltage short duration action potentials with a normal interference pattern and increased polyphasic potentials. Motor nerve conduction may also show lowered velocity without any clinical evidence of neuropathy. Treatment with vitamin D and calcium supplements resulted in improvement in the muscle weakness and EMG changes (Skaria et al 1975). Subjective proximal weakness without any objective deficit may be observed in some patients with filariasis associated with chyluria. Myopathic features were detected in 9/20 patients by electromyography but histopathology showed mild changes only in 2 patients (Ashok et al 1979). The presumptive cause for myopathy is considered to be hypoproteinemia and hypolipidemia secondary to chyluria.

In **endomyocardial fibrosis** (EMF), an interesting condition encountered chiefly in Kerala, EMG features suggestive of myopathy were seen in 85% of cases (n = 20), while in patients with congestive heart failure (CHF) the incidence was 65% (n = 20). The changes were more severe and extensive in EMF than in CHF (Ashok et al 1982).

Electromyography in 13 of 16 cases of **arthrogryposis multiplex congenita** showed a clear cut neuropathic pattern in eight, myopathic picture in two and normal findings in three patients. In the neuropathic group fibrillations, increase in polyphasics and long duration polyphasic potentials were noted. There were no giant potentials. Such change were not only observed in the clinically affected muscles but were also seen in 'normal' muscles. In the myopathic group the characteristic short duration low amplitude motor unit potentials with increase in polyphasic units and full recruitment were observed in clinically affected and unaffected muscles (Bharucha et al 1972).

The electromyographic features in a few patients with **continuous muscle fibre activity** have been studied by a number of authors (Desai et al 1970, Girija et al 1983, Irani et al 1977, Kaur et al 1983, Maheshwari and Padmini 1981). The essential features described by Desai et al (1970) are continuous spontaneous activity of few motor units with increase in firing frequency with ischaemia and transient electrical silence after release of tourniquet pressure. The spontaneous activity persisted after nerve block but disappeared after local infiltration into the muscle, suggesting a terminal origin of muscle activity. General anaesthetic agent did not abolish the spontaneous activity but it ceased after scoline injection. In

contrast Irani et al (1977) observed that a nerve block abolished the activity suggesting a proximal site of origin in the nerve. They also pointed out that the activity may arise from different sites at different times. Kaur et al (1983) in addition observed motor and sensory nerve conduction abnormalities in 5 of their 6 cases. Thus from all these studies it may be concluded that abnormal discharges may originate in distal or proximal part of motor nerve and more than one site of hyperactivity may be present in the same nerve.

Pranesh et al (1980) reporting electro-physiological studies in a patient with **stiff-man syndrome** suggested the possibility of an abnormal and autonomous motor neuron pool as the pathogenic mechanism. The main findings on EMG were (a) spontaneous continuous motor unit potentials with no evidence of electrical silence even on maximum relaxation (b) little or no effect with IV diazepam or general anaesthetic (c) partial abolition of activity with nerve block and spinal anaesthesia and (d) complete abolition of activity with IV tubocurarine.

Vakil et al (1973) examined 23 patients of **cephalic tetanus** with apparent facial weakness. Electromyography showed that there was constant motor unit firing of potentials which were of normal amplitude and duration and there was no evidence of denervation or polyphasic potentials suggesting that there was no true paralysis of muscle. Dastur et al (1977) in 15 cases of cephalic tetanus observed facial paralysis of lower motor neurone type with denervation potentials and loss of motor units in 10 patients. The typical muscle spasm of tetanus was correlated electrophysiologically with spontaneous firing of action potentials which could be abolished by facial nerve block with 2% procaine. The distal latencies were marginally prolonged in 4 patients. These returned to normal with resolution of the disease. In a single case of local tetanus, restricted to one lower limb, Jain et al (1984) observed characteristic EMG findings of repetitive firing of groups of motor unit potentials with aggravation by any form of cutaneous stimulus. The action potentials were however of normal amplitude and duration and there was no evidence of denervation. Motor nerve conduction velocities were found to be normal. After the elicitation of knee jerk in the affected limb, the silent period was not observed, suggesting a failure of inhibition of the activated motor neurons.

Haridasan et al (1979) compared quantitative electromyographic data with two levels of threshold namely 100 uv or 50uv using a fixed fraction of the subject's maximal effort. The data were shown to be independent of sex, age and the strength of the muscle. In muscle disorders such as Duchenne muscular dystrophy and polymyositis, the diagnostic yield was better with 50 uv threshold for analysis than with 100 uv but, in anterior horn cell disease the diagnostic yield was the same with both thresholds. This study also suggested that the increase in amplitude per turn is more in favour of an anterior horn cell disease. When all the three parameters viz. turns,

amplitude and turn per unit amplitude were used, the diagnostic yield was more than with turns and amplitude alone (Haridasan et al 1980).

Electrophysiological studies in the **Guillain-Barre Syndrome** (GBS) have been reported by a number of authors. Prolongation of distal motor latency with either normal or slowed conduction velocity, denervation and sensory nerve conduction disturbances have been observed (Padmini and Maheshwari 1979, Kaur et al 1986, Raman and Taori 1976). Delayed proximal conduction velocity with normal velocity in the distal segment has also been documented (Padmini and Maheshwari 1981). The presence of profuse fibrillations with or without change in nerve conduction velocity has been reported to indicate a poor prognosis. (Raman and Taori 1976). On the contrary, Kaur et al (1986) concluded that combination of reduced conduction velocity and denervation was associated with poor prognosis as compared to the presence of either alone.

Detection of **early signs of ventilatory failure** is of paramount importance in the management of Guillain-Barre' syndrome (GBS) since timely institution of ventilatory support significantly reduces mortality. Clinical features of ventilatory insufficiency, fluoroscopic examination of diaphragm excursion and determination of vital capacity have limitations in the diagnosis of impending respiratory failure. Gourie-Devi and Ganapathi (1985) determined phrenic nerve conduction time using a simple percutaneous technique in 28 patients with GBS and in 32 healthy volunteers. Phrenic nerve conduction time (PNCT) was prolonged in 18 patients and serial studies showed progressive improvement with restoration of normal values in the majority by 12 weeks. Prolonged PNCT had a positive correlation with the extent of the disease, morbidity and mortality. PNCT was a more sensitive parameter than vital capacity or median motor conduction velocity in assessing the severity of the disease and predicting impending ventilatory failure.

Electroneuromyography in 25 patients with **myelo-radiculopathy following anti-rabies vaccination** showed abnormalities in 21 patients. Denervation was the most frequent observation (71%). Motor conduction velocity abnormalities were observed in 60% while sensory conduction was least affected (16%) (Swamy et al 1984).

Motor and sensory conduction study was performed in 40 patients of tuberculoid, dimorphous and lepromatous **leprosy**. Motor and sensory conduction velocity was reduced in all types of leprosy and in all segments of the nerve, both in the upper and lower limbs. The lateral popliteal nerve was found to be the most frequently involved nerve. Contrary to the common belief motor conduction was as frequently affected as sensory conduction (Chopra et al 1983; Singh et al 1977). Phrenic nerve conduction was determined in 40 patients (80 nerves) of leprosy with no clinical or radiologic evidence of diaphragmatic dysfunction (Dhand et al 1988).

Phrenic nerve conduction time was prolonged in eight nerves. The amplitude of evoked motor response was reduced in 14 nerves suggesting subclinical involvement of phrenic nerve. The changes were more marked in multibacillary than paucibacillary leprosy.

Diagnosis of early nerve damage in leprosy has been reported by Antia et al (1975) and Shetty et al (1977). These authors determined the sensory conduction velocity of the index branch of the radial cutaneous nerve. It was observed that in the preclinical nerve lesion in leprosy and in contacts of lepromatous leprosy patients, conduction velocities were either at the lower limit of normal or were marginally reduced. Conduction velocity was clearly more impaired in leprosy patients, who showed minimal sensory impairment in the territory of this nerve than in the contacts and in patients without clinical evidence of nerve involvement. Greater auricular nerve thickening is considered a cardinal sign in the diagnosis of leprosy. However, in some normal individuals the nerve may be thickened and in countries where leprosy is endemic, such individuals may be wrongly diagnosed to have leprosy. It is thus important to assess the functional status of the nerve. Sensory conduction of greater auricular nerve was done in 18 healthy controls (36 nerves) and in 12 leprosy patients (24 nerves). All the 8 thickened nerves and 8 of 16 clinically 'normal' nerves in leprosy patients were found to have conduction abnormality. In addition to the latency and amplitude of sensory nerve action potentials, the difference in these parameters between two sides were also important in assessment of nerve function (Gourie-Devi 1984). Trigeminal and facial nerve involvement are well recognised features of leprosy. The blink reflex (BR) was recorded in 12 patients with tuberculoid leprosy and 4 patients with lepromatous leprosy (Pandya 1975). None of these patients had any weakness of the orbicularis oculi muscle but the supraorbital nerve was thickened in 7 of the 12 patients with tuberculoid leprosy. BR was abnormal in 8 patients of tuberculoid group while all the 4 patients with lepromatous leprosy showed normal findings. The author ascribed the abnormal BR to defect in the afferent pathway.

In the anaesthetic areas in leprosy, pain, heat, cold and touch sensations are affected to a greater extent than pressure and vibration sensations. Joint sense is unaffected. Dash (1968) demonstrated that total destruction of nerve fibres or nerve endings does not occur in all anesthetic areas and a number of end organs probably survive in a state of inexcitability not responding to natural stimuli. By a combination of simultaneous antidromic stimulation of the ulnar nerve with varying stimulus strength and natural stimuli, all the lost sensations could be reproduced within the anaesthetic area. Antidromic stimulation probably alters the excitability of surviving receptors, rendering them amenable to natural stimuli. Acrodystrophic neuropathies due to leprosy (6 patients) and nonleprous neuropathic disorders with plantar ulceration (6 patients) were examined electro-physiologically by recording compound nerve action potential

(CNAP) of the sural nerve in vitro. In leprous neuropathy the large and small myelinated and unmyelinated fibre potentials were abnormal, while in the miscellaneous nonleprous group there was striking abnormality in the CNAP of large and small myelinated fibres but the unmyelinated nerve fiber potentials were less abnormal (Pandya and Chulawala 1981).

Dapsone consumed in two to four times the therapeutic dose resulted in subacute motor neuropathy (Sirsat et al 1987). EMG showed severe denervation in distal muscles of upper and lower limbs and nerve conduction study showed reduction of motor nerve conduction velocity. The sensory nerve conduction velocities however were normal.

Motor and sensory nerve conduction studies in **diabetic neuropathy** had shown significantly lowered conduction velocities (Kumar and Gill 1988, Vijayan et al 1971, Vishwanath et al 1974). Even in patients without clinical neuropathy conduction velocity was slower than in controls but the change was less severe than in patients with neuropathy (Vijayan et al 1971). The distal segments of the nerve showed greater abnormalities than the proximal segment (Kumar and Gill 1988). Lower limbs were more affected than upper limbs. There was no correlation between nerve conduction velocity and age, severity of hyperglycemia and duration of diabetes (Vijayan et al 1971). Gourie-Devi (1985) described electrophysiological features in 6/12 patients with acute symmetrical motor neuropathy in diabetes mellitus. This is considered to be a distinct clinical entity. Electromyography of distal and proximal muscles of upper and lower limbs did not show any evidence of denervation. The motor and sensory nerve conduction studies were normal in 5 patients. One patient had mild sensory conduction abnormality. The neurological deficit improved after adequate control of diabetes in all the 12 patients.

Electrophysiological abnormalities have been reported in other **endocrinal** disorders. Myopathic changes were seen in 22/30 and nerve conduction abnormalities in 6/30 hyperthyroid patients (Rao et al 1980).

Electrophysiological evidence of nerve involvement in **chronic liver disease** was found in 19% of patients. As in diabetic neuropathy lower limbs were more severely affected. There was no correlation with the duration of disease, degree of impaired liver function or altered glucose metabolism (Das et al 1983). In **chronic renal failure** nerve conduction abnormalities are seen in 56 to 100% of patients (Kumar and Nayyar 1987, Sahu et al 1974). Sensory conduction was more often abnormal than motor conduction (Kumar and Nayyar 1987). Delayed motor nerve conduction velocities in children with **protein energy malnutrition** have been described by several investigators (Chopra et al 1986, Ghosh et al 1979, Kumar et al 1977, Mohan et al 1980, Sachdev et al 1971). It was also observed that the nerve conduction was significantly lower in ongoing long-term malnutrition than in acute short duration malnutrition. Further, the

changes were more marked when the onset of malnutrition was below 12 months of age compared to a later age of onset (Ghosh et al 1979). Studies in experimental protein deficiency corroborate the observations on human subjects. Roy et al (1972) observed progressive slowing of motor conduction velocities in all the 6 protein malnourished monkeys from the 3rd week of institution of protein deficient diet. H reflex latencies were normal upto the 3rd week but by the 9th week the H reflex was absent in 5/6 monkeys. These electrophysiological findings correlated well with the ultrastructural observations of myelin sheath abnormalities.

In a study of large number of cases of **acute organo-phosphorus posoning,** Wadia et al from Pune (1974) reported certain interesting EMG features. The nerve conduction velocity was normal or mildly slowed in patients with or without paralysis. Evidence of active denervation was rare but drop out of motor units was fairly common. They were able to demonstrate neuro-muscular block even in the absence of any neurological deficit and upto 7 days after the poisoning. Surprisingly neuromuscular block could not be demonstrated in some even in the presence of clinical paralysis. The authors concluded that the electro-physiological findings pointed to a lesion at myoneural junction and anterior horn cell. Wadia et al (1985) also observed delayed neurotoxicity 9 to 14 days after an episode of organophosphorus poisoning in two patients. There was overwhelming evidence of active and chronic denervation with normal conduction velocities.

The concept that **snake bite** in humans produces a neuromuscular paralysis which improves with neostigmine has been in vogue. Sethi and Rastogi (1981), however, were unable to demonstrate a decremental response to repetitive nerve stimulation in 5 patients bitten by snakes. There was frank evidence of denervation and drop out of motor units which improved rapidly within a few days suggesting a reversible dysfunction of motor neurones.

Arsenic poisoning is an important cause of peripheral neuropathy in north India. Chuttani and Chopra (1979) observed that nearly half of the 20 patients studied had severe denervation. The others had denervation as well as reduced conduction velocity. The changes were more severe in lower than in upper limbs. In a small number of patients a follow up EMG examination did not show any significant improvement.

In endemic **skeletal fluorosis,** the neurological manifestation are considered to be due to myelopathy and radiculopathy. In experimental fluorosis however, evidence of muscle fibre degeneration has been observed. Reddy et al (1978) from Hyderabad, performed electromyographic study in human skeletal fluorosis. There was unequivocal evidence of denervation and reinnervation confirming neurogenic process. Late responses such as F waves and H reflexes, confirmed the involvement of nerve roots in fluorosis (Murthy et al 1986).

Anomalous innervation of muscles poses special problems in nerve conduction studies. Singh et al (1973) examined 274 legs in 137 healthy subjects and found anomalous innervation of EDB by accessory peroneal nerve in 9.5% (26/274 legs). Bilateral abnormalities were most frequent. The left side was more commonly involved when the anomaly was unilateral. A high familial incidence was also observed.

In the indigenous form of **heredofamilial spinocerebellar degeneration with slow eye movements,** Wadia (1984) described electrophysiological evidence of motor and sensory nerve involvement in 13/14 patients examined. The changes suggested a dying-back motor and sensory neuropathy. There are a few more reports on motor and sensory nerve conduction abnormalities in hereditary ataxias (Bansal et al 1988, Sridharan and Mehta 1984).

Electromyography and nerve conduction velocity studies differentiate **storage disorders** like lipidoses and mucopolysaccharoidosis from the **leukodystrophies.** A significantly reduced conduction velocity suggested the latter diagnosis while evidence of denervation favoured the storage disorder (Taori et al 1971).

Documentation of **spasticity** and evaluation of drugs for spasticity has been studied in 15 patients with hemiplegia. H/M ratio was determined in the affected and contralateral limb before and after administration of 10 mg of diazepam. The ratio was significantly higher on the hemiplegic side in patients with severe spasticity but not in the limbs with mild to moderate spasticity. Following administration of diazepam, the ratio decreased on the hemiplegic and on the unaffected side. This change was significant in the severely spastic limbs (Iyer et al 1973).

During the two epidemics of **acute haemorrhagic conjunctivitis** in India (1971 and 1981), polio-like paralysis of the limbs and/or cranial muscles was documented. Wadia et al (1983) detected active denervation in the affected muscle in the first week. By the second or third week a larger number of muscles showed similar changes. Clinically normal neighbouring and/or corresponding muscles of the opposite limbs also showed spontaneous activity. From the second week onwards long duration polyphasic potentials and giant potentials made their appearance which further increased significantly during the fifth week. Motor and sensory conduction velocities were normal except in few patients with paralysis of quadriceps muscle in whom the muscle response could not be evoked on femoral nerve stimulation. Facial nerve conduction was also normal in the majority. Abnormal F wave response with normal motor conduction were seen in some patients suggesting that the site of lesion was in anterior horn cells or anterior roots. Abnormal somatosensory evoked potential and 'H' reflex with normal sensory action potential suggested that the lesion was proximal to the dorsal root ganglion, probably in the root entry zone.

In the majority, the absent ankle jerk was associated with an abnormal 'H' reflex but in a few the 'H' reflex was preserved. Two consistent observations in the blink reflex examination of the paralysed face were an absent or prolonged R1 response and an increased inter-eye latency difference of both R1 and R2 responses. With normal latency these findings indicated a central nuclear lesion. Furthermore, this finding was useful in distinguishing them from Bell's palsy.

Madras pattern of motor neurone disease, an unique variant occurring in the younger age group, associated with bilateral sensory neural deafness, was described for the first time by Meenakshisundaram et al in 1970. Electromyography showed evidence of active denervation and drop out of motor units with giant and polyphasic potentials. The conduction velocities were normal. The EMG of siblings were normal (Gourie-Devi and Suresh 1988, Jagannathan and Kumaresan 1987, Meenakshisundaran et al 1970). Atrophy confined to one upper limb has been variously termed as *juvenile muscular atrophy localised to arms, monomelic amyotrophy* and *spinal segmental muscular atrophy* (Gourie-Devi et al 1984 and 1987, Singh et al 1980, Virmani and Mohan 1985). Single lower limb atrophy included in the latter two terminologies has also been named as *wasted leg syndrome* (Prabhakar et al 1981). Electromyography showed a combination of active denervation and varying degree of chronic partial denervation with reinnervation in the muscles of the clinically affected limb. In a few patients the contralateral, clinically unaffected limb, also showed mild abnormalities. In patients with single upper limb atrophy, the lower limb did not show any EMG abnormality. Patients with one wasted lower limb did not show EMG changes in upper limbs. Motor and sensory nerve conduction studies were normal in these patients. The EMG findings in conjunction with muscle biopsy suggested a lesion in anterior horn cells.

Evoked potentials

Multimodal evoked potentials are being increasingly used in clinical practice to assess the functional integrity of sensory pathways. Dysfunction of the visual, auditory and somatosensory pathways antedating clinical manifestations may be detected, enabling early diagnosis and prompt management. A judicious combination of evoked potentials with established methods of diagnosis such as electroencephalography, nerve conduction, radiology etc. has led to better understanding of the disease process. It has also provided an important tool for prognostication and monitoring of therapy in a variety of disorders.

Anticonvulsant drugs may affect the peripheral and the central sensory pathways. Borah and Maheshwari (1985) studied median nerve somatosensory evoked potentials (SEP) in 45 subjects with epilepsy before initiating anticonvulsant therapy and 6 to 12 weeks later. There was no significant difference in the latency of the N20 wave in epileptics before or after therapy when compared to normal controls.

SEPs have also been used in the evaluation of **thyroid dysfunction** (Dhamija et al 1986). Mild abnormalities were detected in hyperthyroidism (18 patients). These improved after treatment. No significant abnormality was detected in hypothyroidism.

In **Wilson's disease** there are widespread changes in the cerebral cortex beyond the well understood extrapyramidal system. Although no clinical symptoms have been documented, recent studies on visual evoked potentials (VEPs) in 13 patients and brainstem auditory evoked responses (BAER) in 12 patients showed prolonged P100 latency in 7 and III-V interpeak latency in 8 patients, indicating subclinical involvement of visual and auditory pathways (Satishchandra and Swamy 1989). VEP abnormalities correlated with clinical disability but the BAER did not. Similarly VEP abnormalities (pattern reversal checker board and sinusoidal grating stimuli) detected in 47 patients with **Parkinson's disease** correlated with the degree of motor disability. Following 3 months of therapy with L-dopa the clinical improvement was associated with improvement of P100 latency in pattern reversal checker board VEP but not with sinusoidal grating stimuli (Bhaskar et al 1986).

Ataxic hemiparesis can result from lesions at different levels in the neuraxis. Eight such patients were investigated using BAER (Radhakrishnan et al 1982). It was possible to localise the lesion to the pons and medulla in one patient and rostral to mid pons in 3 patients. One patient with a thalamic lesion had normal BAER. In patients with **cerebellopontine angle tumours** BAERs showed abnormalities in all the 18 cases. It is of interest that contra-lateral abnormalities were detected in all large sized tumours. These changes could be attributed to compression or ischaemia of auditory pathway. Abnormalities in conventional audiometry were seen in 83.7%, nystagmography in 82.2%, routine radiology in 72.2% and CT in 94.4% of patients (Upadhyaya et al 1985). **Brainstem dysfunction in congenital hydrocephalus** was assessed by BAERs in 20 children, before and after the insertion of shunt. Abnormalities were noted in 95% of cases in the preoperative phase. These improved following shunt, 50% returning to normal and 20% showing significant improvement. In 20% there was worsening of BAER. This was an indicator of shunt malfunction as shunt revision reversed the abnormalities (Venkataramana et al 1988).

Involvement of optic nerves and chiasm by exudates, arteritis or compression by tuberculoma and dilated 3rd ventricle is known in **tuberculous meningitis** (TBM). Clinical evidence of optic nerve dysfunction may be present in 50% of patients with TBM. Pattern reversal visual evoked potentials (VEP) showed that in 41% of patients with normal neuro-ophthalmic examination abnormalities were found on VEP, indicating subclinical involvement of visual pathway in TBM. With treatment, serial VEPs showed significant improvement in 4 patients (Sridharan and Krishnamurthy 1984).

Monosymptomatic **optic neuritis** and future progression to **multiple sclerosis** is a subject of considerable interest. Blink reflex (BR) and SEP data in 20 patients with optic neuritis were compared with 20 controls. Abnormalities of BR and SEP were seen in 30% and 20% respectively and the combination of both showed abnormalities in 45%. Two patients with abnormal BR developed full blown picture of multiple sclerosis over a short period. The detection of brainstem abnormality in optic neuritis may be useful in predicting the later development of multiple sclerosis (Chand and Gourie-Devi 1985).

In the group comprising of **hereditary ataxias and spastic paraplegia,** VEP and BAER were found to be abnormal. The abnormalities were commoner in Friedreich's ataxia and *cerebellar ataxia plus* syndrome. These were useful in detecting subclinical involvement of visual pathway and brainstem in hereditary ataxias (Bansal et al 1988, Sridharan 1983). In ataxia telangectasia also VEP abnormalities were detected in 2/4 cases, suggesting similarity of features to Friedreich's ataxia (Sridharan and Mehta 1984).

Neurophysiological examination done to localise the site of lesion in auditory pathway in **Madras pattern of motor neurone disease** showed that while BAER could not be obtained, electrocochleography revealed normal cochlear microphonics in 2 patients thereby suggesting that the hair cells of the organ of Corti were preserved while a lesion of acoustic nerve fibres or spiral ganglion could be the cause of deafness (Wadia et al 1987).

Predicting the **outcome in coma** is a challenge. Clinical assessment and vestibular ocular reflex have been quite useful although there are limitations. Studies have been designed to evaluate the relative merits and demerits of the Glasgow coma scale (GCS), cold caloric response (CCR) and brainstem auditory evoked response (BAER) in coma due to stroke, meningoencephalitis and hepatic encephalopathy. (Jain and Maheswari 1984, Jain and Maheswari 1985, Pauranik et al 1987). A good bedside examination using GCS and CCR were still considered to be useful prognostic indicators. Cold caloric response was noted to be a more reliable parameter than BAER in all these groups, as also in patients with head injury (Mahapatra and Tandon 1987). BAER was a more useful predictor than somatosensory evoked potentials in hepatic encephalopathy (Pauranik et al 1987). BAER has certainly a place in assessing brainstem function in situations where adequate clinical assessment is not possible. Caution needs to be exercised in attaching too much importance to CCR and BAER since an abnormal response need not necessarily indicate a bad prognosis and all individuals with normal response may not recover completely.

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Clinical neurology

N. H. Wadia

The practice of neurology as a definite speciality began in India in the 1950s and it soon became apparent that the neurological diseases of 350 million people, as was the population then, needed to be looked at closely. Though the broad spectrum of human diseases as gathered from western textbooks was visible, it appeared through the collective experience of established neurologists that there were considerable differences in the incidence, prevalence etc. of well known diseases. Also some local diseases, hitherto not clearly identified, needed firm definition. This was not necessarily confined to infections of the nervous system or diseases consequent to malnutrition, largely conquered in the developed countries, but those which resulted from the clearly different ethnic, genetic, cultural and environmental backgrounds existing in India. The need to look more closely also arose from the fact that the description of clinical neurology till the end of the second world war was written up from a very small population-base confined to the major cities of Europe and the United States, (especially its eastern seaboard) leaving the diseases of vast populations, notably those of China and the Indian subcontinent, unexamined.

In the 40 odd years that have passed, during which 500 million souls have been added to India, headway has been made and this chapter will attempt to highlight what has been documented.

Infections

In an economically under-privileged environment infections of the nervous system prevail. Poor communication and illiteracy make the prevention of spread of resultant diseases difficult.

Leprosy

This commonest peripheral neuropathy (neuritis) prevalent in India since 1400 B.C. persists despite the availability of curative drugs. Four million were said to be affected in 1985 but this could well be an underestimate (Verma 1988). Nearly half a million new cases (of whom 20-25% are

children) are detected every year and these appear to be more than the number of patients cured, despite the considerable effort made by governmental and private organizations to combat this scourge. The distribution of cases within India is not uniform. A large majority are seen in the hyperendemic areas of Tamil Nadu and Andhra Pradesh in the south and in Orissa and Bengal in the east. The prevalence rate in some districts is as high as 20 per 1,000 citizens. On the other hand, in north and north west India, the prevalence rate is as low as 2 per 1,000. Borderline tuberculoid leprosy is predominant and 80% of cases are of the *non-lepromatous* (paucibacillary) variety.

Though some controversy has arisen regarding the usefulness and choice of a local or an imported vaccine, (Antia and Birdi 1984, 1988; Noordeen 1988) it is generally felt that prevention by vaccination, early diagnosis by paramedics (or simply-trained village elders), improvement in general hygiene and vigorous treatment of early cases will yield results. The recently revised WHO protocol (WHO 1981, Rao et al 1988) of supervised, relatively short course therapy with dapsone, rifamycin, clofazimine and prothionamide is being increasingly followed with reservations on the wisdom of the limits of therapy suggested in the protocol especially for lepromatous leprosy, a longer duration being preferred. Indian Cancer Research Centre (ICRC) vaccine is already under clinical trial and some other trials are about to begin in India under the overall supervision of the Indian Council of Medical Research (ICMR).

Tuberculosis

Physicians and more importantly pediatricians all over India continue to treat patients with tuberculosis of the nervous system. There has been a downward trend in its incidence but the position is far from satisfactory. Outstanding amongst Indian writings on this subject are the reports and reviews (only a few of which are quoted here) from the J.J.Group of Hospitals, Bombay (Udani 1961, 1980, Udani and Dastur 1970, Udani et al 1971, 1972, 1973, Udani and Bhat 1974, Dastur et al 1968, Dastur and Wadia 1969, Dastur et al 1970, Dastur and Lalitha 1973, Dastur and Dave 1977, Lalitha and Dastur 1973, Lalitha et al 1980, Wadia and Dastur 1969) and from All India Institute of Medical Sciences, New Delhi (Tandon 1978, 1979, Tandon and Pathak 1973, Tandon et al 1970, 1975).

Scrutinizing the records of the J.J. Group of Hospitals, Bombay, Lalitha et al (1980) found that admissions to the Institute of Child Health of patients with neuro-tuberculosis fell from 4.4 percent during the period 1951 - 1960 to 1.9 percent by 1971, with a further more gradual drop till 1977. Around the same period autopsies in children revealed that cases of tuberculosis of the nervous system amongst tuberculosis of all organs

showed a decline from 42.6% to 28%. However, it is doubtful if this happy trend seen in a large teaching hospital in Bombay could be projected as a general reflection for the rest of the country.

Nervous system tuberculosis manifests as tuberculous basal meningitis, tuberculous encephalopathy, tuberculoma, tuberculous spinal meningitis with symptoms of radiculomyelopathy and rarely as an intraspinal tuberculoma.

Tuberculous basal meningitis (TBM)

There is voluminous international literature on the subject. Udani and colleagues have drawn attention to atypical features and unusual presentations of TBM (Udani 1980).

Diagnosis of the disease in India depends on a clinician's good sense and a CSF examination. Even in cities with good laboratory facilities, demonstration of acid-fast bacilli confirming the diagnosis has been possible in less than 30% of cases and positive cultures are reported after an unacceptable delay.

Many attempts have been made to develop a rapid and sensitive confirmatory test to detect a specific antibody, antigen or antigen-antibody complex, but so far with little success (Ranadive and Banerjee 1989). A test claimed to be rapid, sensitive and specific to detect tuberculostearic acid, a structural component of M. tuberculosis, has been reported from Hong Kong (French et al 1987), but it has not been adopted in India, because the expensive gas chromatography/mass spectrometry is not generally available.

The **pathology of TBM** has been extensively reported from India. Dastur and Lalitha (1973) and Dastur et al (1970) have shown that the large arteries at the base of the brain were enveloped by the dense basal exudate, which in time *throttled or strangulated* them. Additionally there was often periarteritis and subintimal damage in the acute phase and fibrosis in the chronic stage leading to infarction of the brain.

Dalal (1979) on the other hand has maintained that in his autopsy studies *softening* of cerebral tissue was often found in areas where the luminal narrowing or vasculitis was not pronounced. Conversely marked arterial stenosis was not always accompanied by significant macroscopic or microscopic alterations in the brain parenchyma. He, therefore, contended that the mechanism of cerebral softening in TBM still was not fully explained.

Treatment protocols have varied considerably and the selection of drugs and duration of therapy are often left to a clinician's fancy and the compulsions of each case (compliance, expense, drug availability, surveillance etc.). The most favoured is a four-drug regimen comprising streptomycin, rifamycin, isonicotinic acid hydrazide and pyrazinamide for 2 or 3 months followed by two drugs, usually to a total period of 18 months. However, individual adjustments are made in the choice of these two drugs and the total duration of therapy, depending on the initial and subsequent condition of the patient.

The need to standardize the therapeutic protocol is overdue. Whilst compliance, expense, drug toxicity demand shorter courses the possible hazards of such therapy should not be overlooked (Pandya 1987). The three different regimens studied over 12 months under an ICMR project did not give encouraging results (Ramachandran et al 1986). It appeared that the ultimate outcome depended not so much on the duration of the therapy, as on the stage of the disease when it was started. More careful trials still need to be done.

Tuberculous Encephalopathy

This condition needs to be highlighted. In a series of publications Dastur and Udani (1966), Udani and Dastur (1970), Udani et al (1974) first drew attention to its clinical and pathological features and discussed the pathogenesis. Essentially affecting children the clinical presentation with convulsions, deepening coma, decorticate and decerebrate spasms and/or rigidity and even brain herniation indicated diffuse brain disturbance of varying degree depending on the severity and extent of the encephalopathy. The pathology of this condition is discussed by Das and Shankar elsewhere in this volume.

Tuberculoma

This topic will be dealt with under intracranial space occupying lesions by Kak. Suffice to say that i) the incidence of tuberculoma is slowly declining, ii) early diagnosis and identification are now possible thanks to the CT scan, iii) most tuberculomas do not require surgical removal, antituberculous therapy with close CT monitoring being the order of the day, iv) even previously inoperable pontine or deep hemispheric tuberculoma may resolved under drug therapy without morbidity.

Tuberculous spinal meningitis with radiculomyelopathy

The insufficiently-heeded account of Ransome and Monteiro from

Singapore (1947) was the first to draw attention to this condition with a vivid clinico-pathological description of five patients. Wadia and Dastur's review (1969) made the following points. The symptoms arise as a result of a tuberculous infection which unusually affected the spinal rather than the basal meninges, secondarily involving the underlying roots and spinal cord. The clinical picture depends on the tempo and extent of infection and may be a rapid or slow (subacute or chronic), single or multiple - level, ascending or transverse radiculomyelopathy. In the **subacute form** the patient has low fever, pain in the spine, severe single or multiple root pains and paraplegia or quadriplegia with an ascending or transverse sensory level, depending on the localization of the infection and its effect, compressive or otherwise on the underlying nervous tissue. The clinical picture develops within days, but can progress over 6 to 8 weeks. In a proportion of untreated cases, the infection spreads intracranially causing headac he, vomiting, neck stiffness, mental changes, drowsiness etc. as seen with TBM. The **chronic form** develops slowly, simulating a single-level spinal cord compression such as a tumour from which it cannot be clinically differentiated, except in those with more widespread root pains not coinciding with the spinal cord localization. In the majority of cases, the patient has pulmonary or glandular tuberculosis or a past history of infection or close exposure to it.

The CSF usually shows pleocytosis depending on the severity of infection, raised proteins and a low sugar. In many patients xanthochromia is seen due to a spinal block.

The acute disease was initially mistaken for a Guillain-Barre syndrome or viral transverse myelitis, but the demonstration of a block, xanthochromia and the myelogram were diagnostic.

Treatment with vigorous antituberculous therapy gives good results when initiated early, but permanent incapacitation and mortality from complications of decubitus or urinary infection are not uncommon.

Similar cases were reported by Singh et al (1959) and Bawa and Wahi (1961) and recently a retrospective series has been published (Murthy et al 1988).

Attention must be also drawn to a report by Ahuja et al (1978) who detailed seven somewhat similar cases where the myelogram was normal suggesting that there was no direct compressive element in the pathogenesis of this condition. An autopsy of one of their cases, however, showed spinal meningitis (not reflected in the myelogram), along with necrosis and spongiform degeneration of the spinal cord.

It thus appears that the radiculomyelopathy is not the result of direct compression of the underlying spinal cord or roots but of a series of

pathological changes associated with the infective exudate. This view is supported by the fact that Wadia and Dastur (1969) have demonstrated a persisting block in the myelogram even after full clinical recovery of a patient from the radiculomyelopathy.

Encephalitis

Japanese B Encephalitis (JE) and rabies are the two varieties commonly prevalent in India. Whilst the latter is seen everywhere, the former is restricted to certain areas where recurrent epidemics occur and it is even endemic in some places. Kyasanur forest disease, an indigenous encephalitis described from India is located in a small area in the southern state of Karnataka.

It affects monkeys, but human disease has been reported. Cases of west Nile disease are infrequent and though epidemics of dengue have occurred, the problem posed is nowhere near that of rabies or JE. Though sporadic cases of herpes simplex and post-exanthematous encephalitis have been reported, no new information has been added to the available international literature.

Japanese B Encephalitis

The disease was first recognized in patients from the North Arcot district of Tamil Nadu, South India in 1955 and serologically confirmed (Webb and Pereira 1956, Work and Shah 1956). The JE virus was isolated from wild mosquitoes in the same year (Dandwate et al 1969) and it was recovered from the brain of patients at the Christian Medical College, Vellore in 1958, where the serological tests had been carried out earlier (Webb et al 1964). In 1973, a large epidemic occurred, a thousand miles away in West Bengal, north-east India, principally in the Bankura and Burdwan districts. Subsequently outbreaks of JE appeared in other northern areas, especially Uttar Pradesh (Mathur et al 1982). (Table 1.)

The disease was confined to rural India and amongst the poor. Every village had a case or two during epidemics. In the south, children under 15 years were most affected, while in the north and north-east no age group was spared (Rodrigues, 1984). The outbreaks occurred commonly during the monsoon, when mosquitoes multiply. Thirty eight strains of the virus have been isolated from mosquitoes (Dhanda and Kaul 1980). Pigs harbour the virus and act as intermediate host. Neutralizing antibodies to the JE virus were found from 33% of pigs in the North Arcot district and 83% in the Dibrugarh district of Assam (north-east India). Besides pigs, cattle-egrets and pond-herons act as viral reservoirs. Man to man transmission of the virus by mosquitoes does not occur as the concentration of the circulating virus is low in human blood. Cattle can be asymptomatically infected by the virus, but as in humans, the viremia is low and no transmission occurs

Table I. Epidemics of Encephalitis in Different Parts of India–1973-1981

Area and Year	*Cases*	*Deaths*	*Case-fatality rate (%)*
Burdwan and Bankura, West Bengal, 1973	763	325	42.6
Burdwan District, West Bengal, 1976	307	126	41.0
Tirunelveli District, Tamil Nadu, 1977 –1978	298	99	33.2
Kolar District, Karnataka, 1977 – 1978	71	18	25.4
Burdwan, Bankura, Birbhum and other districts, West Bengal, 1978	1256	544	43.3
Gorakhpur and Deoria Districts, Uttar Pradesh, 1978	1734	515	29.7
Kolar District, Karnataka, 1979	670	158	23.6
Anantapur and Chittoor Districts, Andhra, 1979	340	71	20.9
Gorakhpur and Deoria Districts, Uttar Pradesh, 1980	1386	455	32.8
Dibrughar District, Assam, 1980	100	44	44.0
South Arcot District, Tamil Nadu and Union Territory of Pondicherry, 1981	633	151	23.85
Anantapur, Chittoor, Kurnool, Guntur and Prakasan Districts, Andhra Pradesh, 1981	789	274	34.7
Kolar District, Karnataka, 1981	487	116	23.8
	8834	2896	30.6

Taken from "Acute Viral Encephalitis commonly prevalent in India" (Ref. No. 13).

(a dead-end-situation). If cattle were an active reservoir, JE would have run riot over the country, as the cattle population of India is enormous.

The disease manifests in the classical manner, and the mortality is high in the acute phase. Gourie-Devi (1984) reported 53 deaths out of the 133 cases studied by her in Bangalore, south India. As the epidemics continue, prophylactic vaccine from Nakayama NIH strain is usually given to persons at risk in the area. A mixed vaccine, with a broader antigenic spectrum made from Nakayama, Bankura and Kolar strains of the virus may be more effective.

Rabies

Incidence estimates are hard to make as this endemic disease can go unrecognized or unreported especially in rural areas. The Government of India report of 1980 (Central Bureau of Health Intelligence 1981) mentioning 611 annual deaths seems an underestimate when as many as 36 fatal cases of rabies over 5 years have been seen from only one hospital in Bombay (Wadia and Bhatt 1989). Stray dogs are the principal carrier (90%) but jackals also transmit the disease (Indian Council of Medical Research, Rabies 1967).

It presents mostly in the well known hydrophobic (furious, fulminant) form, but attention has been drawn from India as elsewhere from the east to the possibility of misdiagnosis when it presents as **paralytic rabies.** This form is distinguished by the fact that the disease manifests initially with paralysis due to spinal cord involvement rather than as an encephalitis. As the distinctive hydrophobia is not obvious, it is also called **dumb rabies.** Twenty percent of patients present thus, with an ascending paralysis often initially mistaken for the Guillain-Barre syndrome till convulsions, disorientation, confusion and other symptoms of encephalitis appear. Hydrophobia is conspicuously absent. A high index of suspicion is required to make the diagnosis early, especially as the dog might have bitten months before the illness and only careful questioning reveals the diagnosis.

Tangchai and Vejjajiva (1971) from Thailand found at autopsy the classical inflammatory changes caused by the rabies virus in the peripheral nerves, spinal nerve roots and dorsal root ganglia viz. leucocytic infiltration, proliferation and hypertrophy of Schwann cells, degeneration of nerve fibres and oedema in the peripheral nerves nearest to the animal bite. However, Chopra et al (1980), in a clinico-pathological study of paralytic rabies from Chandigarh, north west India, drew attention to changes in the peripheral nerves of patients which they believed were not directly due to the viral infection. A primary demyelination produced by the protein component of the virus having a cross-antigenic action on the myelin protein is suggested. The peripheral nerves here showed segmental demyelination and remyelination, Wallerian degeneration, and myelinated fibre and axon loss.

All cases in India have proved fatal, but the longest survival of any case anywhere (25 days after the onset of the disease) has been reported in an autopsy proven case from Bombay (Udwadia et al 1989).

Kyasanur Forest Disease

A new disease affecting the villagers and wild monkeys of the Kyasanur forest of Shimoga district in the south Indian state of Karnataka, was reported in 1957 (Work and Trapido 1957). A comprehensive report entitled Kyasanur Forest Disease, 1957-1964 was published after a team of researchers, with the Virus Research Centre (VRC) Pune as the nodal agency isolated the virus from man and monkeys, prepared the antigen, identified the vector and described the pathological changes.

The disease is caused by the Kyasanur forest disease (KFD) virus, which is a RNA virus of the family Togaviridae, genus Flavivirus, belonging to a subgroup known as the Russian spring summer encephalitis virus (RSS). The vector is the tick Haemaphysalis (Trapido et al 1959) which transmits the disease essentially amongst monkeys, but 10% of the population of a local village can get affected. Wadia RS (1975) has described the disease amongst laboratory workers in VRC, Pune. This is the only tick-borne encephalitis in India.

Both sexes are affected and children suffer most. It manifests (Wadia RS 1975) as a biundulant fever, with constitutional symptoms and myalgia in the first phase, and headache, vertigo, mental disturbance focal neurological signs and neck stiffness in the second phase of the fever, which usually comes after an interval of 2 to 3 weeks. Perversion of taste and general debility persist for long.

The CSF shows pleocytosis and raised proteins. The virus can be isolated in all cases for 5 days, and in many upto 10 days. During the second phase, one has, therefore, to depend on haemagglutination inhibition (HI) and complement fixation (CF) to confirm the diagnosis.

No human autopsies are available, but Iyer et al (1959) found changes of encephalitis in only two out of the 22 monkeys they autopsied. The virus could be isolated from their brains. The brunt of the disease fell on large parenchymal visceral organs. Renal tubular damage was frequent.

Clinically and pathologically the disease resembles haemorrhagic fevers described from the Soviet Union (Bhat et al 1966) and also the far-eastern haemorrhagic fever. As KFD has not caused any major health problem, no special health measures have been taken, but forest dwellers are advised to wear protective clothing to prevent tick-bite.

Poliomyelitis

Despite vaccination to eradicate poliomyelitis for more than 30 years, the disease has not abated in India. Its reported incidence even today is

approximately 20 - 40 per 100,000 population per year and nearly 500 cases are said to occur daily (John 1984, ICMR Bulletin 1988). The crippling effect of this disease can be seen by the fact that the incidence of lameness amongst pre-school children is 1 to 2 per 1000 per year. The disease continues to be endemic in India. The reasons given for this failure are many and include vaccine failure, low vaccine acceptance, insufficient awareness of its value, uncontrolled circulation of the wild virus through subclinical cases and vaccine deterioration.

Happily a fresh assault on this problem has been once again mounted. It has been felt that oral polio vaccine is the only cost effective tool for developing countries (ICMR Bulletin 1988). Vaccine production will be soon started on an industrial scale producing more potent vaccines and the hope is that poliomyelitis will be ultimately eradicated in the not too distant future.

Enterovirus 70 disease: (acute haemorrhagic conjuctivitis associated with neurological manifestations)

In March, 1971 an epidemic of acute haemorrhagic conjunctivitis (AHC) began in India, affecting several million people throughout the country (Wadia 1973, Wadia 1989). In Bombay alone, a rough estimate mentioned 5,00,000 cases. It was part of a pandemic which started in Ghana in 1969, and spread across half the world upto Japan. In the countries, where it had appeared, it was simply considered as an acute, short, self-limiting infection confined to the eyes, which spread among the poor living in overcrowded colonies.

It was from west India that the first observations regarding neurovirulence of the virus were made. Wadia demonstrated two patients with an acute, hypotonic, areflexic paralysis of the lower limbs closely following AHC and suggested that this new disease was due to a polio-like virus causing both the AHC and the spinal disease (Wadia et al 1983, 1989). Kono et al (1972), who had simultaneously isolated a new enterovirus from the eyes of Japanese patients (later designated enterovirus 70), on becoming aware of this evidence of neurovirulence (Kono et al 1973) injected the virus they had isolated into the lumbar cord of monkeys to produce hind-leg paralysis confirming the Indian clinical observations. Independently ophthalmologists Bujarborua et al (1972) and Saxena et al (1972) from north India described patients with cranial nerve palsies associated with the AHC.

Soon in a collaborative effort, Kono et al (1974) reported significantly high antibody titres against the Japanese virus (type J 670/71) in the serum of Indian patients, both with AHC alone and with the neurological disease, proving that the same enterovirus had affected patients in both countries causing both AHC and the paralysis.

Subsequent to the Indian reports (Wadia et al 1972,1973, Bharucha and Mondkar 1972, Bujarborua et al 1972, Saxena et al 1972) the neurological manifestations of this disease were reported from other parts of the world, where the conjunctivitis had visited (Kono et al 1974, 1976; Phuapradit et al 1976; Hung et al 1976; Kuroiwa 1977).

Recurrence of such local epidemics and even pandemics had been anticipated and in 1981, another pandemic appeared in Africa and the Indian subcontinent, from where it spread by travellers to many countries in central America, Florida and Carolina. Once again millions had the eye disease, and the reports confirming the earlier neurological observations from various centres in India indicated that paralysis may have affected several thousands (ICMR Bulletin 1985, Wadia 1989). Whatever doubts there were about the specificity of the neurological syndrome and the invasion of the CNS by the virus were laid to rest when once again with Japanese collaboration, high and rising neutralizing antibody titres were detected not only in the serum, but also the CSF of patients with the neurological disease and de novo synthesis of antibodies was demonstrated in the CSF (Kono et al 1981, Wadia et al 1983). These were confirmed later by others (Katiyar 1983, Chopra 1986). Recently Taniya et al (1989) using the immunoglobulin capture Elisa technique have been able to identify EV 90-specific IgG and IgM antibodies in the serum and CSF, suggesting that this may be the most sensitive laboratory method to diagnose the disease and do serum surveys in epidemic and endemic areas.

The disease is bimodal, the AHC and the occasional neurological disease are separated by a variable though usually short quiescent (latent) period on an average of 3 weeks. Rarely the paralysis has been known to precede the AHC. On the other hand the latent interval has been as long as 120 days. The interval is shorter in those with cranial nerve palsies than the spinal disease.

The conjunctivitis is usually bilateral, lasts for 3 to 7 days, presents usually with itching, pain, congestion, photophobia, lacrimation and sub-conjunctival haemorrhages. Accompanying malaise is common.

The neurological disease is often heralded over one to three days by fever, body aches, headaches through the first days of the paralysis, which is of the lower motor neurone variety affecting motor cranial or spinal nerves or both. In the Indian national registry, which recorded and analysed 581 patients (ICMR Bulletin 1985, Wadia 1989), 380 developed only limb paralysis, 104 cranial nerve palsies and 97 had both in various combinations. The spinal disease begins with acute pains in the spine and limbs with occasional burning paraesthesiae. The lower limbs are more frequently affected. The paralysis is hypotonic, asymmetrical, patchy. The related deep reflexes are lost. Sudden buckling of the knees at the onset is not uncommon. In more severe cases, three or even all limbs and

respiratory muscles get affected. Uncommonly an isolated upper limb paralysis is seen. One or more motor cranial nerves can be paralysed, but a seventh nerve palsy is most frequent, and when isolated can be mistaken for a Bell's palsy. Extensive facial, bulbar and spinal paralysis can simulate Guillain-Barre syndrome. Transient retention of urine, vertigo, paraesthesiae, patchy sensory loss and extensor plantar response are very occasionally seen at the onset.

The neurological disease usually spares children. Young adult males are most affected. Pregnancy, exertion, intramuscular injections during the incubation period are additional factors which precipitate paralysis. Recovery begins within weeks and continues for months, but the final outcome depends on the initial severity and the extent of the paralysis. Death has been reported in the severe cases. The overall picture resembles polio-myelitis remarkably closely except that children are relatively spared. Though no direct postmortem evidence is available, laboratory tests (CSF, EMG) and the demonstration of an EV-70 specific antigen in the microglial and/or neuronal cells in the spinal cord of three fatal cases with a poliomyelitis-like illness during the 1981 epidemic (Pal et al 1986) indicate that the disease is indeed a poliomyelitis - a direct viral infection of the anterior horn cells and motor cranial nuclei by EV-70.

During the 1981 epidemic, a few patients with encephalitis, optic neuritis, papilloedema (with small ventricles), acute polyneuritis and Devic's disease closely following AHC were described (Wadia 1989). Their numbers were small and no alternate cause found. Whether these were coincidental or due to EV-70 infection, was never firmly established. These may be rare manifestations of this infection, probably due to an immunological response in the CNS to the virus rather than by its direct invasion.

In an epidemic, the classical neurological case leaves no room for differential diagnosis. Difficulty arises in cases seen at the two ends of an epidemic, in sporadic cases, in cases where no clear history of AHC is available, and those with a long latent interval. Investigations are required for such cases.

Confirmatory tests include viral identification, serological tests, CSF examination and EMG. Virus can be isolated from the conjunctiva by well-established tissue culture techniques provided eye swabs are taken within the first three days. Pal et al (1983) have also developed a rapid, simple, inexpensive, immuno-fluorescence diagnostic test on smear preparation of eye swabs to detect cytoplasmic viral antigens in conjunctival cells using reference EV-70 sera. A high degree of specificity is claimed and an added advantage is that the test can detect subclinical infection and convalescent carriers. Though isolation of the virus from the CSF is difficult, Pal et al (1983) have suggested that detection of the antigen in the CSF would indicate viral invasion into the CNS.

Serological tests comprise virus neutralization (NT) and haemagglutination (HIT). A four-fold rise or more in serum antibody titres between paired sera points to a recent infection. A titre of 1:16 or greater in a single sample indicates past infection. Taniya et al (1989) have recently recommended the adoption of the immunoglobulin - capture Elisa technique as a sensitive and convenient diagnostic laboratory test to identify EV-70 specific IgG and IgM antibodies.

In the acute phase of the illness, there is a remarkable increase in the cells and proteins in the CSF especially in the spinal cases. The cellular response settles rapidly though the proteins remain elevated, so that a delayed CSF examination may give a false albumino-cytological dissociation leading to misdiagnosis with Guillain-Barre syndrome. Tests to detect EV-70 antibodies and EV-70 specific antigen similar to those done in the serum can be carried out in the CSF. Besides absolute values, a reduced serum - CSF ratio of neutralization antibody titre, IgG and IgM strongly indicates entry of virus into the CNS.

Extensive electromyographic examination has been done of these cases in India (Wadia 1972,1973,1981, Katiyar et al 1983, Chopra et al 1986, Wadia and Ramamurthy 1987) which localised the lesion at the anterior horn cell level and differentiated this disease from other acute polyneuritis including Guillain-Barre syndrome. Using single fibre and macro EMG techniques, P.N. Wadia and Ramamurthy (1987) were even able to suggest some criteria for assessing long term recovery.

The real incidence of AHC has not been worked out anywhere, but an eyeball estimate in Bombay alone in 1971, (Wadia et al 1973,1989) mentioned 5,00,000 cases and Hung and Kono (1979) estimated a global incidence of 10 million. In 1981, careful health surveys in the villages of Goa, west India (Srinivasa et al 1984) and around New Delhi, north India (Wadia et al 1989) showed that nearly a quarter of the population had conjunctivitis. Projecting this figure for the entire population then of 700 million of India, seems palpably incorrect, but a rough assessment of 30 to 40 million cases made by Wadia et al (1983) appears to be an underestimate.

The incidence of CNS manifestations of this virus is also not known. Hung and Kono (1979) relying on a post-epidemic serological survey in Changhua (Taiwan) came to the conclusion that there was one patient with the CNS disease for every 10,000 with the AHC. In a retrospective compilation for a national registry of neurological cases for the Indian Council of Medical Research, (ICMR Bulletin 1985,Wadia et al 1989) data could be gathered of as many as 581 patients from only 27 cities in India, though only 28 neurologists, 9 general physicians and one ophthalmologist had cooperated and had reliable records. One hundred and seventy three cases were reported from Bombay city alone with a population of 7 million and 79 from

the much smaller city of Varanasi. Wadia (1989) felt that 15,000 cases of paralysis was not too high an estimate allowing for unreported, misdiagnosed and insufficiently documented cases.

It can thus be seen that what appears to be an innocent conjunctivitis can have crippling consequences for some. Adequate warning of recurrent episodes with more severe implications have been sounded from India for the health authorities to take note of here and elsewhere (Wadia et al 1972,1973,1983). As epidemics of conjunctivitis are known to occur with other pathogens including viruses which do not cause paralysis, it has been suggested (Wadia 1983) that this disease should now be labelled Enterovirus 70 and not simply acute haemorrhagic conjunctivitis to mount a greater alert.

Cysticercosis

It is fair to assume from the reports available that cysticercosis has not diminished in India. Most of our earlier knowledge of its prevalence comes from the landmark papers of Dixon and Hargreaves (1944) and Dixon and Lipscomb (1961). The latter reported 450 cases of cysticercosis over a span of about 20 years from the British Army in India, leaving unsaid the large numbers in the rest of the country. Yet today's surveys reveal no less. Stool examination of 250,000 patients hospitalised in north India over a period of 17 years (1964-1981) showed taeniasis in 0.5-2% of the cases (Mahajan 1982). In labour colonies and slums, where pigs were raised, this figure rose to 12-15%, and 8-10% of slaughtered pigs harboured cysticerci. It was also said that 2.5% of all intracranial space occupying lesions (Tandon 1983) and 2% of focal epilepsy (Wani et al 1981) seen in a hospital in New Delhi were due to cysticercosis. Similarly Mani et al (1974) mentioned that 2.2% of unselected patients with epilepsy in Bangalore, south India were due to this disease. It is quite likely that there is equal prevalence of this disease all over the country wherever over population, poor hygiene and economic conditions, and pig-raising prevail. Regional surveys may be necessary to prove this, though on the basis of autopsy and surgical data it is claimed that cysticercosis is more prevalent in the north and north-west of the country (Tandon 1983). It seems also certain that with the advent of computerized tomography showing hitherto unseen parenchymatous lesions in the brain, the enormity of the problem may become clearer.

This disease prevails in countries where pigs thrive unattended and their meat is eaten undercooked but it is not uncommon in India, where the consumption of pork is much less than that in South America or China or to see pure vegetarians with the disease. The ova are spread through vegetables contaminated with the night soil of persons, or from unclean hands of cooks harbouring the taenia solium. Auto-infection of patients with the tape worm does not seem to be very common, because stool surveys have shown that only a small percent of Indian patients with cysticercosishave a tape worm in their gut (Tandon 1983).

The prevalence of the disease apart, one may well ask if there are any particular differences in its presentation as compared to countries in Central and South America, East Europe, or Africa where it is also widely prevalent. It is believed (Tandon 1983) that in India parenchymatous invasion of the brain by many cysticerci is more common than a single lesion, and the meningeal racemose, and ventricular type of the disease more prevalent in Mexico, South American countries and Poland is infrequently seen. Though diverse clinical presentations of cysticercosis are seen as elsewhere ranging from convulsions, to progressive dementia, raised intracranial pressure etc. attention has been drawn (Tandon 1983) to an unusually common form of manifestation here resembling pseudotumor cerebri. A high percentage of patients came with symptoms of raised intracranial pressure, with or without fits. Few, if any localizing signs were found and ventriculography revealed small somewhat squashed ventricles (at times with multiple indentations) named by the authors vividly as throttled ventricles. Diagnosis only became evident when a subcutaneous nodule of cysticercus was detected, or a biopsy made during an operation to reduce the markedly raised intracranial pressure revealed a cerebral cysticercus. Autopsy of these patients often showed a large number of living and dying cysts "as if a shot-gun has hit the brain", and oedema. In earlier days, this variety of the disease was often misdiagnosed as benign intracranial hypertension if no other evidence of cysticercosis was detected elsewhere. The CT scan by showing the lesions in vivo has made the diagnosis much easier.

Attention has also been drawn from India to a rare variety of disseminated cysticercosis where literally thousands of cysticerci invade the body muscle-mass, the brain and even some other organs like the heart. One such case has been reported from Brazil (Armbrust-Figueirdo et al 1970). 18 patients have been reported from India, but the recently available medical literature from the People's Republic of China (Zhu and Xu 1983, Zhi-Biao et al 1985) shows that it has been seen there frequently. The first such case was described by Krishnaswami (1912) serving with the British army in Burma, and the other cases have been referred to in a recent account by Wadia et al (1988).

These patients presented with a striking, often rapid Sandow type enlargement of muscles called pseudo-hypertrophy (resembling a myopathy), progressive dementia, behaviour disorder and intractable epilepsy. Signs of raised intracranial pressure and localization of lesions, if any, were usually muted. The often-present subcutaneous nodules, indicated the diagnosis. McRobert (1944) vividly described such a patient as a man aged 24 years, who in a matter of six months had come to resemble "a professional wrestler to the amusement of his friends and dismay of his household". So intense has been the preoccupation with the enlarged muscles that in almost all publications more discussion has been devoted to the pseudohypertrophy rather than to the massive dissemination of cysticerci which caused it.

Wadia et al (1988) have now pointed out that this type of disease results from an invasion by living cysticerci, which give rise to symptoms simply by occupying a large amount of space without causing any local reaction in the host tissue. Thus the expansile muscles enlarge and progressive cerebral symptoms appear with or without intracranial hypertension. To support this view, they showed CT images of living cysticerci in the brain, and for the first time ever also in the muscles of their 3 patients (Figs 2,3) backed by biopsy and autopsy evidence. Except for mild occasional pericystic inflammatory reaction, no obvious polymyositis was seen. The cysticerci were embedded in the brain without causing any local oedema. Autopsy examinations have shown that living cysticerci are symbiotic with human tissue and set up a local reaction only as they die. This can now be appreciated during life on the CT scan. An indirect support for their view comes from the fact that except in one instance, no radiologically visible calcification (a mark of dying or dead cysticerci) was seen in the muscles of these patients despite the large numbers of cysticerci present.

It appears that this form of the disease results from a poor immune response of the host tissue to the entry of the cysticercus, and represents the other end of the spectrum of cysticercosis, from the commoner type in which the patient has no symptoms or presents with occasional fits due to few calcified dead or dying cysticerci seen radiologically in the muscles and now much better by computerized tomography of both brain and muscles. Wadia et al (1988) have urged, as a result of their observations, greater use of CT of muscles in the understanding, investigation and management of cysticercosis.

They have also cautioned against careless and unsupervised use of praziquantel. Whereas much rightful acclaim has been given to this new drug, side reactions including rapidly developing coma soon after the first few doses have been reported (Wadia et al 1988, Verma et al 1987). To avoid this, Wadia et al (1988) have suggested the judicious use of the CT scan of the brain and muscle in any case of cysticercosis to judge the larval load, and proceed with caution, if it be heavy. Supervising personally the therapy, priming well in advance with steroids, beginning with an initial low dose and working it up slowly to give a longer course and repeated courses are some suggestions worth considering. The experience of Chinese neurologists with similar patients has been different. They have used doses of 120 to 180 kg./day without running into any serious complications (Zhu and Xu 1983, Zhi-Biao et al 1985) raising the question of ethnic susceptibility amongst Indians to the drug.

Cerebral malaria

The physician practising in India has to guard against misdiagnosing a case of cerebral malaria as viral encephalitis. The clinical features are somewhat similar. The diagnosis can be made at once by a blood smear for P. falciparum. It is rarely negative.

Immediately after the second world war, the annual incidence of malaria in India was 75 million cases with 0.8 million deaths, many from cerebral malaria, in a population of 350 million! (Sharma 1983). With a massive anti-malarial campaign, the incidence was lowered to 0.1 million cases, and no deaths in 1965-1966. Following the resurgence of the mosquito there were 6.46 million cases annually by 1976, of which 11.65% were due to P.falciparum, many with cerebral manifestations. What was more disturbing was the appearance of a focus of P. falciparum resistant to chloroquine in Assam in 1973. It spread to many other parts of north-east India, with a proportionate increase to 25% due to this strain and increasing mortality (WHO Regional Publication 1987).

Today, despite implementation of containment programs the position is hardly better with the annual incidence hovering a little under 2 million cases, and the spread of the resistant strain of P. falciparum to the western coast of India.

The drug for treatment of all kinds of malaria is chloroquine but the demand for intravenous quinine as a drug of choice is rapidly rising to combat the chloroquine resistant strain.

Familial and Congenital Disorders

Heredo-familial spinocerebellar degeneration

No epidemiological survey of this group of disorders has been made, but hospital-based data from different parts of India is available (Jolly et al 1966, Sumra and Virmani 1972, Wadia RS and Amin 1976, Wadia NH and Desai 1980, Jagannathan 1985, Bansal et al 1988). The largest series of 200 cases was reported by Jagannathan. All these records are weakened by the fact that none of them were backed by autopsy data, so important in this disease. It appears that this is not an uncommon disorder as seen in the neurology departments of our country, and many of the subtypes described elsewhere are seen here too.

There is one difference. There is a greater prevalence of a variety of olivopontocerebellar degeneration (OPCD) distinguished by slow saccadic eye movements and peripheral neuropathy in India. Though Mass and Scherer described an autopsy proven sporadic case of this variety from Germany in 1933, Wadia and Swami (1971) from India, first drew attention to the type-specificity, hereditary nature and greater prevalence of this disease in India.They had seen 9 Indian families since 1962. Autosomal heredity was clearly established in most of them. Wadia and colleagues went on to report (i) the oculographic confirmation of the slow saccade (Kulkarni and Wadia 1975), (ii) the electromyographic and sural

Table II: Survey of Literature. Heredo-Familial Spinocerebellar Degeneration

COUNTRY	*REFERENCE*	*FAMILIES*
CANADA	SHARPE	2
ENGLAND	OPPENHEIMER	1
FRANCE	CAMBIER et al.	1
	SIGWALD et al.	1
GERMANY	MASS AND SCHERER	1
INDIA	KINI AND VENUGOPAL	1
	WADIA N.H.	25
	WADIA R.S. et al.	5
ITALY	AVANZINI et al.	1
JAPAN	OZAWA et al.	3
SCOTLAND	KOEPPEN et al.	1
TAIWAN	LAI AND HUNG	1
U.S.A.	KOEPPEN AND HANS	1
	MURPHY AND GOLDBLATT	1
	SEARS et al.	1
	STARKMAN et al.	1
	ZEE et al.	2
	PLAITAKIS et al.	3

Taken from "A Hereditary Ataxia in India" (Ref. No. 18).

nerve biopsy evidence of peripheral neuropathy for the first time in this major subgroup of OPCD (Wadia 1971,1977,1984, Wadia et al 1980), (iii) constant evidence of olivopontocerebellar and spinal cord degeneration in four autopsies (Fig 4) (Wadia 1977,1984 and 1989),(Figs 5,6) (iv) CT and MRI imaging during life (Wadia 1989). (Figs 7,8) Specific degeneration of the neurones in the paramedian pontine reticular formation was shown to explain the saccadic slowing and the relative sparing of the flocculus of the cerebellum correlated with the intact smooth pursuit eye movements (Plaitakis 1987, Wadia 1984, Buttner-Ennever et al 1985). The former findings for the first time indicated the location of an anatomical substrate in humans for the *burst* and *pause* neurones, till then believed to be necessary for the generation of normal saccades only on experimental evidence in monkeys.

Between the reports of Mass and Scherer (1933) and Wadia and Swami (1971) there was only one autopsy proven family reported by Sigwald et al (1963) from France. Though no electromyographic or cinematographic record of eye movements was available, the voluntary and reflex eye movements were described as slow and the overall clinico-pathological picture suggested that this family had suffered from the same disorder. Garcin and Man (1958) also from France, described *viscous* voluntary eye movements in spinocerebellar degeneration of various types and referred to some earlier literature describing single families with a similar ocular disorder. Kini and Venugopal (1967) also reported the cases of a father and daughter from Calicut, south India with slow eye movements and mentioned that the clinical features "were compatible with a diagnosis of olivopontocerebellar degeneration". All these papers suffered from inadequate clinical, electro-oculographic and autopsy examinations.

Subsequent to the publication of the paper by Wadia and Swami (1971) reports from various parts of the world, usually of single families, often comparing them with those of Wadia and Swami have appeared. In some of these families, autopsies had been performed and olivoponto-cerebellar degeneration found. Details of these have been reviewed by Wadia (1984,1989). No case has been reported from Germany since that of Mass and Scherer (1933), whilst in India, Wadia (1989) alone, has seen 26 families originating from different parts of India and reports from elsewhere in the country are available (Kini and Venugopal 1967, Wadia RS et al 1976, personal communications from colleagues). He maintains that this is the most common clinically identifiable hereditary ataxia in India, not excluding Friedreich's ataxia.

The patient presents with symptoms and signs of a progressive symmetrical cerebellar ataxia, and he or his relatives are usually unaware of the ocular disorder, which is a supranuclear ophthalmoplegia remarkable in that there is an increasing reduction in the velocity of the fast spontaneous or reflexly induced (saccadic) eye movements, without a limitation in their

range. The viscous eye movements are compensated by a characteristic quick jerking of the head to scan the surroundings, which a sharp relative aware of the disease in his family may detect as an early sign. By contrast, the slow pursuit or tracking ocular movements are normal. The deep reflexes are often suppressed. There may be dementia, involuntary movements, distal wasting, impairment of vibration and postural sensibilities in the lower limbs. There are practically no signs outside the nervous system. The disease is essentially autosomal dominant and new mutations regularly occur. The average age at onset in the Indian patients was 27 to 28 years, and life expectancy, 13 years after recognition of the disease. The patients came from the three dominant communities of India (the Hindus, Muslims and Christians) in proportion to their total numbers. Uncommon as it is elsewhere, it has been reported amongst whites and blacks in U.S.A. and Canada and in all races.

Cranio-vertebral anomalies

These congenital anomalies, principally basilar invagination and atlanto-axial dislocation, though reported for nearly a century (Greenberg 1968) fill a considerable part of the time and attention of the Indian neurologist and neurosurgeon as witnessed by the many reports from India, and the frequent symposia held to sort out the management problems posed, especially by atlanto-axial dislocation. To List (1941) must be given the credit of drawing attention to these anomalies sharply. He wrote that "among the developmental anomalies of the spine, the congenital malformations of the occipito-cervical area have not called forth the clinical attention they deserve, but have been considered until recently as mere anatomic curiosities". He described the neurological, radiological, and surgical findings in 7 American patients and confirmed them by autopsies in two. He clearly mentioned that the clinical prsentation of congenital atlanto-axial dislocation (CAAD) was different from that of basilar invagination, Arnold-Chiari malformation and the Klippel-Fiel anomaly. In the early fifties, McRae (1953) and McRae and Barnum (1953) wrote two important clinico-radiological papers from Canada and pointed out (i) the distinction between basilar invagination and CAAD and mentioned that the two rarely co-existed; (ii) that CAAD was commoner of the two; (iii) that the neurological manifestations of occipitalization of the atlas were mostly due to associated CAAD.

Wadia (1960) was struck by the frequency of these anomalies amongst Indians, and also by the distinctive myelopathy of CAAD and described his neurological and radiological findings in seven patients with CAAD seen in a short span of three years. Since then a large number of papers have appeared, some compositely discussing cranio-vertebral anomalies (Bharucha and Dastur 1964, Chopra et al 1988) and others specifically dealing with CAAD (Wadia 1967,1973,1989, Pandya 1972, Sinh 1976, Desai and Mohire 1983, Rao et al 1983, Shukla et al 1984, Bhatia and Mehta 1988).

Wadia (1989) has gathered 605 cases of cervico-medullary compression due to CAAD published or personally reported from some major regional national centres in different parts of India.(Table 3) The actual number of diagnosed and unreported cases would be two to three times more. Compared with this, Greenberg's review (1968) of all types of atlanto-axial dislocations, mentioned only 94 cases (excluding Wadia's 34 patients) of the congenital variety since Giacomini's first case of 1863 and not all of them had neurological signs. No large series has appeared from anywhere outside India since then. Similarly, over a span of nearly 30 years, Spillane et al (1957) and Van Gilder and Menezes (1985) have been the only ones to make substantial reports of cranio-vertebral anomalies (including CAAD) from the West.

It appears that CAAD forms a major part of the cranio-vertebral anomalies seen in India as shown by 69% of the 82 cases in a recent series of symptomatic cranio-vertebral anomalies amongst Indians (Chopra et al 1988).

Wadia (1960,1967,1973,1989) has stressed that though atlanto-axial dislocation due to rheumatoid arthritis, infection etc. present with pain and stiffness of the neck, patients with the congenital variety often come to a neurologist with symptoms of medullo-spinal junction compression. The symptoms may be transitory on sudden flexion of the neck, persisting for a few minutes or hours and occasionally, days. Such episodes (due to acute transient compression of the cord) of quadri-paresis, paraesthesiae below the neck, or sudden unconsciousness without convulsions sweating or pallor may recur, leaving behind in later attacks, increasing signs of a high cervical myelopathy. On the other hand, many patients simply come with signs of progressive upper cervical cord compression indistinguishable from that due to any other cause. He has stressed the importance of eliciting history of transitory attacks by direct questioning, as it helps to distinguish CAAD from other disorders of the cervico-medullary junction.

Almost all patients have pyramidal signs, often an asymmetrical quadriparesis. Loss of vibration and posture sense in limbs causing clumsiness of hands is next common. Wasting of hands, forequarter dissociated sensory loss, cerebellar signs, lower cranial palsies and Horner's syndrome are much less frequently seen. Occasionally short-lasting symptoms of brainstem or occipital lobe ischaemia such as diplopia, vertigo, dysarthria, ataxia, lower cranial nerve palsy, hemisensory loss and blindness due to embarrasment of the vertebrobasilar circulation by the dislocating atlas may accompany the signs of the cord compression. Wadia (1989) has also pointed out that very occasionally these may be the sole signs of CAAD leading to a misdiagnosis of primary disease of the vertebrobasilar arteries. In many patients the neck is short and other congenital anomalies elsewhere in the body may be seen clinically or on radiology of the spine. Patients with basilar invagination usually do not

Table III: Large Series of CAAD from major Regional National Neurological Centres - 605 Cases.

Authors	*Years*	*Number of cases*	*City in India*
Wadia	1957 – 1988	114	Bombay
Desai, Mohire	1957 – 1983	63	Bombay
Hegde, Das	1958 – 1982	65	Bangalore
Chopra, Jawalkar, Kak, Gulati	1970 – 1987	55	Chandigarh
Bhagwati	1972 – 1986	99	Bombay
Bhatia	1974 – 1988	66	New Delhi
Shukla, Nag, Gupta, Lal	1977 – 1979	33	Lucknow
Rao, Raut	1978 – 1988	110	Trivandrum

Taken from "Neurological manifestations of Congenital Atlanto-axial dislocation" (Ref. 23).

have transitory attacks, but present with signs suggesting a posterior cranial fossa disorder: cerebellar ataxia, lower cranial nerve palsies, diminished corneal reflex, dissociated sensory loss in the upper limbs, pyramidal and posterior column signs and occasionally those of raised intracranial pressure. CAAD presents as a myelopathy.

Radiological and now CT scan examination in Indian patients have confirmed McRae (1953,1960) and McRae and Barnum's (1953) earlier observations of 3 distinct types of anomalies which can be consistently and confidently diagnosed. Wadia (1989) has summarized the information succinctly.

In type I there is occipitalisation of the atlas and often fusion of C2 to C3 into a 'block' vertebra. The odontoid is usually stumpy. The superior lateral articular facets of the axis are often deformed producing instability of the joint and a progressive irreducible dislocation with the skull and atlas moving forward and the dens backwards or backwards and upwards so that the medullospinal junction rather than the spinal cord is squeezed between the odontoid process and the posterior margin of the occipitalised atlas. This upward and backward vertical dislocation was mentioned by Wadia as early as 1967 when he pointed out that such a dislocation of the dens gives rise to a misdiagnosis of basilar invagination if the conventional Chamberlain's, McGregor's or Fischgold's lines are used to make a radiological diagnosis. Further, the CT scan and autopsy of these patients have shown that the transverse and other binding ligaments are poorly developed, increasing the instability of the joint.In type II, the apical part of the dens is congenitally not fused with the basal part and is 'free-floating', premitting forward dislocation of the atlas on the axis. Usually no other associated bony or ligamentous anomaly is seen. The C1-2 segment of the spinal cord is squeezed on neck flexion and released on straightening up as the dislocation is usually fully reducible. Because of this it has been stressed that a flexion radiograph of the spine must always be asked for in high cervical myelopathy as this condition is easily missed.Type III: Radiographically only a wholly or partly reducible dislocation of an otherwise normally structured joint is seen. The C1 segment of the spinal cord is compressed as the dislocation is only antero-posterior and not vertical. This variety was called 'chronic atlanto-axial dislocation' by McRae (1953,1960). An example of type II is shown in Figure 9.

Dastur et al (1965) and Dastur (1979) have given a fairly detailed account of the pathology after studying 11 operated and autopsied Indian cases. The pathogenetic mechanism causing the dislocation and the cord compression has been discussed in the papers of Wadia and Dastur quoted earlier, and well summarized by Wadia (1973,1989). Much has been written on the embryological development and various maldevelopments of the odontoid process and well reviewed by Greenberg (1968). Maldevelopment or malfunction of the transverse ligament, the odontoid process, lateral articular facets between the atlas and axis; and occipitalisation of the atlas

throwing an extra strain on the atlanto-axial joint when C2 and C3 are fused result in compression of the uppermost cervical cord, or medullo-spinal junction if the dislocation is upward and backwards (vertical dislocation). A dural band can form at the site of compression adding to the narrowing of the spinal canal. Syringomyelia is an uncommon association.

The correct management of these patients has still not been resolved. Initially posterior decompression by removal of the posterior arch of the atlas or the rim of the foramen magnum, and sometimes the spine and lamina of the axis was performed with unacceptable morbidity and mortality (Dastur et al 1965). Subsequently, a variety of operations have been carried out by our surgeons (Sinh 1976, Chopra et al 1988) with varied results. Wadia (1989) believes that no single operation is suitable for the varied type of anomalies seen and has provided an algorithm approach (Fig 10) to surgical treatment after identifying by imaging the type, site and degree of compression.

Environmental Disorders

Although malnutrition is still widespread especially amongst children of the rural poor, systematic surveys of its impact on the nervous system are not available. Data gathered from urban hospitals do not truly reflect the correct position. Wadia (1979,1987) maintains that in his own experience and from published Indian data it seems that Wernicke - Korsakoff's syndrome, central pontine myelinolysis, Marchiafava-Bignami disease, and cerebellar cortical degeneration, which form the main chapters on nutritional disorders of the nervous system written in many classical western textbooks of medicine are uncommonly seen in the malnourished. Continuing chronic deprivation seems to affect the nervous system in a different way than malnutrition reported in western alcoholics.

Swaminathan (1978) and Srinivas et al (1986) came to the same conclusion, the latter questioning, "but how common are the pure nutritional disorders of the nervous system?". Studying 100 adults of households earning less than Rs.500 (US$45) a month, they found 95% of them to be under or malnourished, their diet showing deficiency of proteins, calories, iron and B complex with corresponding clinical signs of anaemia, glossitis, oedema, underweight, anorexia, yet none showed clear signs of neurological disease. Long-standing inadequacies of calories and nutrients elicit available mechanisms of adaptation resulting in low weight for height, reduced caloric expenditure and lower work capacity, but neurological disease does not occur. They drew attention to the contrast with prisoners of war, who being previously well-fed, developed neurological signs when rapidly deprived of nutrition in camps and jails. Yet as Denny-Brown (1947) has mentioned a critical threshold exists beyond which effects of malnutrition appear in the nervous system. That threshold, seems to be higher in those

chronically deprived from early life than in the prisoners-of-war of developed nations.

The indentifiable groups of nervous system disorders seen in India are :

i) The vitamin B-complex deficiency.
ii) Vitamin D-deficiency - osteomalacic myopathy.
iii) Protein calorie (energy) malnutrition.

The Vitamin B-complex deficiency

Whereas a large number of patients with pellagra have been seen in pockets in Andhra Pradesh (Gopalan 1970) and Rajasthan (Shah et al 1972) especially in certain lean seasons, no similar large-scale disorder related to Vitamin B deficiency including beri-beri has surfaced in India in the last 40 years. However, no appropriate rural-based survey has been made and studies in urban city hospitals have essentially unearthed nutritional deficiency in alcoholics. These have been reviewed by Wadia (1979). Further, a small amount of literature has accumulated on vitamin B12 deficiency essentially related to malabsorption rather than sheer deprivation (Jeejeebhoy et al 1967, Wadia and Swami 1970, Dastur et al 1975) and the burning feet syndrome (Gopalan 1946).

Pellagra

This disease is on the wane but there was a time not too distant, when it was said (Gopalan 1969) that "in Hyderabad 1% of admissions to general hospitals and (in certain seasons) 8-10% of admissions to mental hospitals are cases of pellagra". A similar situation was seen in Rajasthan, north west India (Shah and Singh 1967, Shah et al 1972). Diarrhoea, dementia and dermatitis were often present, but additionally peripheral neuropathy, myelopathy and even amblyopia have been mentioned, though there was some doubt whether these were related to lack of nicotinic acid itself or to other associated deficiency. Electroencephalography has revealed irregular or absent alpha rhythm, excess theta activity, at times in bursts, and even delta waves (Srikantia et al 1968, Krishnaswamy and Gopalan 1971) which rapidly reversed along with the clinical signs after a single injection of niacin.

Traditionally pellagra is known to affect the poor, subsisting mainly on a diet of maize, containing unavailable bound nicotinic acid and low amounts of tryptophan (which can be synthesized in the body to nicotinic acid). The disease is not seen, therefore, in the regions where rice and wheat are eaten as staple food. In the areas around Hyderabad where pellagra is seen, it is millet jowar (sorghum) which is consumed and not maize. To unravel this contradiction, Gopalan and colleagues (Gopalan and Srikantia

1960,Raghuramulu et al 1965, Gopalan 1969, 1970, Krishnaswamy and Gopalan 1971, Gopalan and Narasingha Rao 1972, Belvady et al 1963, 1968) in a series of publications based on clinical observations and animal experiments, put forward the unitary theory that pellagra was caused by an excess of dietary leucine derived from both maize and jowar, causing an increase in the nicotinic acid requirement by interfering with the tryptophan and nicotinic acid metabolism. This theory did not meet with universal acceptance (Truswell et al 1963).

Vitamin B_{12} deficiency syndrome

Neuromyelopathy

It is well known that Addisonian pernicious anaemia and resulting classical subacute combined degeneration are seen very rarely amongst Indians, yet overt or covert malabsorption of vitamin B_{12} does cause a similar neuromyelopathy, especially if there is additional malnutrition as in imbalanced vegetarianism (Jeejeeboy et al 1967, Wadia and Swamy 1970, Dastur et al 1975). All the patients of Jeejeebhoy et al (1967) and Dastur et al (1975) were vegetarians as also most of those of Wadia and Swamy (1970). Random examinations of serum of normal vegetarians in India has shown significantly lower levels of vitamin B12 than in non-vegetarian controls (Satoskar et al 1961, Mehta et al 1964, Dastur et al 1972).

Whereas the patients of Jeejeebhoy et al (1967), presented with neuromyelopathy, Wadia and Swami (1970) and Dastur and colleagues (1972) pointed out occasional atypical features like cerebellar ataxia, bladder paralysis, cutaneous sensory loss on the trunk apeing spinal cord compression, and proximal muscle weakness resembling myopathy in addition to or overshadowing the signs of neuromyelopathy. Mental changes, visual disorder and optic atrophy, known to occur with subacute combined degeneration, were seen in a rather higher proportion (6 out of 14) than usual in the patients of Wadia and Swami (1970). Dastur et al (1972) estimated the levels of the other B vitamins, besides B_{12} in their patients and found raised level of folate, normal levels of thiamine, nicotinic acid and pantothenic acid and reduced levels of riboflavine (B_2), total pyridoxine (B_6) and pyridoxal. On administering vitamin B_{12} the serum folate level fell, whilst the vitamin B_2, B_6 and B12 rose to normal levels. they postulated and commented on an intricate relationship between the various B-vitamins in this disorder.

Infantile Tremor Syndrome

This clinical syndrome, affecting infants between 6 to 24 months, and

manifesting as rapid tremors, apathy, hypokinesia, moderate anemia, light coloured hair and skin pigmentation was first described by Pohowala (1960) in central India. No cases have been seen outside India and the incidence of the disease has reduced in the subsequent decades. Jadhav et al (1962) saw similar patients in Vellore and found megaloblastic bone marrow **and reduced serum vitamin B_{12}.** The serum and breast milk of the mothers also had reduced vitamin B_{12} and some had megaloblastic bone marrow. Administration of vitamin B_{12} even in a small dose cleared the tremor and other signs, leading Jadhav and colleagues to the conclusion that this was an unusual vitamin B_{12} deficiency disease.

Confirmation from others was not forthcoming. Tandon and Bajpai (1973) saw 212 such infants over 10 years in Lucknow suggesting its national prevalence but failed to find the laboratory evidence of vitamin B_{12} deficiency. Brain biopsies suggested that this was probably a variety of meningoencephalitis as conjectured by Pohowala (1960) initially.

Vitamin D deficiency, osteomalacia and myopathy

Pains in the limbs, proximal (especially pelvic muscle) weakness, exaggerated lordosis, and waddling gait amounting to a myopathy have been well-recorded in nutritional osteomalacia since Scott's vivid description in her extensive survey in India (Felton and Stone 1966, Singhal 1966, Report of the ICMR 1967-1968, Wadia and Swami 1970, Vaishnava 1975, Skaria et al 1975, Dastur et al 1975, Irani 1976).

Malnourishment, multiple closely spaced pregnancies, almost continuous lactation and lack of exposure to sunlight through wearing the all-covering burkha compound to cause the deficiency. Electromyography has shown evidence of a myopathy (Skaria et al 1975, Irani 1976), whilst histological examination revealed a normal muscle or non-specific fibre atrophy (Dastur et al 1975, Irani 1976). A dramatic recovery of strength and rapid reversal of electromyographic changes were seen on administration of vitamin D. This led Irani (1976) to postulate that in this disorder, there was a reversible transient block of muscle fibres without actual fibre damage (a metabolic myopathy). Dastur et al (1975) contended that the muscle disorder was not a myopathy, but simply a combination of disuse and malnutrition, a view which was hard to accept, because in the course of the same research, they found on histology degenerative changes similar to those seen in muscular dystrophies in patients with exactly similar reversible muscular weakness and electromyographic abnormalities accompanying osteomalacia due to hyperparathyroidism, Wilson's Disease, prolonged phenytoin consumption etc. Their conclusion that nutritional and non-nutritional osteomalacic muscular weakness were different, has not been confirmed yet by others.

Protein-energy (calorie) malnutrition

Kwashiorkor and marasmus are the names given to the manifestations of extreme malnutrition resulting from low protein and calorie intake in infancy and childhood, but more subtle forms of under nourishment exist, mostly amongst the children of the so-called third world. Initially named protein - calorie malnutrition (PCM), it is now customary to call it protein-energy malnutrition (PEM) and an enormous amount of literature, both clinical and experimental, too numerous to quote at length has accumulated on the subject of its impact on the developing nervous system, especially the brain. The Indian contributors have been significant and are well referred to in recent reviews (Wadia 1979, Agarwal 1984, Tandon and Gopinath 1984, Chopra and Dhand 1988). .

It has been shown that the developing human brain is most vulnerable during the vital period of rapid growth, which begins in the 13th week of gestation and continues to the third or fourth year of life. During this period, myelination, dendritic arborization and connection and glial cell multiplication occurs. Similarly myelination of the peripheral nerves begins between the 14th and 18th week of foetal life and remains very active upto the fourth post-natal month, continuing more slowly over the years. There is evidence to suggest that if significant PEM occurs, not only is its effect immediate, and more ominous, permanent despite correction of the malnutrition.

PEM in its varied forms affects one fourth of the world's children (Chopra and Dhand 1988). Closer to home, Udani mentioned the staggering figures of some degree of malnutrition amongst two-thirds of the 120 million children of India, under the age of 5 years, of which approximately 3 to 4 million have frank Kwashiorkor or marasmus.

The acute effects : Besides the general features of Kwashiorkor, the immediate neurological effects are apathy, irritability, disinterest, slow learning, generalized weakness, muscle wasting, hypotonia and hyporeflexia. In some children, a myopathic waddling gait, difficulty in rising, proximal muscle weakness and wasting of the axillary folds allowing the child to slip easily through the hands when raised off the floor are seen (Udani 1954,1960,1962,Cravioto et al 1966, Sachdev et al 1971, Patel et al 1972). Udani, after a study of 59 children, principally between the ages of 5 months and 5 years found mental changes, tremor (kwashiorkor), rigidity, upper motor and lower motor neurone signs (the latter being more common), occasional sensory changes and signs of dysfunction of the autonomic nervous system.

Electroencephalography has shown diffuse or focal slow waves or a disorganized background (Engel 1957, Patel et al 1972). Proper nourishment even at this stage has resulted in reversal of the abnormality

and normal electroencephalograms have been recorded by Taori and Pereira (1974) after several years in children who had been earlier deprived.

Pneumoencephalography (Patel et al 1972) and CT scans (Stoch et al 1982) have shown evidence of cerebral atrophy especially in the more severely malnourished. A reduction in the total brain weight and cerebellar cell population (even allowing for the reduced body-weight and height of a severely malnourished child) has been recorded (Dobbing and Smart 1974). A wide range of biochemical changes and alterations in brain metabolism have also been observed. This subject has been reviewed by Chopra and Dhand (1988).

Electromyography has also shown abnormality in the muscles and peripheral nerves (Sachdev et al 1971, Kumar et al 1977, Ghosh et al 1979). Small motor units, occasional fibrillation potentials and delayed conduction velocity were recorded in 40 to 70% of patients, Ghosh et al (1979) making the point that the degree of conduction delay depended on the severity of malnutrition.

Quantitative and qualitative changes in the histology of sural nerve and quadriceps muscle have been reported by Udani (1954), Dastur et al (1975), Udani et al (1975), Dastur et al (1977) and Dastur et al (1982). Their main findings were a generalized smallness of muscle fibres resembling arrested fibre growth. In a small number of cases there was some evidence of denervation in the form of group-fibre atrophy and also rounding edges of fibres suggesting myopathy. The sural nerve biopsies showed a persistence of small diameter fibres (less than 5.4 um), indicating an arrest or delay in development of medium and large myelinated fibres.

The delayed effect: Dobbing (1974,1976) noted that permanent structural and functional modifications which outlast the duration of the restriction can occur in the brain if PCM occurs during the period of maximum brain growth. The type of change envisaged does not show itself as a gross anatomical anomaly, nor as pathologically detectable destructive lesions as seen in cerebral anoxia or hypoglycemia, but as functional disturbances of the brain from distortions and deficits in the ultimate mature brain due to "the dislodging of the intricate components of the growth program away from their delicately ordained interrelationship".

Much of the information regarding this has been gathered from animal experimentation and observations, but many longitudinal studies on humans from India and elsewhere have been completed to test this belief (Mehta et al 1964, Cravioto et al 1966, Champakam et al 1968, Patel et al 1974, Stoch et al 1982, Galler et al 1985). Champakam and others (1968) working in the Nutritional Research Laboratories, Hyderabad, where several hundred cases of Kwashiorkor were treated in a period of 8 years,

observed 19 such children. Their ages were 18 to 36 months at the time of admission to hospital and at final assessment 8 to 11 years. Specially modified tests to meet the needs of local culture and illiteracy were devised to test mental function like reasoning, organization of knowledge, memory and perception. Carefully matched controls amongst neighbours with the same socio-economic background were similarly tested. The final conclusion was that there was a significant impact on the mental function of children, who were exposed to PCM early in life. Galler et al (1985) carrying out a similar study, stressed the impairment of fine motor skill and coordination in such individuals.

Neurotoxins

A vast number of natural (biological) and man-made (non-biological) neurotoxins exist in our environment, too numerous to be detailed, but here reference will be made to some resultant neurological diseases seen in India. Whilst the age-old disease lathyriasis is a prime example of biological neurotoxicity, endemic fluorosis, manganese poisoning and pesticide toxicity are some examples of diseases due to non-biological neurotoxins. Arsenical neuropathy is one example of self-administered toxicity seen in India. Reference is made to clioquinol toxicity (common in Japan) to point out some Indian observations.

Lathyriasis (Lathyrism)

Lathyriasis now known to be due to consumption of the legume Lathyrus Sativus, has been endemic in certain parts of India for centuries. A product of deprivation such as follows war, pestilence, famine, or continuing regional poverty, this disease once prevalent more universally has resisted all attempts to banish it from central and north-east India and neighbouring Bangladesh, where in certain lean seasons even epidemic upsurges occur. Its prevalence has been estimated as 0.3% to 2.5% (Ludolph et al 1987). Famine affected Ethiopia and some other neighbouring states in Africa are the only other parts of the world where this disease persists.

Ganapathy and Dwivedi's studies (1961) through the Indian Council of Research have shown that this disease is much commoner in India amongst the male adult able-bodied working population thus adding to their woes. However, village women are disinclined to seek hospital treatment. The most affected ages are between 5 and 40 in males and 6 and 20 in females. The condition is essentially a spastic paraparesis, which can appear either acutely, subacutely or insidiously, the former mode being most common. The patient often awakens one morning to find his legs week, causing him to fall. Severe cramps often accompany or herald the paralysis which

can be precipitated by undue exertion or exposure to inclement weather. Less commonly a subacute onset of walking disability or a more chronic progressive weakness and increasing handicap over the months are known. As early as 1922, Acton working in India graded the disability according to the support required in walking. Most patients continue to walk slowly without a stick ('no-stick stage'), but others need one or two sticks, often made from the branch of a tree for support ('one-stick' 'two-stick' stages). Those with no access to modern ambulatory devices may be reduced to the 'crawler' stage, moving around on hands and knees. Added to this are an unknown number of asymptomatic persons with minimal neurological signs. Sensory and bladder disturbance are far less common, but a recent report (Ludolph et al 1987) has mentioned that 34% of patients complained of paraesthesiae and perverse sensations in the legs at the onset and 5.6% had hesitancy of micturition.

Symmetrical bilateral spastic weakness of lower limbs, with exaggerated tendon reflexes with or without clonus and extensor plantar responses are the common findings. Spasticity appears to cause greater handicap than weakness, the adductors of the thigh, the quadriceps and the gastrocnemius being most affected. In the late stages contractures add to the problem.

All sorts of abnormal gait are seen depending on the degree of disability. The mildly affected merely walk stiffly dragging the foot but a bizarre gait and posture with flexed hips and knees and a backwardly angled trunk is not uncommon (Ludolph et al 1987). Those with more severe disease, show a weaving or jerking gait, walking on their toes (because of continuous gastrocnemius contraction) with bent knee and scissoring of legs.

Very rarely, examination may show mild spastic weakness of the upper limbs or exaggerated tendon reflexes. Though Cohn and Streifler (Ludolph 1987) found clinical evidence of lower motor neurone dysfunction in 7% of their 200 post-war European patients, peripheral neuropathy has not been reported in Asians, and the wasting of lower limbs has been attributed to disuse. However, recent studies quoted by Spencer et al (1986) and Spencer and Dastur (1989) using contemporary methods of neurophysiological examinations have brought forth evidence of a peripheral nerve dysfunction, usually mild, even in Asian patients. Whilst this has been earlier explained as an outcome of the commonly accompanying malnutrition, parallel studies using the same methods in primate models of lathyriasis in macaques have refuted this explanation by showing distal changes in peripheral nerves of well-fed monkeys. This means that a small proportion of patients with severe lathyriasis can have overt or covert toxic peripheral neuropathy or neuronopathy.

It has now been established that lathyriasis is a self-limiting neurotoxic, stereotyped disease whether it affects Asians, Ethiopians or Europeans. It can affect otherwise well-nourished individuals, though most have

concurrent malnutrition. The patients are poor, indigent villagers, who have consumed matri or kesari dal (chickling pea, Lathyrus Sativus) as staple food all their lives, or during emergency following floods or droughts. 200 to 400 gms of lathyrus sativus per day for one to three months is sufficient to cause the disease, though even shorter periods have been mentioned (Spencer et al 1986). Some believe that sudden increased intake of the pea can lead to a more acute attack, coming more quickly after consumption than in those taking smaller amounts over longer periods. Ludolph et al (1987) suggested that those who developed the paralysis suddenly had more severe permanent handicap, though two girls in their series were severely paralysed at onset, but had only mildly spastic gait when examined much later. The disease can regress if the consumption of the pea is stopped or reduced early enough.

Though the link between between lathyrus sativus and the neurological disease had been known for many years (Ganapathy and Dwivedi 1961), the putative neurotoxin in the 'dal' was not identified till 1964. Credit goes to two groups of Indian scientists (Rao et al 1964, Murti et al 1964) who independently isolated and identified a free aminoacid, beta-N-oxalyl amino alanine (BOAA) from the lathyrus seed as the toxic causative principle of human lathyrism. Two alternative names have also been suggested for the beta-isomer of the neurotoxin, namely beta-N-oxalyl-L-alpha beta-diaminopropionic acid (oxdabro or OPA) and L-3-oxalylamino-2-aminopropionic acid (OAP) (Roy et al 1986).

Further proof of neurotoxicity has been obtained from animal experiments. Though literature in the 19th and early 20th century stated that the chickling pea can cause neurotoxicity in several animal species, a model of the human disorder in animals fed with the lathyrus sativus seed had not been produced till very recently. Now investigations in Hyderabad, India; Dhaka, Bangladesh; and New York, U.S.A (Spencer et al 1986) have reported an animal model, realistic and reliable enough to conduct further biological and pharmaceutical studies in this disease.

Scant neuropathological examinations have shown degeneration of Betz calls and of the anterior and dorsolateral corticospinal tracts in the thoracic, lumbar and sacral parts of the spinal cord. No anterior horn cell degeneration in the lumbosacral cord has been demonstrated to support the view of slight lower motor neurone disease in some patients' lower legs. The Macaque-monkey model has, however, shown degeneration in both the corticospinal tracts and the distal parts of the peripheral nerves, even in well fed monkeys.

Economic and social factors, and age-old habits have defeated all attempts to prevent the consumption of this poisonous dal. Regrettably the lathyrus sativus seed is still paid as wages for work done and the pea used as staple during droughts, many villagers not being convinced that it causes

lathyriasis. Sethi et al (1979) mentioned that the lathyrus sativus is still the third largest pulse crop in India, and the reasons are not far to seek in an economically deprived environment. It provides a nourishing diet of high-quality proteins and carbohydrates, it is easy to cultivate, it has rapid growth and hardiness against weather and pests, it requires little water, and the cooked legume is quite tasty. Besides no other cheap source of food or crop has been made available to the villagers, and no easy, practical and fool-proof method of detoxifying the legume has been suggested to them.

The race has, therefore, begun for a safe strain, but all these properties, besides non-toxicity, will have to be present in this strain and made known to the villagers by education to make it replace the entrenched chickling pea. It is obvious that genetic development of a hardy strain without BOAA or other toxic compounds is the answer, but even here one further problem arises. The unusual and appealing taste of the legume seems to depend on its BOAA content. The aim, therefore, seems to be to develop a safe strain with just enough BOAA content to make it acceptable to the palate, yet low enough to make the legume non-toxic for both the young and old. The fall out of such discovery will have far reaching implications eliminating human suffering, yet providing good, cheap, nutritious food for the poor.

Endemic fluorosis

In several districts of the states of Punjab, Andhra Pradesh, Tamil Nadu, Karnataka and Kerala, the fluoride content of the drinking water is intolerably high exposing several million people to the risk of fluorine intoxication. At least half a million persons suffer from what is called endemic fluorosis. A certain amount of fluoride is required by the body but if the concentration exceeds 2 mg/l in water, then depending on the length of exposure and several other factors, intoxication begins.

Fluorine has a natural affinity for bones and teeth and any excess of fluoride combines with calcium phosphate to cause dental and skeletal fluorosis. More rarely other organs may be involved. The dental changes affect permanent teeth, with loss of enamel translucency, mottling and appearance of yellow lines. The bony changes comprise osteosclerosis and with increasing years of exposure, osteophytosis and exostosis. The bones exposed to greatest stress are the most affected and the vertebral column is commonly involved. The narrowing and stenosis of the spinal and root canals cause the neurological manifestations by direct compression of the spinal cord or roots. In advanced cases pressure on the spinal and radicular arteries may compromise the blood supply. Narrowing of the auditory canal may be seen.

The neurological complications of fluorosis are rare when one considers

the vast numbers with the skeletal disease, which causes pains, aches, stiffness of joints, increasing deformity of the long bones specially of the lower limbs and spine. The neurological signs can be best described as radiculomyelopathy and depending on the level and degree of stenosis, root pains, paraesthesiae, wasting of limbs, spastic para or quadriparesis, retention of urine, impotence can occur. Progressive bilateral perceptive deafness is not uncommon. Rarely peripheral neuropathy, probably due to compression from deformed knee joints, has also been reported, but direct fluoride toxicity has also been questioned.

Besides the landmark paper of Shortt et al (1937) many interesting accounts of this disease have been written from India, and almost all the neurological cases have been reported from here. Reviews by Siddiqui (1973), Raja Reddy (1979) and reports by Singh and Jolly (1961), Singh et al (1961) cover most of the neurological literature on the subject.

Manganese Poisoning

India has one of the world's richest manganese ore deposits and the mining industry is spread all over the country with underground and surface mines. Irregular mining practices and improper ventilation can lead to greater inhalation of the manganese dust with consequent intoxication. This happened in India during the nineteen fifties, when there was a great international demand for manganese ore and Niyogi, an alert civil surgeon located in the mining district was the first one to report cases arising from this (Niyogi 1958). Berry and Bidwai (1959) studied the same material in somewhat greater details. The government of India was concerned enough to appoint a special commission of enquiry, which after visiting mines and ferro-manganese plants in different parts of the country and examining patients, published an exhaustive report on various aspects of the subject (1960). Out of a total of 1132 workers examined, 28 patients were found and 11 of them were brought to the J.J.Hospital for detailed study in the neurological department (Wadia 1964).

In the early stages of intoxication, the patients complained of asthenia, anorexia, irritability, insomnia and somnolence, heightened sexual libido followed by impotence. In a few of them, short or long periods of acute mania with at times violence, irrelevant talk, and restlessness were reported. The main clinical picture was one of Parkinsonism with a masked face, low monotonous speech, severe rigidity, abnormal postural reflexes, and a tendency to walk on toes (cock walk). Tremors were less remarkable. A constant and distinguishing feature was that of sham mirth or pathological laughter, which became hilarious when a group was examined. At times unprovoked weeping was noted.

There were seven other patients mentioned in the report of enquiry with pure spastic paraplegia, simulating lathyriasis, who did not have the

Parkinsonian features, but some showed sham mirth and had a past history of maniacal outbursts. The commission was unable to comment if these were cases of coincidental lathyriasis amongst the mine workers or if this was an unusual form of manganism, as these mines were located in the lathyriasis belt, but three of these patients were sure that they had never consumed the chickling pea (Lathyrus sativus).

Pesticide toxicity

To promote a green revolution in agriculture and to combat insect-borne disease, pesticides of all kinds have been increasingly produced in India from the nineteen fifties with attendant increase in toxicity. An idea of this can be had from the statements such as "nearly 60,000 tons of pesticides are entering the Indian environment every year", "accumulation of DDT in the body tissues of Indians is the highest in the world" and "Indians are ingesting 20-40 times as much DDT as Britons" (Nag 1986).

Pesticide toxicity is well known and reviewed by Schaumburg and Spencer (1980). Nag (1986) has painstakingly compiled information pertaining to India. Whereas acute intoxication takes place by accidental ingestion of the pesticide, chronic low grade toxicity can develop by consumption of food grown in the soil where pesticide is used or sprayed. Residues of pesticides like DDT, malathion and lindanes were found in about a fourth of the 400 food stuffs collected from the different markets of Calcutta. Pesticides have been found in vegetables, fruits, cereals, meats, milk, eggs and even pond water giving an idea of the enormity of the problem of unchecked pollution of the environment.

Nag (1986) summarized the information on acute and chronic toxicity following exposure to pesticides in different parts of India, stressing that this is not uncommon. Whereas her experience with chronic intoxication is no different from that which has been already reported in the literature, her review of the outbreaks of acute poisoning raises much concern and is worth recalling here.

These outbreaks of toxicity have occurred mostly due to uninformed mishandling of the pesticide, or accidental exposure to it, when many members in a community or village get simultaneously and suddenly exposed to a large amount of pesticide. For example, in the Lakhimpur Kheri district 286 persons were affected by what was called **epidemic epilepsy.** Farmers of this region were supplied benzene hexachloride (BHC), a commonly used pesticide, for application on their sugar crop. Ignorantly they used it as a food grain preservative. One hundred fifty of these cases were investigated by Khare et al (1977). They complained of recurrent convulsive seizures preceded often by auditory and visual aura, headache, confusion and memory lapses, impaired vision and staggering gait. Findings on examination included abnormal mental state, pyramidal

signs, myoclonic jerks, tremor, cerebellar ataxia, posterior column disorder and sixth and eight nerve palsies. Impaired vision was found in as high as 60% of patients. A similar epidemic also occurred in Sitapur district of the same state in the same year and was reported by Nag et al 1977. These patients presented with epilepsy, but few signs were found. In both epidemics, grossly abnormal electroencephalograms with diffuse epileptiform activity were seen. Nag (1986) has mentioned that the frequency and severity of seizures and the extent of neurological disorder probably depended on the amount of ingestion of the pesticide. There were patients, who came in status epilepticus and others had few seizures at long intervals. Similar cases with slight variation in the clinical picture have been seen in various other states and 196 deaths have been reported from Kerala from ingestion of wheat contaminated accidentally with parathion.

Arsenical Polyneuropathy

This has been well described in the western literature and the only reason to include it here is to draw notice to the unusual source of intoxication and its common occurrence in north-west India since the nineteen fifties (Chuttani et al 1967). A detailed review of this has been written by Chuttani and Chopra (1979), who mentioned that the main source of arsenic was in pills and powders given by practitioners of indigenous medicine and when arsenic is added to a tincture of ginger for potentiating the action of alcohol or to opium to enhance its effect for addicts. Data gathered over 10 years at the Postgraduate Institute of Medical Education and Research, Chandigarh showed that 24 out of 205 patients with peripheral neuropathy seen between 1970 and 1976, and 11 out of 570 between 1977 and 1979 were suffering from arsenic poisoning.

Peripheral neuropathy appears amongst opium addicts when they consume 0.039 to 0.4 mg of arsenic in 100 gm of opium, though individual susceptibility, duration of consumption, and daily dose are also important determining factors. As the intoxication is gradual and in a low dose, the tell-tale gastrointestinal symptoms of anorexia, vomiting and diarrhoea are not outstanding and fail to draw attention to the poisoning, but pigmentation, palmar erythema, hyperkeratosis of palms and soles with exfoliation are seen in nearly 50% of patients and should be looked for.

The peripheral neuropathy can be acute at times though it is mostly of a progressive, symmetrical, sensory-motor type due to axonal degeneration, with marked abnormality of the sensory action potentials and delayed motor nerve conduction.

Difficulty has been experienced in distinguishing this from alcoholic and nutritional peripheral neuropathy in which dermal lesions (due to pellagra) and diarrhoea also occur and the diagnosis is all the more difficult if the

patient has a combined addiction to alcohol and opium. High levels of arsenic in the blood, urine, hair and nails are diagnostic.

Subacute myelooptico neuropathy (SMON) due to clioquinol intoxication

Tsubaki et al (1971) first implicated the drug clioquinol in the causation of a mysterious disease (initially believed to be a viral infection) which afflicted 10,000 Japanese since 1955. The patients presented with abdominal pain, distal and ascending paraesthesiae, objective cutaneous and deep sensory loss, sensory ataxia, absent ankle jerks and occasional pyramidal tract signs. It seemed to be a Japanese malady, but interest in India was aroused as on a conservative estimate 480 million tablets of clioquinol were sold here annually. Wadia (1973,1977) observed that though SMON was seen in India occasionally, it was rarely due to clioquinol. In a retrospective and prospective study of patients spanning nearly a decade, he could find only 9, who could be diagnosed as SMON due to clioquinol with some degree of confidence. The contrast with Japan was stark, but no easy explanations were available. He also observed that the peripheral neuropathy component was not seen in Indian patients. The ankle jerk was present in 8 of the 9 patients. The motor and sensory nerve conduction velocities were normal with no distal denervation. This first observation outside Japan, led to some fresh questioning whether peripheral neuropathy occurred at all in clioquinol intoxication. Schaumburg and Spencer (1980) reviewed the Japanese data and conducted similar experiments, but could not confirm the Japanese findings. Their own histological examinations showed a normal peripheral nervous system. Baumgartner et al (1979) suggested an alternative explanation. As the neuropathology of SMON showed a distal degeneration (a central dying-back phenomenon) in the axons of the posterior and lateral columns of the spinal cord a similar degeneration could occur in the centrally directed short axons of the ganglion cells distributed to the anterior horn cells involved in the monosynaptic tendon reflex. This may explain the absent ankle jerk without any peripheral neuropathy.

Support for this was later given from Japan itself by Shibasaki et al (1982). Re-examining five long-standing Japanese patients with SMON, they found abnormalities in the short-latency somatosensory evoked potentials on stimulating the median and posterior tibial nerves which indicated normal peripheral nerve conduction, but a marked attenuation of the cortical component and delayed central nerve conduction. They concluded that the pathophysiology of SMON was mainly "a central distal axonopathy" without peripheral neuropathy, substantiating the initial Indian observations.

Miscellaneous Diseases

Cerebrovascular diseases

Cerebrovascular diseases predominate in neurological practice as

everywhere else. Though there is only one population-based epidemiological survey (Sunder Rao 1971, Abraham and Daniel 1972) considerable data gathered from large urban teaching hospitals over 30 years does give some measure of the problem faced here (Chand and Caroli 1961, Bharucha and Umerji 1962, Padmavati et al 1963, Dalal et al 1968, Bansal et al 1973, Venkatraman et al 1977). Two recent reviews cover the information adequately (Dalal 1982, Jain and Maheshwari 1986).

During the year 1968-1969, a staged study of the entire population of the town of Vellore and two adjacent rural blocks was begun (Sunder Rao 1971, Abraham and Daniel 1972). The total population surveyed was 2,58,576 persons and 147 were found to have suffered from a genuine stroke with hemiplegia. The prevalence rate was calculated as 56.9 per 1,00,000 population (68.5 males and 44.8 females). The rate was more in Vellore town and it increased with age. In the second phase of the study from 1969 to 1971, the population was kept under careful surveillance and a two-year prevalence and annual incidence rate for 1,00,000 population was obtained as 84 and 13 respectively. These figures were not necessarily reflective of the rest of the country and were rather low when compared with those of other nations. There are explanations for this. The age distribution pattern of Indians was considerably different from that of the developed nations and with the average life expectancy then of 52 years, the population-at-risk from stroke was well below that seen in large aging populations. Besides, the study was restricted to hemiplegic strokes with residual signs, leaving quite a few small, reversible and posterior circulation strokes uncovered.

Dalal et al (1968) conducted a prospective seven-month study of 127 consecutive hospitalized patients with recent stroke. They performed appropriate angiography in 112 of them and 45 came to autopsy so that the information gathered was quite detailed. They came to the conclusion that acute stroke comprised 1% of all admissions and 4.5% of medical admissions to a large urban hospital, figures comparable with the retrospective studies mentioned earlier. 82.7% were considered to have ischaemic stroke and the rest had cerebral haemorrhage. It was noted that despite the poor nutritional status of their patients, thrombosis associated with atherosclerosis was the chief cause of a non-embolic ischaemic cerebral infarction. This conclusion was later backed up by Dalal (1971,1976) in an international collaborative study of geographic pathology on cerebral atherosclerosis when it was demonstrated that the atherosclerosis index as seen in the circle of Willis was nearly the same at autopsy in Indians as in Americans or Japanese patients. Mathur and Kashyap (1965) on examining 400 medico-legal autopsies came to the same conclusion.

It was during the course of this early study of cerebrovascular diseases amongst Indians that Dalal (Dalal et al 1968, Dalal et al 1971) made the important angiographic demonstration of fragmentation of cerebral emboli, which was considered to be due to spontaneous intravascular clot lysis.

purification for immunodominant fraction to be applied in immunodiagnostic tests is in progress both at NIMHANS and at Astra Research Centre India, Bangalore. More research is needed in this country on this disease entity of NCC which still needs definition and perfection with special regards to clinical suspicion, specific diagnosis and specific therapy.

Shankar, Deshpande and Vasudev Rao from NIMHANS (1978) showed the coexistence of cysticercal cyst and Japanese encephalitis in patients studied at autopsy. Srinivas, Vasudev Rao and Deshpande described the encephalitic variant of cysticercosis (1980). Virendra Kumar and Gourie-Devi (1986) have analysed the clinico-pathological correlation of neurocysticercosis in a retrospective analysis of neurological case records (1986).

Other parasitic disorders seen in India

Amoeba, the malarial plasmodium, echinococcus, visceral larva migrans have been reported in the CNS. Raja Reddy et all (1972,1984,1986) found 1% of intracranial space occupying lesions in India to be parasitic. They described 5 patients with hydatid cysts (3 cerebral, 2 intradiploic cranial) and 6 cases of cysticercosis. Spinal hydatid disease was encountered by Ashok et al (1987), Suresh Narain et al (1987). Sushma Kapoor et al (1976) have described encephalopathy due to visceral larva migrans.

Bhatia et al (1971) have reported menigoencephalitis due to soil amoeba. Vasudev Rao et al (1988) have reported primary amoebic cerebellar abscess. Alka Gogate reported primary amoebic meningoencephalitis and isolated Naegleria fowleri from swimming pools in Bombay which could be potential cause of amoebic meningoencephalitis (1984,1985).

Guinea worm infestation of tuberculoma has been reported by Dinakar et al (1977), encephalopathy in association with ascariasis by Basu et al (1979), toxoplasmosis of the brain by Sanathanarath et al (1986), polyneuropathy in kalazar by Vijayan et al (1981).

Fungal infections of the central nervous system

A variety of fungal agents have been associated with CNS lesions, the most common being cryptococci, aspergillus, mucor, candida and cladosporium. Nocardial lesions are still being classified as fungal by many workers though the organism has now been categorised under higher bacteria.

Reports of fungal infections have come from different parts of India. Ramamurthi et al (1954) have also reported on cryptococcal fungal granuloma in neurosurgery. Dastur described his experiences at the department of neurosurgery,K.E.M.Hospital, Bombay with cerebral

years of age were most affected and the pathological examination suggested a form of juvenile or premature atherosclerosis. Multiple micro and large cerebral infarcts both old and recent, and extensive opening of the collateral circulation explained the variegated symptomatology of minor transient symptoms and major strokes. Patients with practically no palpable pulses have been known at times to be symptomless or merely blind in one eye, whilst others present with an acute severe, irrecoverable hemiplegia. Thus there appear to be two pathological conditions causing a common clinical syndrome - arteritis in young females and premature atherosclerosis in middle-aged males.

Cerebral venous thrombosis: Cerebral venous thrombosis is not uncommon. Whereas most cases are believed to be in close association with pregnancy and puerperium, Nagpal (1983) found an equal distribution amongst sexes, most cases falling in the third decade. Srinivasan and Natarajan (1974) made a prospective study of 90 consecutive cases of stroke related to puerperium gathered over only 3 years in Madurai (south India), and found that 85 had cerebral venous thrombosis and 5 had cerebral arterial occlusion. They reported an incidence of 4.5 per 1000 obstetric admissions, which was large when they compared it with the incidence in the west of 1 per 3000. This supported the earlier Indian reports (Prakash and Singh 1960, Janaki and Thomas 1963, Agrawal 1968, Jolly et al 1971, Srinivasan and Ramamurthi 1971). Studying this condition further, Srinivasan (1984) concluded that in their centre 15 to 20% of strokes in the young were related to puerperium.

Pelvic sepsis was not found to be a major contributory factor. Increased platelet adhesiveness (Prakash et al 1970), abnormal lipid profile (Prakash et al 1970, Chopra 1978), raised plasma fibrinogen (Srinivasan 1984) and consumption of synthetic steroid contraceptives (Nagpal 1983) have however, all been incriminated. In Nagpal's series of young males with cerebral venous thrombosis, the common thread was consumption of illicitly brewed alcohol.

Intracerebral and subarachnoid haemorrhage: Whereas patients with intracerebral haemorrhage due to uncontrolled hypertension are seen as frequently as anywhere else, there has been much discussion about the incidence of subarachnoid haemorrhage, congenital berry aneurysm, and angioma. It was long believed that spontaneous subarachnoid haemorrhage and aneurysms occur less frequently in India (Ramamurthi 1965,1969, Mathai and Chandy 1965). Ramamurthi (1969) came to the conclusion after reviewing the available Indian literature and his own experience that the difference was real. Mathai and Chandy (1965) stated that "spontaneous subarachnoid haemorrhage", angiomatous malformations and aneurysms are rare, and angiomatous malformations are a more frequent cause of spontaneous subarachnoid haemorrhage than are aneurysms". With more observations some re-evaluation is being done and even Ramamurthi and

Rajeshwari (1974) mentioned that subarachnoid haemorrhage was not uncommon after all, but aneurysms seemed to elude them. With the establishment of neurosurgery in Kerala (south India) it became obvious that subarachnoid haemorrhage, aneurysms and angiomas were not uncommon at all, raising the question of better detection or greater incidence there. Tandon (1987) prefacing a recently written-up report on a six-centre clinico-pathological epidemiological study of subarachnoid haemorrhage (1972-1975) under the ICMR, concluded that "the commonly accepted predisposing factors for development of a saccular aneurysm such as anomalies of the circle Willis, media defects at the junctional areas, atherosclerosis were found as frequently in Indian subjects, as reported from other parts of the world" and that "the frequency of intracranial aneurysms was much higher than was believed hitherto, though still not as high as reported from the west and Japan," and the relative frequency of aneurysms and arteriovenous malformation was the same as elsewhere.

The last word on the subject has not been spoken, and further comments on the subject and a more recent review of the literature is written by Kak in this volume.

Motor Neurone Disease

The universally recognized classical motor neurone disease (MND) and spinal muscular atrophy are seen frequently enough in India. A careful survey conducted in the town of Gowribidanur lying 80 km. north of Bangalore and 144 villages around it covering 57,660 individuals from a population of 1,19,290 revealed the prevalence rate of MND as 4 per 100,000 (Gourie-Devi et al 1987). Though it surveyed an infinitesimal portion of the variegated population of India, it probably reflects the prevalence of the disease in our country, and matches the prevalence rate of 5 to 7 per 100,000 in various parts of the United States, and is similar to the averaged rate of the disease as surveyed in various countries by Kurland and Mulder (1987) and Gourie-Devi (1987). One difference which seems to have appeared from some Indian studies was that the onset of the disease was on an average a decade earlier amongst Indians.

Similar data has not been gathered for spinal muscular atrophy, but an ICMR muscle clinic at the K.E.M. Hospital, Bombay, reported 83 fully investigated cases from 740 patients with muscle diseases seen between 1965 to 1983. There appears to be no significant difference in the presentation or course of the disease from the general pattern (Desai et al 1987).

What has attracted special attention in India is the frequency with which three benign varieties of MND affect the young, between the ages of 10 and 30 years - the Madras MND, monomelic amyotrophy (juvenile MND) and the wasted leg syndrome.

The **Madras MND** received its name as it was described in 1970 (Meenakshi Sundaram et al 1970, Jagannathan 1973) from the capital city of Madras of the southern state of Tamil Nadu. The disease seems to affect south Indians, as can be seen from other reports from Vellore (Mathai et al 1984) and Bangalore (Gourie-Devi and Suresh 1988). Three patients -who were not south Indians- have been reported from Bombay (Wadia PN et al 1987). Two of the twelve seen by Gourie-Devi and Suresh (1988) were also not of south Indian origin. 10% of cases of all motor neurone diseases seen in the Institute of Neurology, Madras (Jagannathan and Kumaresan 1987) and 3.7% in the National Institute of Mental Health and Neurosciences, Bangalore, were of this variety. The characteristic features are the age at onset below 30 years, absence of family history, very slowly progressive course with no reported mortality as yet, weakness of the limbs, lower motor cranial nerve paralysis and bilateral deafness. Bilateral facial palsy, dysphagia, palatal weakness with occasional nasal regurgitation, dysarthria due to a wasted, weak tongue are the common features of the disease. The atrophic paralysis of the limbs is asymmetrical in nearly half the number of patients and the distal muscles are more affected, the disease being usually first detected in the hands and forearms. The tendon reflexes are more often abnormal than not, being reported as absent in 35% and brisk in the 25% who have a spastic gait. No sensory loss or cognitive dysfunction have been reported. The remarkable observation is that a third to a half of the patients have bilateral progressive, usually disabling deafness, which can be detected early in some by audiometry. The deafness usually accompanies the other symptoms but may follow and rarely even precede them. It is claimed that the clinical picture is clearly distinguished from spinal muscular atrophy and other motor neurone diseases in the young.

Muscle enzymes like creatine phosphokinase and lactate dehydrogenase are usually not elevated in the serum except, rarely, when the disease moves at an accelerated pace. Valmikinathan et al (1973) report that reduced plasma citrate level is indicative of this disease. There is a disturbance of carbohydrate metabolism as seen by a lag glucose tolerance curve and increased fasting plasma pyruvate level even two hours after the glucose load. An altered citrate-pyruvate ratio is considered as diagnostic of the disease.

Electromyography and muscle biopsy have confirmed the clinical impression of a neurogenic atrophy due to a progressive anterior horn cell disease. Without much evidence Jagannathan (1973) had merely stated that the deafness was due to the degeneration of the brain-stem auditory nuclei. Pure tone audiometry, electrocochleography, and brain-stem auditory evoked response study have shown that the deafness is sensory neural, and results from loss of cells in the spiral ganglion located in the cochlea (Wadia PN et al 1987). The intact caloric responses indicate a very selective process sparing the vestibular neurones.

The aetiology of the disease or why it has essentially affected the Dravidian population of India are not known. No genetic or environmental factors such as toxins, malnutrition and infection have been implicated in the causation of the disease. Though no autopsy study is available, clinical and laboratory examinations suggest that it probably results from progressive degeneration of selected sets of neurones, mainly those located in the anterior horn of the spinal cord, the lower motor cranial nuclei and the spiral ganglion of the cochlear nerve.

Benign single limb amyotrophy : Although *benign* amyotrophy confined essentially to one limb, has been recognized by neurologists in India for more than two decades (Wadia 1973,1987) more careful study with a long follow-up, electromyography and muscle biopsy have been only recently reported (Singh et al 1980, Prabhakar et al 1981, Gourie-Devi 1984, Gourie-Devi et al 1987, Chopra et al 1987). There are essentially two subtypes with some subtle differences between them, now generally called *monomelic amyotrophy and the wasted leg syndrome.*

The monomelic amyotrophy : Earlier referred to as *juvenile motor neurone disease* (Wadia 1973) in India, this type has also been labelled as juvenile muscular atrophy localized to arms (Singh et al 1980) and non-familial spinal segmental muscular atrophy in *juvenile and young subjects.* The disease is usually recognized before the age of 30 years, the peak incidence being at 20 years. Only a few manifest the disease below the age of 15. Men are more commonly affected. The disease is essentially sporadic and confined to one upper limb, but in a very few the other upper limb may become affected later, though to a lesser degree. The patient presents with wasting and weakness of one hand and forearm, often accompanied by a fine tremor, which seems to disturb him as much as the weakness. The proximal muscles may, infrequently, be affected, but never without the distal. Fasciculations, minipolymyoclonus of the outstretched hand, and increase in weakness with appearance of pain and stiffness on exposure to cold have been observed. The tendon reflexes in the affected limb are depressed. The plantars always remain flexor. The atrophy may worsen slowly over two to four years leaving behind a permanent but stable disability.

Similar isolated affection of the lower limb has been reported by Mohan and Virmani (1982), Gourie-Devi (1984) and Gourie-Devi et al (1987). This does not appear to be common. The number of patients with lower limb affectation described by Gourie-Devi was probably inflated as she included some patients with the wasted leg syndrome mentioned below, which according to Chopra et al (1987), on very reasonable grounds, is a separate entity.

Electromyography (Singh et al 1980, Gourie-Devi 1984) has shown loss of motor units, increased polyphasic potentials and fasciculations indicating

denervation of muscles. With normal motor and sensory conduction velocities,the disease appears to be in the anterior horn cells. Muscle and nerve biopsy supported the EMG findings of neurogenic atrophy.

The wasted leg syndrome: This type of amyotrophy also mainly affects men between 10 to 30 years of age, but is confined to one lower limb. There is some evidence that the majority of patients are engaged in hard manual labour. It is unlike monomelic amyotrophy, non-progressive and often discovered accidentally by the patient or pointed out by another person. There is almost always no complaint of weakness. The whole leg is usually thin, though in some, the calf or quadriceps may be exclusively affected. The power in the leg is almost always normal. Deep tendon reflexes are preserved and occasionally depressed. Often there is no disability, limp or shortening of the limb. Electromyo-graphy, nerve conduction study and muscle biopsy point to a neurogenic muscular atrophy. No autopsy has been possible. It is assumed that these patients had subclinical or undetected mild poliomyelitis in childhood. Some doubts have been raised on this guess (Wadia 1987) because poliomyelitis is rarely confined clinically and more importantly electromyographically to one limb, and whilst poliomyelitis is still rampant in India, the wasted leg syndrome is rare. Though noted by neurologists all over the country for many years, the largest, well worked-up series of 62 patients seen over 14 years, is from the Postgraduate Institute of Medical Education and Research, Chandigarh (Chopra et al 1987).

Though significant clinical differences between the two types of single-limb atrophy exist, there is controversy (Chopra et al 1987, Gourie-Devi et al 1987) whether these two are aetiologically different conditions

Epilepsy

As anywhere, patients with epilepsy make up the largest group referred to a neurologist in India after those with a headache. The ICMR set up a large five centre collaborative study whose preliminary report gives much useful information. The prevalence of this disease has not been worked out on a national scale, but three carefully designed epidemiological studies based more in rural and semi-urban areas than capital cities show somewhat different prevalence rates. Mathai (1971) reported an overall prevalence rate of afebrile, recurrent and active epilepsy as 9 per 1,000 population from Vellore town and the adjacent villages in the south Indian state of Tamil Nadu, a figure higher than that reported from developed countries, as also from the two other Indian studies from Ballabgarh in north India, and from Gowribidanur in Karnataka, south India. In the former study,the prevalence rate was found to be 4 and in the latter 4.6 per 1,000 population. Gourie-Devi (1987) found a difference between the semi-urban and rural populations: 2.5 per 1,000 in the semi-urban and 5.6 in the rural areas.

Incidence apart, attention needs to be drawn to two indigenous conditions which have been of special interest to Indian neurologists namely 1) a reflexly excited epilepsy, called hot water epilepsy and 2) the management of patients with a recent attack of focal or generalized convulsion in whom a single ring or disc enhancing lesion appears on the CT scan.

Hot water epilepsy (HWE): Though this reflexly excited epilepsy was first reported by Allen (1945) from New Zealand, and later from other parts of the world (Satishchandra et al 1988) as case reports, attention to its greater frequency amongst south Indians was focused first by Mani et al (1968,1972) and later by Subrahmanyam (1972). A recent large series (Satishchandra et al (1988) from Bangalore (south India) reporting 279 cases gathered between 1980 and 1983 sums up the information admirably. Epileptic seizures are precipitated when hot water is poured rapidly over the head or,less commonly,the trunk from a vessel as is the usual bathing practice. The attacks occur towards the end of the bath (Mani and Rangan 1988). In some, cold water can also reflexly precipitate the fit. The age at onset may be as wide apart as 2 months and 58 years, though 50% had their first attack before age 10 years and nearly 80% before age 20 years, males being predominant (Satishchandra et al 1988). The attacks continue for many years and the mean duration of symptoms was 5.1 years. The seizures are of the simple or complex partial variety, but generalized tonic seizures also occur. Patients with hot water epilepsy made up nearly 4.4 percent of all those with complex partial and generalized tonic-clonic seizures seen by Satishchandra et al (1988). A history of non-reflex (spontaneous) or even hot water epilepsy can be obtained in some patients and relatives. Treatment is effective in a good majority and the drugs used are phenobarbitone, phenytoin, carbamazepine and primidone.

It is interesting that another variety of reflex epilepsy that is precipitated by eating is not uncommon amongst the rice-eating south Indians and Sri Lankans it being clearly more frequent than amongst other races.

Recent seizure and 'ring' or 'disc' enhancing lesion on CT Scan : With the advent of the new imaging techniques, a previously unobserved lesion in the brain following an epileptic seizure has been reported, raising many questions. (Fig.11) Air encephalography or angiography were not refined enough to show small parenchymal lesions related to the fit. The patient was labelled as suffering from idiopathic epilepsy and symptomatically treated. What we are now observing on the CT scan is the presence of a low attenuation area in the territory from which the focal seizure is suspected to have risen. It enhances as a 'ring' or a 'disc' after administration of contrast . Such an image is often seen after the first attack of focal seizure in a patient who has not had any disease in the past, no other symptoms or signs, and no family history of epilepsy. It may even appear in those, who have had several such attacks over say a year, when a CT is performed for the first time after the last attack.

The questions raised are :

1. In this 'ring enhancing lesion the cause or effect of the focal seizure?
2. If it is the cause, what is its etiology?
3. If it is the effect, why is a ring lesion not seen more often with focal epilepsy or status epilepticus from which vast numbers are affected?
4. Why does such a lesion disappear, often within weeks by itself with only anticonvulsant therapy in some patients?
5. Why does it persist in others?
6. Why has it been more frequently seen amongst Indians or at least reported most frequently from India, when focal epilepsy is seen world wide. A new case or two in a month would not be uncommon in a busy Indian neurologist's or neurosurgeon's practice (Wadia RS et al 1988).

A spate of reports have emerged from India in the last few years (Wani et al 1981, Goulatia et al 1987, Sethi et al 1985, Wadia RS et al 1987,1988, Chandy and Rajshekhar 1988, Bhatia and Tandon 1988) and some tentative answers given. As tuberculosis still persists in India and some patients had associated tuberculosis, the initial response of Indian neurologists and neurosurgeons was to call such a lesion a microtuberculoma and start antituberculous therapy. It soon became obvious as more evidence was gathered and follow-up and biopsy of such lesions made that there was nothing specific about this image. A variety of disorders such as focal encephalitis, an isolated cysticercous and a pyogenic microabscess were unearthed. Recently Katrak (personal communication 1988) was surprised to find on biopsy that such a lesion was due to a larval granuloma of spirometra Mansoni, a tape worm of cats and dogs (sparganosis). Bhatia and Tandon (1989) have come across identical lesions caused by histoplasmosis, blastomycosis, sarcoidosis, vascular disorder and infectious vasculitis. Debate also continues on whether such an image can be caused simply by local hypervascularity or metabolic changes following a focal seizure, especially as some of these lesions disappear without any specific treatment bar anticonvulsants.

Bhatia and Tandon have evaluated the position admirably and set out guidelines for management of such a patient with focal epilepsy. (Fig.12)P

Painful ophthalmoplegia

This disease variously called as the Tolosa Hunt syndrome, *superior orbital fissure syndrome, Collier's syndrome or oculomotor neuritis* is frequently seen by neurologists and ophthalmologists in India. Mathew and Chandy (1970) and Mathew (1973) gave a comprehensive account of their experience in Vellore, south India, but reports emerged simultaneously from other areas of the country (Krishna 1972, Wadia 1973) as well as from Ceylon (Ratnavale 1968) and Thailand (Steele and Vasuvet 1970) promoting the impression that there was a common disease in this part of the world.

The onset of ophthalmoplegia is acute and is accompanied or immediately preceded by severe pain in and around the orbit or by hemicrania. According to Mathew (1973), the pain may antecede the ophthalmoplegia by weeks. The third cranial nerve is commonly paralysed, followed by the sixth and fourth. A total ophthalmoplegia is not uncommon. The pupillary reflex remains unaffected in the majority. Low fever and malaise are often present. The disease is usually self-limiting, the pain subsiding in a few days, though the paralysis takes longer to recover. Corticosteroids often give dramatic relief from pain but do not hasten recovery of power.

Recurrent attacks,at times over many years, involving the same oculomotor nerve or others of the same or opposite side can occur. Nearly half of the patients complain of sensory disturbance in the ophthalmic division of the fifth nerve, and the optic, facial and hypoglossal nerves have been occasionally known to be affected in the same attack or later. This has led some authors to designate this syndrome as recurrent cranial polyneuritis, although Mathew (1973) believes that the two are different.

The cerebrospinal fluid is usually normal but Krishna (1972) found raised protein and cells in a third of his patients. Most laboratory tests have yielded negative results but the ESR can be high in some patients. Mathew reported finding microfilaria Bancrofti in the blood of five out of 14 patients in whom it was looked for, a finding not confirmed by anyone else. He also mentioned positive Rosewaller and RA tests and found LE cells in a few of his patients.

Various theories regarding the causation have been propounded, but none proven so far. Wadia (1973) has felt that as some similarity exists between Bell's palsy and this disease, a common etiology may be found.

The differential diagnosis between this condition, diabetic oculomotor palsy and an intracranial aneurysm arises when a patient with an acute painful third nerve palsy is seen. The sparing of the pupil is believed to be an important diagnostic sign of painful ophthalmo-plegia, as opposed to an aneurysm. CT and angiography may be needed to make sure of the diagnosis.

Eale's Disease

Though Silfverskiold (1947) and White (1961) mentioned the involvement of the nervous system in Eale's disease, recent attention has been drawn to a greater number of such cases from India (Singhal and Dastur 1976, Singhal 1987) where the ophthalmic manifestation of the disease in the form of visual impairment, periphlebitis, retinal haemorrhages, neovascular formation and retinitis proliferans are not uncommon.

The patients were all male, and the majority presented with acute or

subacute paraplegia, urinary retention and sensory loss from a lesion in the upper dorsal cord. Occasionally cervical cord, brainstem and still more rarely cerebral symptoms and signs were seen. Remissions and relapses occurred but on the whole disability was permanent and death followed complications of decubitus and urinary infection. Pleocytosis and elevated proteins were reported in the acute phase of the illness. The neurological disease usually appeared after an interval of weeks, but also extended to some years. Differential diagnosis includes multiple sclerosis and chronic spinal meningitis but the tell-tale eye disease is diagnostic.

Pathological examination of one of the patients (Dastur and Singhal 1976) showed extensive vasculopathy, with various stages of venous change extending from proliferation and dilatation to haemorrhage, or to thickening with hyalinisation. They saw perivenular demyelination with relative preservation of axons but no inflammation. They postulated that the condition represents a separate syndrome of venopathy with episodic demyelinating retino-encephalo-myelopathy, arising through a hypersensitivity mechanism.

Tropical Spastic Paraplegia (TSP)

This condition which has aroused so much current interest has been noticed in India for more than two decades. Among the first to describe it was Mani from South India (Mani et al 1969, Mani 1973, Richardson et al 1989). He saw 45 patients who formed a group apart, over a period of 5 years amongst 249 paraplegics. Males were predominant.

The dominant signs were a disabling paraplegia with striking spasticity, milder affection of the upper limbs in about half, distal paraesthesiae, impaired vibration and postural sense in the feet, and disorder of micturition. Careful inquiry into their diet, habits, family background and various investigations revealed no clues as to etiology. In a few patients, the CSF showed increased proteins and cells. Autopsies were done in two atypical cases, one showing diffuse chronic meningomyelo-pathy, but Mani himself expressed reservations about the significance of these findings.

Somewhat similar cases have been reported in clusters from other equatorial regions of Africa, South America, Jamaica, Seychelles and interestingly also from Japan (Roman et al 1989). In these cases an association with a virus (HTLV-1) has been established, whilst in the Indian cases, so far it has been not.

Patients with a less well defined picture of chronic progressive myelopathy of unknown etiology affecting essentially the thoracic cord have been seen by neurologists all over India (Wadia 1973, Singhal 1984) for well nigh a quarter of a century, but it is uncertain whether they belong to the same nosological category as TSP. Singhal (1984) has even wondered if long-

term follow-up and more sophisticated and extensive investigations would reveal that some of these patients and those with acute relapsing or single-episode myelopathy would be suffering from multiple sclerosis.

Multiple Sclerosis

Whereas all that has been said before relates to diseases common amongst Indians, the outstanding example of what is not common is multiple sclerosis (MS). A dreaded disease in the west, it has little bite so far in India. Recent reviews (Jain and Maheshwari 1985, Singhal 1987) appear to have covered most of the Indian literature since Bharucha and Umerji's (1961) analysis of 151 cases from 10 centres. These reviews mention MS as "rare" and stress some differences between the manifestations of the disease amongst Indians and the Caucasians of the West.

Jain and Maheshwari (1985) claiming to review "the entire literature on MS in the Indian subcontinent over the past 3 decades" mentioned that MS constituted only 0.05% of all neurological admissions to hospitals (large teaching) in south India, and 1.58% in the north, perhaps suggesting that the disease may be a little commoner away from the equator. Singhal (1987) calculated the prevalence rate based on a rough estimate as 0.17 (Madras, south India),0.61 (Vellore, south India) and 1.33 (Bombay, west India) per 100,000 population. Even allowing for statistical pitfalls these figures are very revealing. Supportive of this is a study of MS amongst immigrants in greater London (Dean et al 1976) which included Indians and Pakistanis, which revealed an extremely low incidence amongst adults (first generation immigrants) similar to that in the country of origin.

Both reviewers have also stated that MS manifests itself somewhat differently in Indians as opposed to Caucasians and was similar to that seen amongst other Asians, a view subscribed to also by Kuroiwa of Japan (1982). There was a higher incidence of optic nerve involvement both at the onset and during the course of the disease and the acute variety of Devic's disease was proportionately more predominant. Impaired cutaneous sensibility upto a level on the trunk and relative paucity of cerebellar signs were remarked on. Poser (1989) after an exhaustive and critical global review of MS has contested this view stating that "one should seriously question the validity of the 'Asian form' of the illness" because of failure to adhere to recognized diagnostic criteria, and inclusion of 'possible' cases and other demyelinating diseases. Singhal (1987) believed that definite MS was more common in the higher socio-economic group whilst Devic's disease affected the poorer more frequently.

MS has been reported from all parts of India with its variegated ethnicity, but Wadia (Singhal and Wadia 1975, Wadia 1986) had long felt that there was a clearly greater prevalence amongst the tiny, distinctive insular community of Parsis (Zorastrians) who number less than a 100,000 in India,

most residing in Bombay. This impression has recently been supported by two careful prevalence studies in that community (Bharucha et al 1988, Wadia and Bhatia 1989) and Singhal's (1987) figures of seven Parsis amongst the 127 patients drawn from a huge population in and around Bombay.

Bharucha et al (1988) carried out a door-to-door survey of 14,010 Parsis covering as much as a fifth of the community in Bombay, and found three definite cases of MS. They calculated the prevalence rate to be 21 per 100,000. Similarly Wadia and Bhatia (1989) reexamined all traceable Parsi patients in the two neighbouring cities of Bombay and Pune and found as many as 15 with definite MS on prevalence day out of a total population of 53,452, of which the majority (50,053) were in Bombay, giving a prevalence rate of 25 per 100,000 for that city. They argued that even allowing for observer bias, small numbers, low birth rates, greater longevity the prevalence rate was too high in this small isolate than amongst Indians generally, to be lightly brushed aside as a statistical aberration. Unlike the observations of Jain and Maheshwari (1985) and Singhal (1987), the manifestation of MS in Parsis was no different from that seen amongst Caucasians. The explanation for the contrast in prevalence in this isolate must be found in their history of ancient emigration from amongst the Caucasians of Europe, their distinctive life style, food habits, culture and their genetic profile as evidenced by higher incidence of G6PD deficiency and the prevalence of Ry (CDE) genes.

Finally, the low incidence of MS amongst Indians generally, must lie in the prevailing environmental and genetic factors, which are yet to be analysed. Wadia et al (1980,1981) and Singhal (1982) found no excess of the histocompatibility antigens HLA A3 and HLA B7 amongst Indian MS patients as observed amongst Caucasians. Wadia et al (1980,1981) and Trikannad et al (1982) have stressed a significant association of HLA -B12 antigen and MS amongst Indians, an observation not confirmed by Singhal (1982) or any others.

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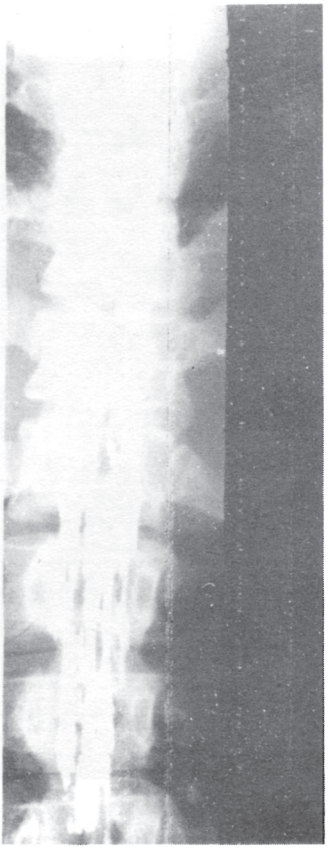

Fig. 1 : A myelogram showing an irregular block of the myodil column in the lower thoracic cord. The myodil column itself is ragged.

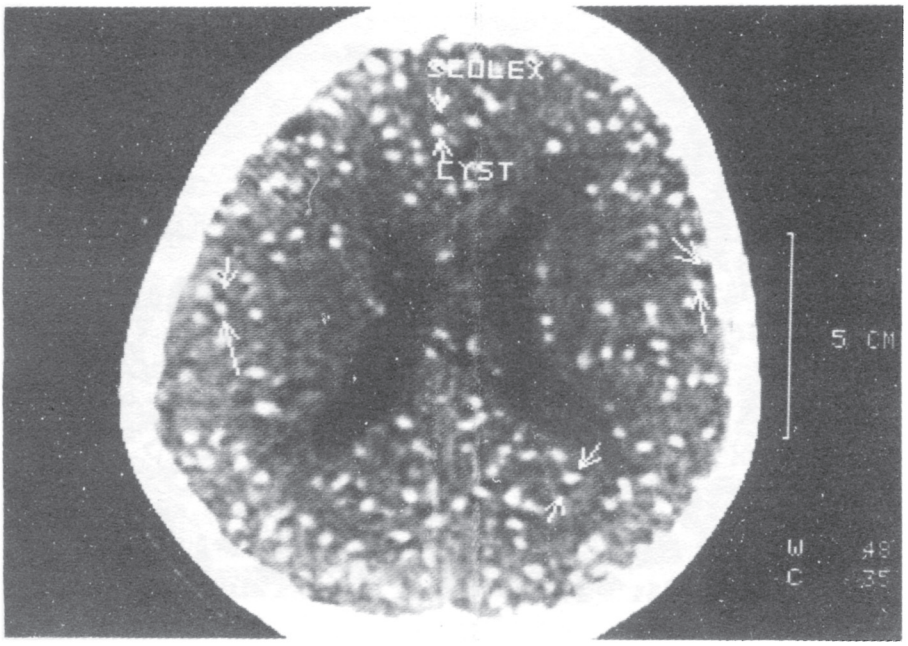

Fig. 2 : An unenhanced CT scan of the brain showing a vast number of living cysticerci giving "a sky on a starry night" effect. The scolex and cyst are marked by arrows.

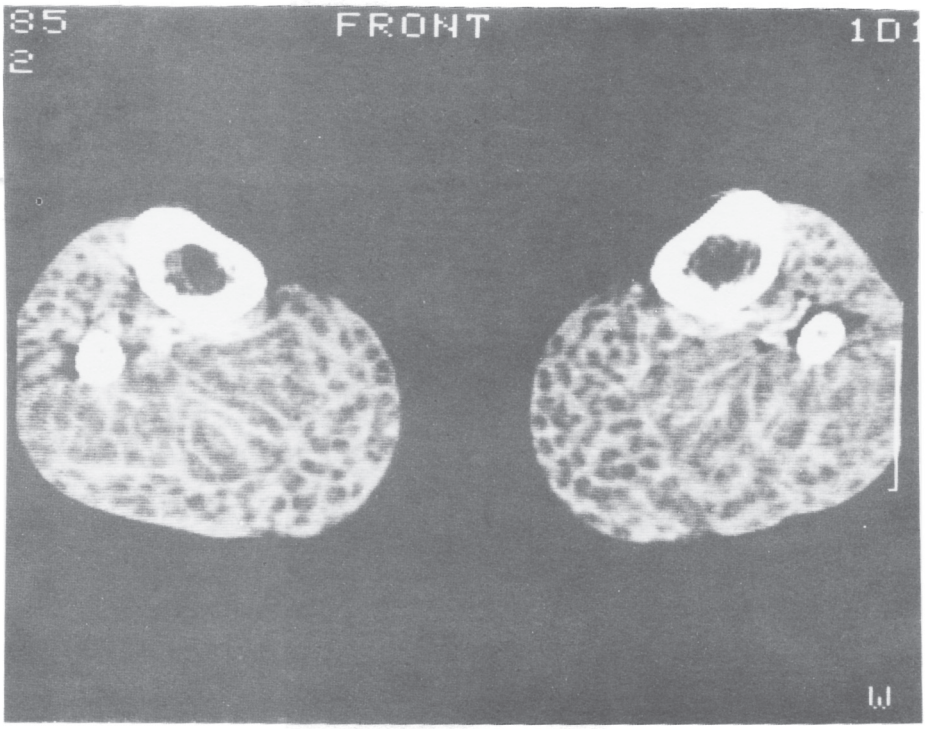

Fig. 3 : Pre-contrast CT scan of both calves infiltrated with a large number of cysticerci giving a "honey-comb" effect. The scolices within the cyst cannot be easily appreciated here but become clear on magnification.

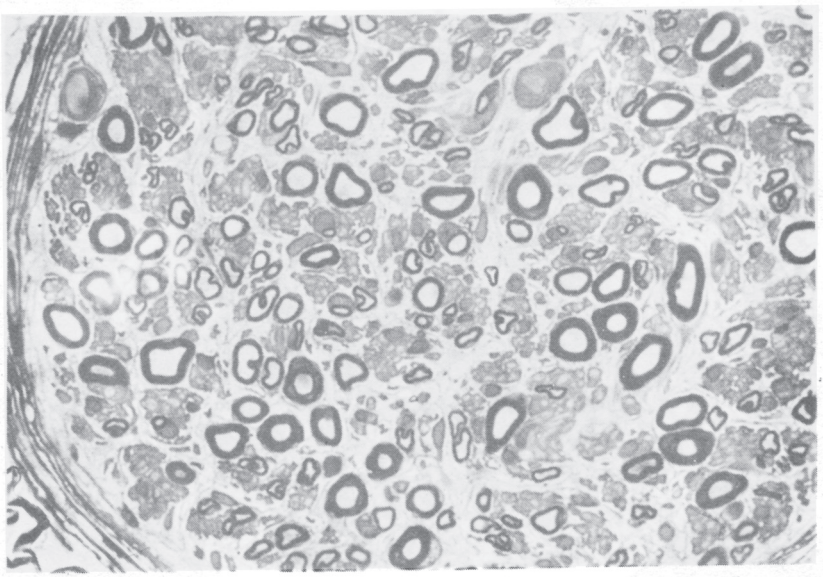

Fig. 4 : Semi-thin sections of the sural nerve of a patient with OPCA and slow eye movements showing gross fall-out of myelinated fibres especially the large ones. (Toluidene Blue X530).

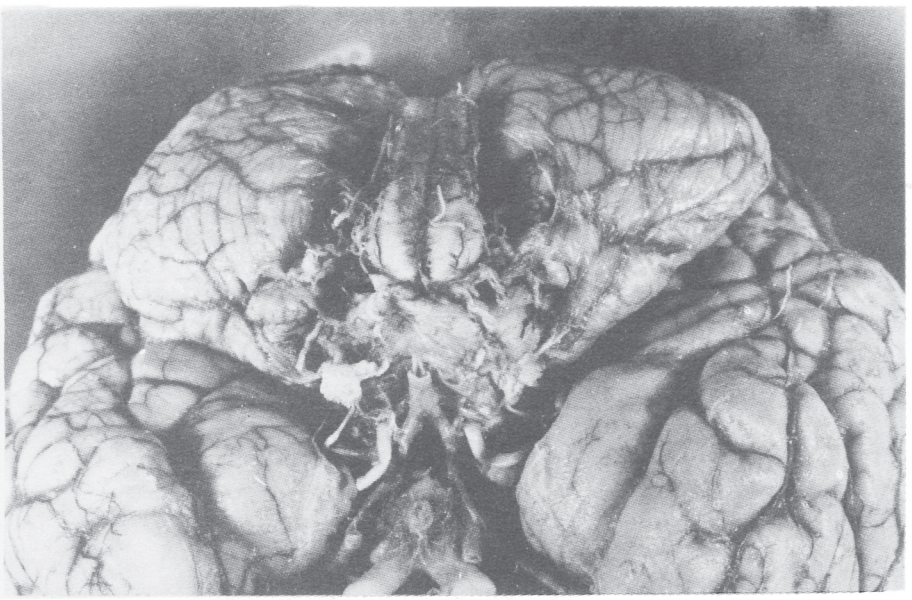

Fig. 5 : A magnified view of the base of the brain of a patient with OPCA and slow eye movements showing remarkable atrophy.

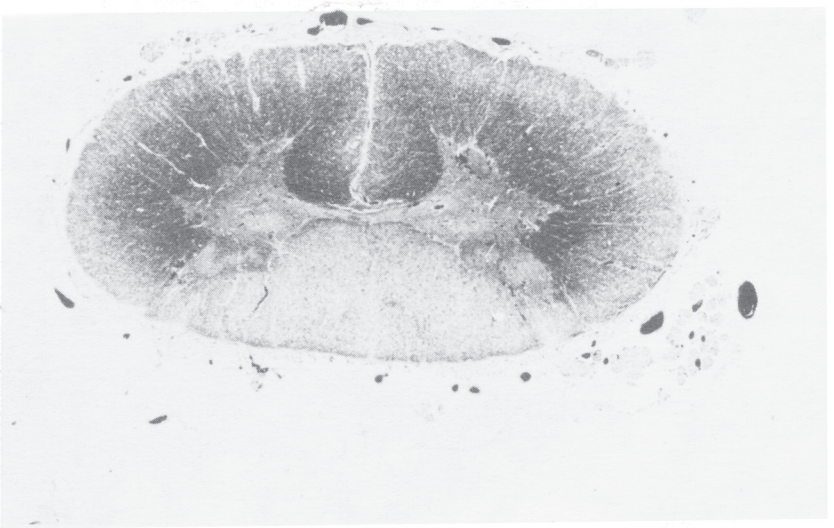

Fig. 6 : A myelin stained section of the lumbar cord of the same patient showing gross degeneration of the posterior columns.

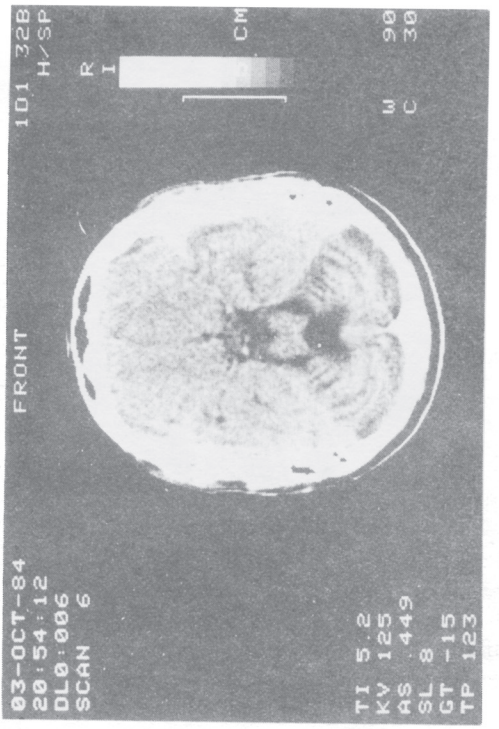

Fig. 7 : Axial CT section through upper pons revealing widened cerebellar folia from cerebellar atrophy, enlarged fourth ventricle, and atrophy of the brachium conjunctivum and lateral surface of the pons (causing a "molar tooth" effect) seen in this disease.

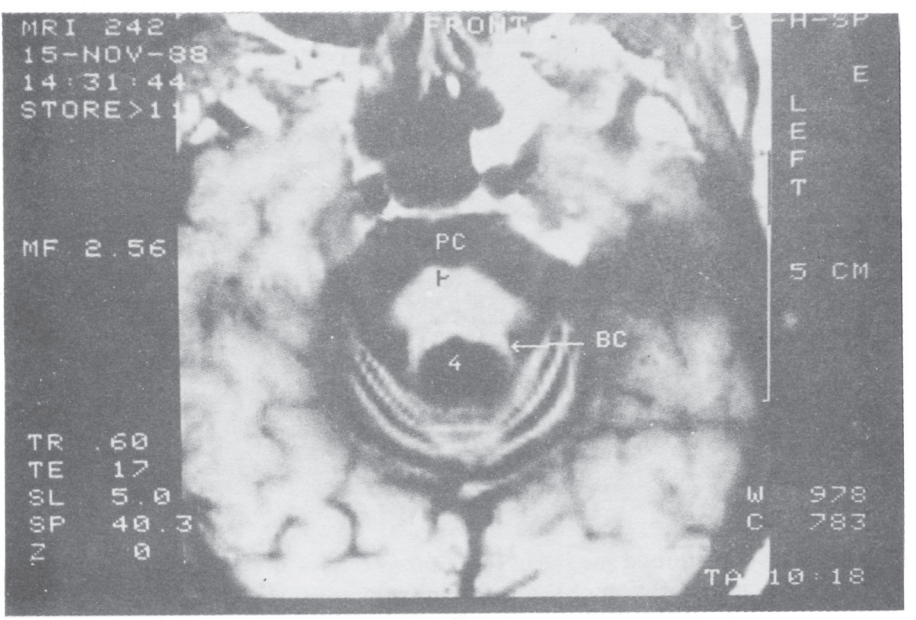

Fig. 8 : An axial section of the MRI of the same patient showing atrophy of the cerebellar vermis, brachium conjunctivum (BC) and pons (P). The pontine cistern (PC) is considerably enlarged and the fourth ventricle (4) is ballooned.

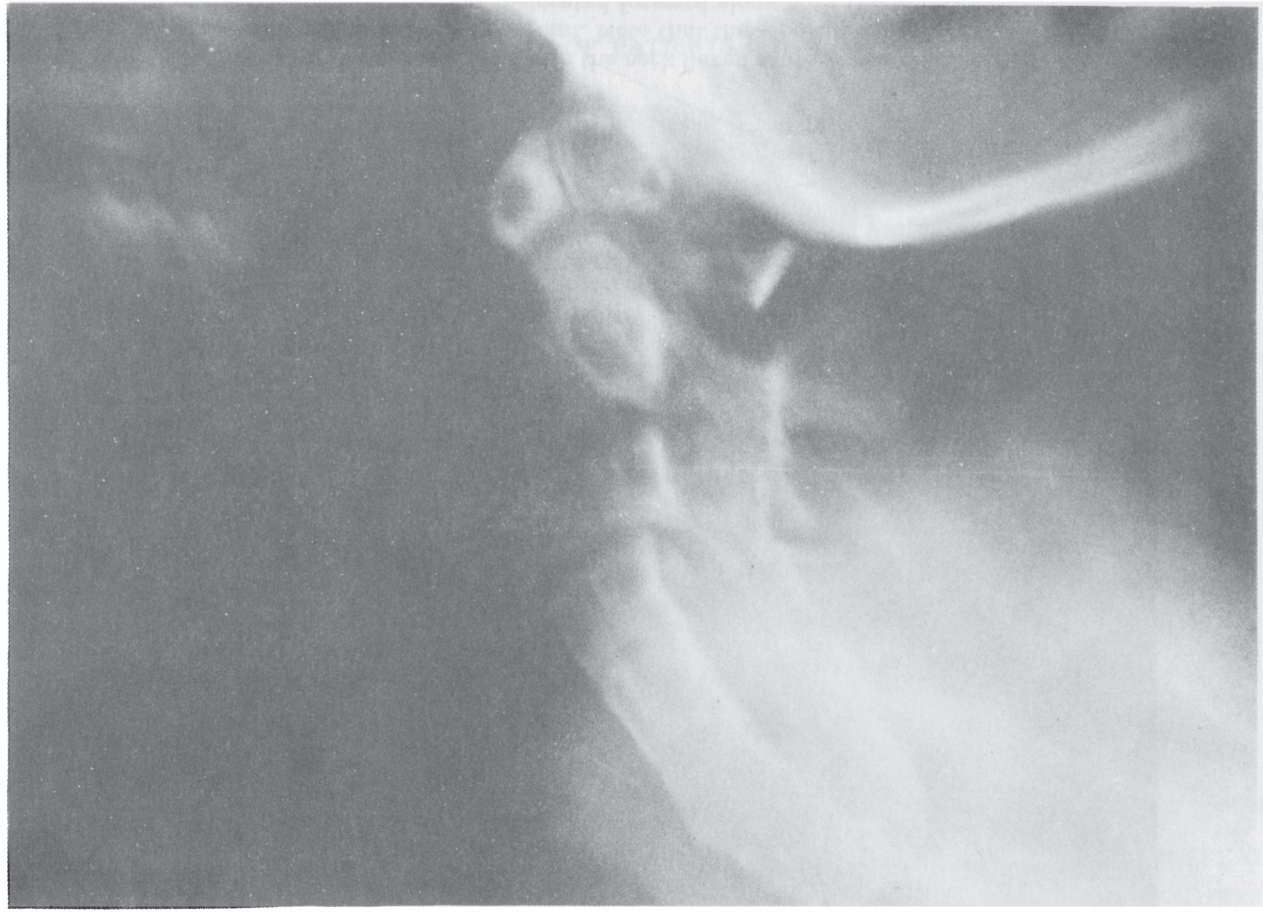

Fig. 9a : Lateral tomogram of the cervical spine in the neutral position.

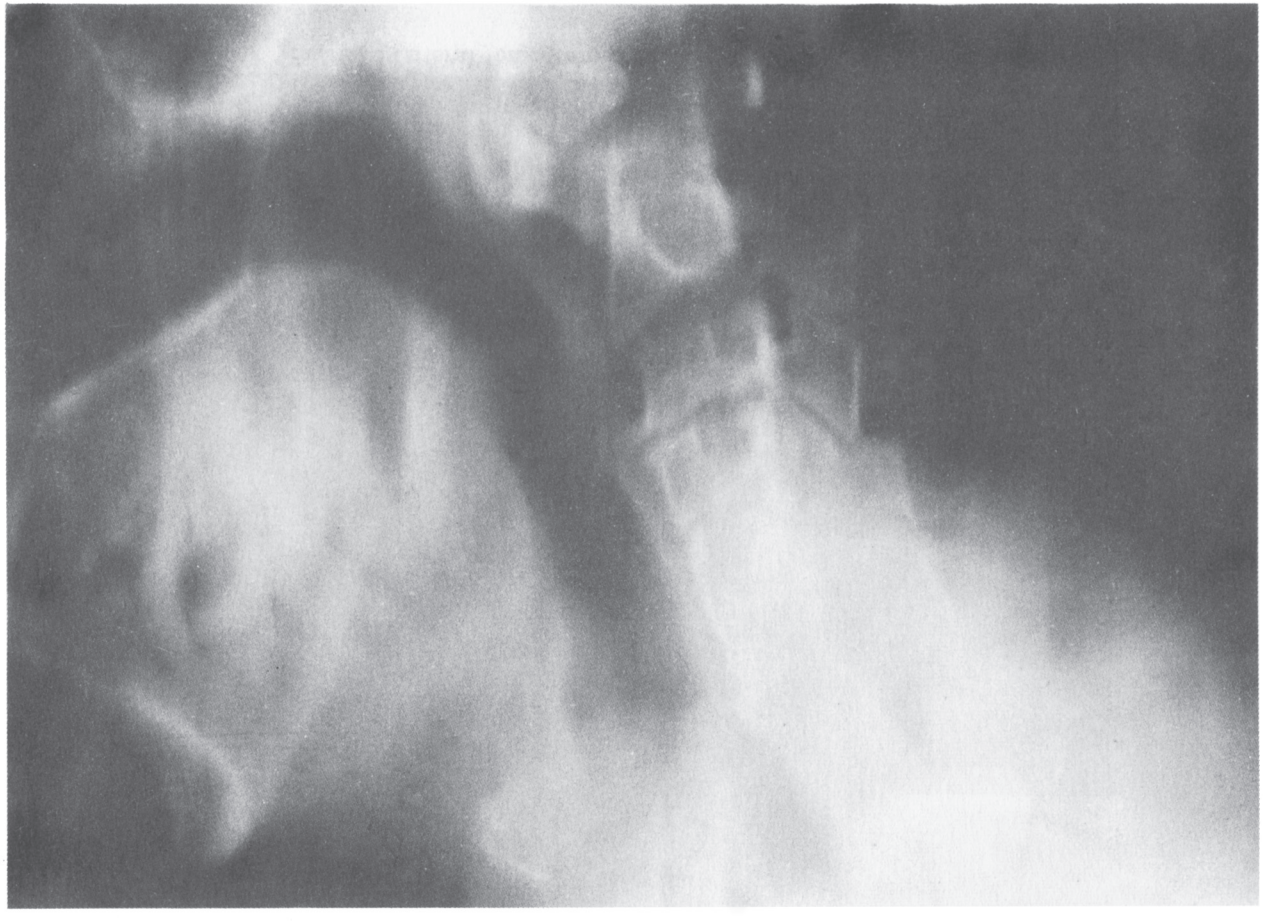

Fig. 9b : Tomogram of the same patient with the neck flexed showing remarkable dislocation of the atlanto-axial joint. Note that the separate apical part of the odontoid process has dislocated forward along with the anterior arch of the atlas.

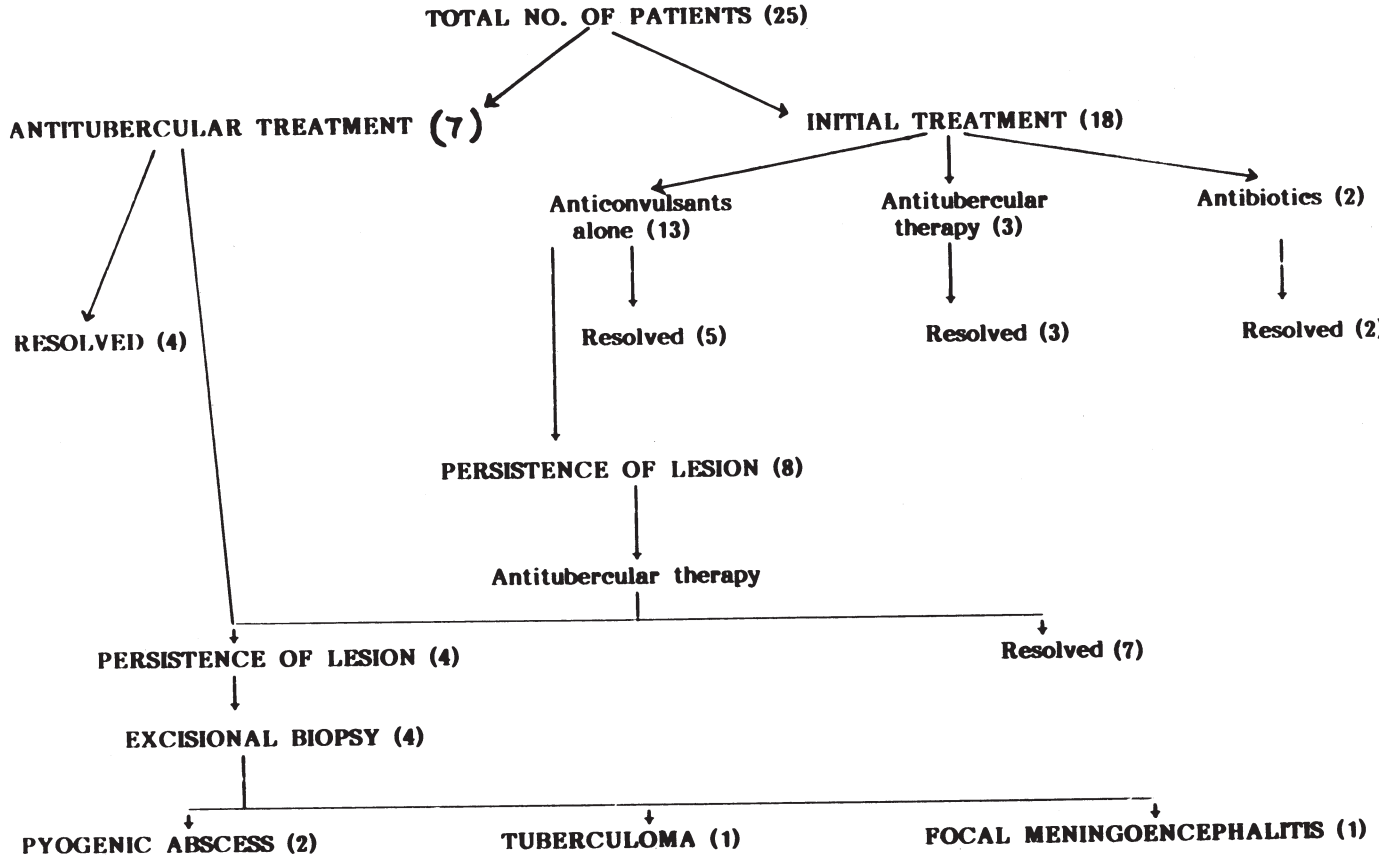

Fig. 12 : Protocol suggested by Bhatia and Tandon for the management of a patient with focal seizure and a 'ring' or 'disc' enhancing lesion on the CT scan.

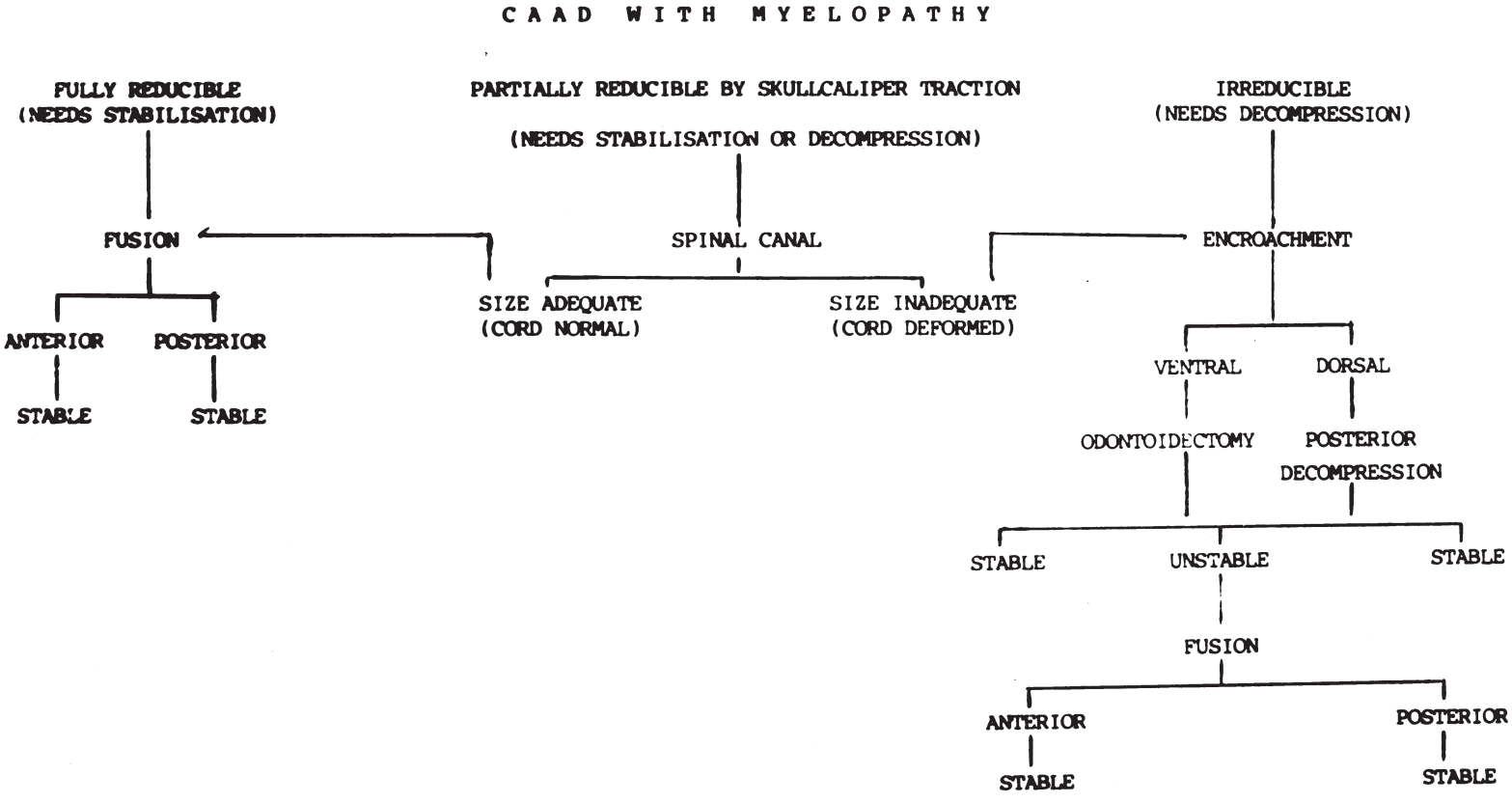

Fig. 10 : An algorithm approach to surgical treatment of congenital atlanto-axial dislocation.

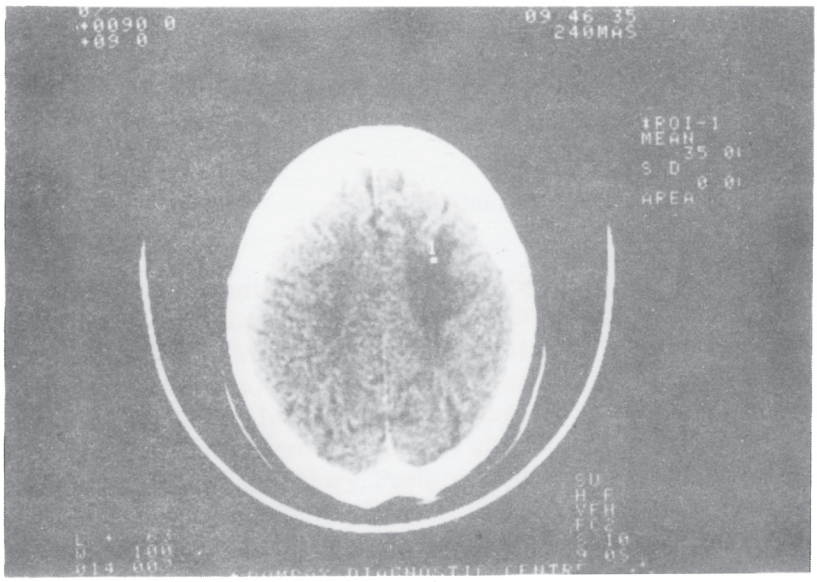

Fig. 11a : Pre contrast axial CT scan of a patient showing a low attenuation area (oedema) in the right fronto-motor region following a recent focal epileptic seizure in the left limb.

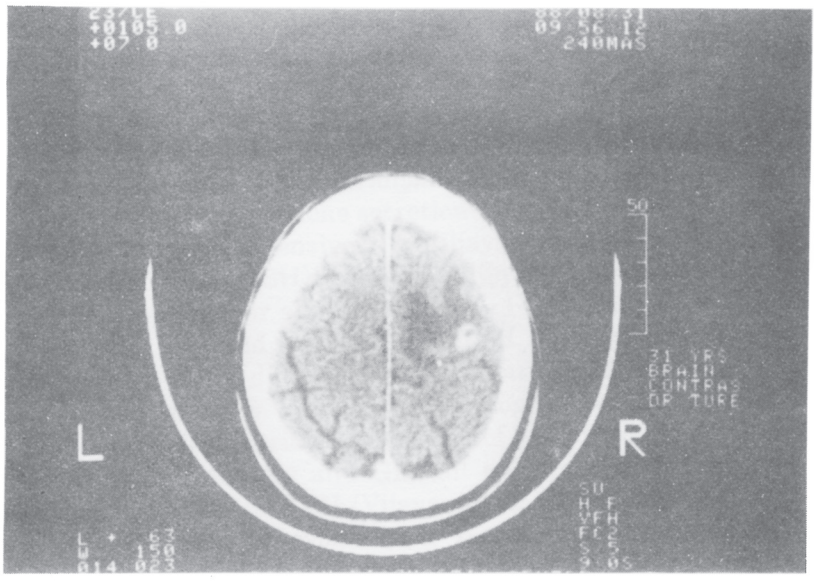

Fig. 11b : Appearance of a ring lesion in the same area after administration of contrast.

Neuroendocrinology

R.J. Dash

Several Indian scientists have been engaged in basic and clinical research in neuroendocrinology since Professor B K Anand's pioneering work in the 1950s on hypothalamic control of food intake (Anand et al 1951). Later Anand and Bajaj studied hypothalamic regulation of the secretion of insulin (Bajaj et al 1974). Investigators at the Department of Life Sciences, University of Hyderabad (Vijayan et al 1976,1978,1979,1987) and at the Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh (Dash et al 1985, Kaul et al 1972,Rastogi et al 1973,1974,1976, Siali 1984) have carried out in-depth basic and clinical studies in hypothalamic regulation of pituitary-target gland axis. Significant contributions have also been made by Moudgal et al at the Department of Biochemistry, Indian Institute of Science, Bangalore; Sheth et al (1982, 1984) and Anand Kumar (1986) at the Institute for Research in Reproduction, Bombay on hypothalamic peptides in contraception. Professor Udupa and his colleagues at the Institute of Medical Sciences, Varanasi are studying the neuroendocrinology of adaptation to stress. Some important contributions made by these investigators are summarised below.

Control of hypothalamic regulation of pituitary hormone synthesis and release.A number of neurotransmitters have been studied to elicit their effect on pituitary hormone secretions. Experimental studies in rats have been undertaken extensively by Vijayan et al to elucidate the effect of GABA on GH and TSH secretions (Vijayan et al 1968). Both intravenous and intraventricular administration of GABA induced a dose-dependant increase in GH and a decrease in TSH. However, as bicullin, a GABA antagonist, alone did not alter circulating GH and TSH, GABA was considered unlikely to be the physiological regulator of GH and TSH secretions. Intraventricular injections of VIP increased LH (in low dosage), PRL (in high dosage) and GH (all dose levels), but had no effect on circulating FSH and TSH (Vijayan et al 1979a). Incubation of pituitary with VIP fialed to evoke such responses, suggesting hypothalamic involvement in VIP induced alterations in pituitary hormone secretion. These observers also noted a sex influence on CCK induced increase in PRL secretion. This was evident in females only. Concomitant administration of proglumide, the CCK antagonist abolished the effect of CCK on PRL secretion. Following careful incubation studies with tissues from different parts of the brain, the site of action of CCK was localised to the hypothalamus (Vijayan et al 1987).

Another neurotransmitter regulating hypothalamus is neurotresin. It decreased circulating levels of PRL when given via the 3rd ventricle in ovariectomized rats. It had no effect on pituitary tissue in-vitro (Vijayan et al 1979b). Substance-P increased circulating LH and PRL, acting apparently on the hypothalamus and the pituitary (Vijayan et al 1979b). Intraventricular administration of serotonin or quipazine (a 5HT receptor stimulant) led to a dose related increase in PRL and decrease in TSH. These effects could be abolished by simultaneous administration of cyproheptadine, a serotonin antagonist (Krulich et al 1979). Intraventricular dopamine (DA) or piribidil (a DA receptor agonist) increased plasma GH but decreased TSH. Epinephrine and norepinephrine increased both GH and TSH. These observations suggest TSH supression by the central dopaminergic system and GH stimulation by dopaminergic, adrenergic and noradrenergic systems, presumably by stimulating the release of growth hormone releasing hormone from the hypothalamus (Kaul et al 1972) .

Modulation of secretions of anterior pituitary hormones by opioids and histaminergic systems have been studied systematically in man. Administration of morphine sulphate (15 mg) intravenously to healthy men induced a rise in GH and PRL but fall in gonadotropins and ACTH (and cortisol). In acromegalics too, a rise in GH and fall in cortisol were noted (Dash and Sethi - unpublished). Intravenous cimetidine (a H2 receptor antagonist) administered to normal subjects resulted in significant increase in PRL, but showed no effect on circulating cortisol, TSH, FSH and GH. This suggests a possible role of histamine-H2-receptors in modulating PRL secretion in man (Kaul et al 1972).

Extensive clinical studies have been carried out using hypothalamic releasing hormones and insulin hypoglycemia to evaluate alterations in hypothalamopituitary-target gland axis in health and disease. Circadian variations in pituitary responses to GnRH-TRH-insulin hypoglycemia were noted for GH,PRL and cortisol but not for TSH, LH and FSH (Rastogi et al 1976) . Thus, the circadian variations are evident when the provocative stimuli act through the central or hypothalamic mechanisms. TSH response to TRH was higher in women than in men, suggesting estradiol modulation of TSH-TRH response (Rastogi et al 1973). Short term ethinyl estradiol pre-treatment to men, failed to provoke TSH response to TRH comparable to that in women (Rastogi et al 1974). Sleep related alterations in GH and PRL secretions were noted in acromegalics and in patients with large pituitary prolactinomas. Normal sleep was restored in the majority following effective surgery (Dash et al unpublished). Higher LH and FSH responses to GnRH increased progressively from pre-puberty to menopause (Dash et al 1985). GnRh response studies were found extremely useful in diagnoses of central precocious puberty and hypogonadotropic hypogonadism (Dash et al unpublished).

LH, FSH and PRL responses to GnRH-TRH were studied in amenorrhoea-

galactorrhoea due to pituitary prolactinomas and in female rhesus monkeys made hyperprolactinemic by sulpiride. The appropriate responses were blunted in humans. However, in the hyperprolactinemic monkeys the LH responses were either blunted or normal but the FSH responses were exaggerated. Administration of clomiphene citrate established the normal gonadotropins-GNRH responses and ovulation in 50 of the monkeys (Sialy 1984).

Hypothalamic Peptides in Contraceptive Research :In the recent past, newer approaches to contraception have been developed based on LHRH and its analogues. Contraception has been achieved in animals with GnRH analogues and with monoclonal antibodies against the dominant antigenic determinants of GnRH decapeptide. Various carrier proteins have been used for linkage with the GnRH molecule to generate antibodies. These include bovine or human serum albumin, thyroglobulin, tetanus toxoid human lactoferrin etc. (Talwar 1985). The antibodies so generated have also been utilized to study the mechanism of action of hormones including immuno-localisation of the hormone in the synthesizing cell and the hormone receptor complex on the target cells. Anti GnRH antibodies not only blocks gonadotropin secretion from pituitary but also decreases the hCG production from placenta (Talwar 1985). GnRH and its analogues also affect accessory reproductive organs. They reduce ornithine decarboxylase (ODC) and glucosamine-6-phosphate synthase activities and thereby inhibit cell growth and proliferation (Reddy et al 1985).Inhibin, the Sertoli cell factor has been extensively studied at the Institute of Research in Reproduction, Bombay. It has been purified, sequenced and cloned by Sheth et al (Sheth et al 1984). It has now been re-defined as complex of glycoprotein subunits, alpha and beta. Inhibin subunits have the unique ability to form homo or hetero-dimers with divergent biological activities (McLachlan et al 1988).

Two distinct inhibin like proteins have been isolated from human seminal plasma (hsp) of which the glycosylated fraction, a 19 KD prostatic protein has FSH supressing activity (Thakur et al 1978). This protein has been characterized as a 94 amino acid residue of which the 28 carboxy terminal aminoacid constitutes the bioactive site (Arbatti et al 1985). Sheth et al have reported a number of studies defining the control of pituitary FSH secretion by inhibin in vitro (Sheth et al 1982,1984).

Another distinct 35 amino acid protein has also been isolated from hsp which supresses GnRH stimulated FSH release in the whole mouse pituitary culture and also supresses serum FSH in castrated male rats (Ramasharma et al 1984). Using antiserum to inhibin 1-30, these investigators have also detected inhibin-immunoreactivity in hypothalamus and pituitary extracts (Ramakrishna et al 1984). Chronic administration of an ovine testicular inhibin was effective in supressing FSH in the castrate male monkeys, and in maintaining low FSH, decreased

spermatogenesis and infertility in intact male monkeys (Moudgal et al). CSF - a separate neuroendocrine system :In addition to the vascular and neural connections of hypothalamus and the median eminence, a neural channel linking the cerebral ventricles (and so the CSF) and the portal blood vessel of median eminence has been described (Anand Kumar 1986). The tanycytes in the ependyma of the median eminence have long basal processes extending from the 3rd ventricle to the portal vessels. The luminal surface of tanycytes undergo morphological changes depending on their exposure to steroids. They balloon out during preovulatory phase when exposed to estrogens or estrogen plus progesterone. They apparently transport substances from CSF to median eminence and vice-versa. Other groups of multipolar neurons ,(like the supra-ependymal neurons) send their axon terminals to other parts of the brain to make synaptic contacts with the luminal surface of other ependymal cells. The neuronal system may synchronize any endocrine signal perceived by the nerve cells and transmit it to ventricular ependymal cells. This neuronal system with its morphological response to hormones and a large variety of biologically active hormones in CSF form an important cellular and humoral pathway in neuroendocrine interaction (David et al 1974).

Hypothalamic regulation of food intake and glucose homeostasis :The role of hypothalamic dysfunction in the development of extreme obesity has been investigated. Lesions in lateral hypothalamus resulted in complete cessation of eating and death of the animal from starvation. Further experiments in rodents confirmed that the lateral hypothalamus is apparently important for facilitating feeding behaviour, whereas the ventro-medial hypothalamus exerts an inhibitory effect on this feeding centre by relating the behaviour as regards eating to the state of energy balance in the body (Kopelman 1988). Investigators have suggested a relationship between electrical activity from the hypothalamic centre and gastric contraction in hunger (Sharma et al 1961).

Several loci of hypothalamus and CNS have been implicated in control of carbohydrate metabolism. These include hypothalamus, floor of the fourth ventricle and the lower spinal cord (Anand et al 1951). Stereotactic electrical stimulation of lateral hypothalamus in monkeys led to increase in circulating GH, cortisol, blood glucose, free fatty acid and subsequently of serum insulin (Bajaj et al 1974).

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Neuro-ophthalmology

G. Natchiar

Neuro-ophthalmology, an offshoot of ophthalmology, has improved and refined diagnostic and therapeutic modalities for ailments of the visual apparatus of neurologic origin. The newer diagnostic aids such as CT and MRI Scans, visual evoked potentials, ERG and, in the west PET scans have greatly added to our knowledge.

A neuro-ophthalmology unit was established at the Government Ophthalmic Hospital, Madras in 1954. It functioned in conjunction with the department of neurosurgery at the Madras Medical College. The first full-fledged neuro-ophthalmic clinic in India was started in the Government Erskine Hospital, Madurai Medical College, Madurai in October 1965 by G. Venkataswamy. R. Krishnamoorthy, the then assistant professor of ophthalmology was in charge of the clinic from October 1965 to April 1969, when the author assumed the charge. Help and guidance came readily from M. Natarajan, the then professor of neurosurgery. His interest and enthusiasm have not waned even after his retirement in 1985.

In November 1974, the eye department of Government Erskine Hospital conducted a neuro-ophthalmic course, again the first of its kind in India. Residents and postgraduates from all over the country attended lectures and demonstrations by eminent teachers in ophthalmology and neurosciences.

A neuro-ophthalmic unit was established at the Aravind Eye Hospital and Postgraduate Institute of Ophthalmology, Madurai, in the year 1977. The unit has conducted neuro-ophthalmic courses and workshops in 1980,1985 and 1987.

Similar neuro-ophthalmic clinics are run by Rajendra Prasad Institute of Ophthalmic Sciences, AIIMS, New Delhi; Medical Research Foundation, Madras; and Joseph's Eye Hospital, Trichinopoly.

Some neuro-ophthalmic contributions are reviewed below.

Congenital Anomalies

Kulseshta and Chaabra's work on atypical arhinocephaly unilateralis with microphthalmos(1965), Singh and Menon's work on colobomatous dysplasia

of optic disc with homonymous field defects and epilepsy (1984) and the descriptions of duplication of optic papilla (Lamba et al 1987), retino cerebral angiomatosis (Gahlot et al), double levator palsy (Prem Prakash et al), primary optic atrophy associated with hereditary neurological disorders (Nair and Safarullah), orbital meningocoele (Kulseshta and Sharma, 1965) and craniostenosis (Bagchi 1967) are some contributions worth studying.

Traumatic Disorders

Misra et al (1987)'s report of a case of tension pneumocephalus following orbital roof fracture, that of contralateral optic nerve injury reported from Siliguri in north Bengal (1985) supplement Mathew et al's descriptions of the spectrum of ocular manifestations in head injury. The author has recently (1988) reviewed her experiences in the diagnosis and management of traumatic optic atrophy. The subject of direct optic nerve injury has been dealt with at length by Jain et al (1983).

Inflammatory/Infective disorders

Kulseshta et al (1960) evaluated the therapeutic effects of retrobulbar hydrocortisone in optic neuritis. Gahlot et al (1976) have reported on optic disc oedema secondary to chronic sinusitis. Dhir et al described orbitocranial aspergillosis. Swaminathan (1978) and Kalyanaraman have reported on ocular manifestations of tuberculosis of the central nervous system. Clinical features were correlated with CAT Scan findings in 167 patients. Reddy et al (1973) have described bitemporal hemianopia produced by suprasellar cysticercosis.

Neoplastic disorders

Neurilemmoma of orbit (Kulseshta et al 1961), optic nerve glioma (Kulseshta et al), intraosseous, ectopic and orbital meningiomas (Misra et al 1978), retrobulbar neuritis secondary to sellar tumours (Gahlot et al 1974), ocular manifestations of pituitary tumours (Gahlot et al, Gulati and Jain 1963) neurofibromatosis with orbital meningioma (Jain et al 1973), optic disc tumours (Badrinath et al 1983) and ocular manifestations of nasopharyngeal tumours are some aspects covered by recent authors. Swaminathan and Kalyanaraman have discussed the value of colour fields in the diagnosis of pituitary tumours. Jain and Gulati have described medullo-epitheliomas (1963) and Gulati et al (1974) optic pathway gliomas.

This author has reported on bilateral proptosis due to orbital infiltration by acute myeloid leukemia and discussed neuro-ophthalmic aspects of nasopharyngeal tumours in a series of 42 patients. In a further study of 33 patients the author had described the possible neuroophthalmic manifestations in cerebellopontine angle tumours. She has also described

involvement of the visual pathways in Albers-Shonberg disease (osteopetrosis). Similar observations have also been made by Kulseshta et al.

Degenerative disorders

Findings on fundoscopy in cases of tuberous sclerosis have been described by Badrinath et al. Ocular manifestations of cerebrovascular insufficiency have been described by Swaminathan et al. The Indian experience in multiple sclerosis has also been presented by Jain and Maheshwari. Singhal had also shared his experiences with multiple sclerosis. Profile of multiple sclerosis in various regions of India have been put forth by Verma and Ahuja (Delhi and its surroundings), Chopra et al (north west India) and Singhal and Wadia (western India).

Miscellaneous

Other contributions include those on methyl alcohol poisoning with optic neuropathy and orbital apex syndrome (Kulseshta et al 1969), Anton's syndrome (Menon et al 1968), cranial motor nerve palsies (Menon et al) and Raeder's syndrome.

This brief review is based on feedback obtained in response to a questionnaire sent to all the ophthalmic centres in India.

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Neuropsychiatry

A. Venkoba Rao

'I conclude that man as a whole is a larger affair....than any single method of minute inquiry - be it chemical, physical, pathological, microscopical or psychophysical - will ever unfold....there is work enough for as many methods of studies of mind as are rationally based'.

— Henry Maudsley (1900)

Neuropsychology in ancient Indian writings

Mind - Its nature and seat

The speculations and concepts on the nature of the mind and its location have been as many as the number of systems of philosophy and schools of medicine. At no time did there exist a system of empirical psychology in ancient India. 'Indian psychology is based on metaphysics; the psychological accounts of some problems, e.g. perception of the self, perception of the universe, etc. are unintelligible without consideration of metaphysical foundation' (Sinha 1958, 1961). Indian psychology is based to a greater extent on such techniques as introspection and observation, and much less on experimentation. Although, mind has been considered as equivalent to soul, there is ample evidence to suggest that it was referred to as a psychological instrument and one of the organs of senses. In ancient Indian writings, mind was given the status of the sixth sense organ. In the Rig Veda, mind (manas) was regarded as the seat of thought, with emotion dwelling within the heart (Das Gupta 1952). However, the Atharvana Veda lists mind and consciousness (*citta*) as different organs; mind is considered as an inner organ and citta represents thought. The Atharvana Veda also accords to the heart the importance of being the seat of mind. A verse in the Atharvana Veda says: 'O Mitra and Varuna, take away the thinking power from the heart of this woman, and making her incapable of judgement, bring her under my control.'

Several systems of Indian philosophy regard the mind as one of the sense organs. For example, *Nyaya-Vaisesika* holds that mind is an inner instrument for perception. According to the Sankhyan school; mind, ego, and intellect together form an 'internal organ' whose chief function is to

receive impressions from the external environment and respond to them suitably. This equipment has sensory and motor organs as accessories. 'This whole apparatus, consisting of the internal organ, and its several accessories, may be taken as roughly corresponding to the brain and the nervous mechanisms associated with its function according to modern psychology'(Hiriyanna 1960)

Among the ancient medical thinkers, the views of Caraka, Susruta, and Bhela on the seat of the mind merit attention. Caraka thought that the mind resided in the heart, together with pleasure, pain and cognition. He qualified his statement by saying that the heart is not the place where these faculties stay, but that they depend upon it for their proper functioning. 'If the heart is wrong, they also go wrong; if the heart is well, they also work well. Just as rafters are supported by the pillars, so are they all supported by the heart'(Das Gupta 1952). The heart attained a prominent place in the Carakian system. It was considered the centre of the currents of physical and psychological activities. To Susruta, the heart, 'the lotus with nine gates' is the seat of mind. In his writings he declared, 'The body consisting of the limbs, knowledge, the senses, the five objects of the senses, the soul as invested with attributes, the mind and thoughts are all established in the heart. Heart is the center of sensations, consciousness, and mind' (Das Gupta 1952). Caraka's and Susruta's views are similar to those of Aristotle on the subject. To Aristotle the brain was itself an organ with the important role of regulation of the body temperature, thereby acting as a refrigerating agent. 'When the nutrient streams upwards through the blood vessels' wrote Aristotle,'its refuse part is chilled by the influence of the region, and forms defluxions of phlegm and serum. We must suppose, to compare small things with great, that the like happens here as occurs in the production of showers. For when the vapour stems up from the earth under the influence of heat and is carried into the upper regions, so soon as it reaches the cold air that is above the earth, it condenses again into water owing tc refrigeration, and falls back to the earth as rain' Woollam (1958).

On the other hand, Bhela, probably as old as Caraka, remarkably considers the brain to be the centre of mind - 'a view unique in Sanskrit literature'. (Das Gupta, 1952) This corresponds to the Hippocratic view and the modern concepts. '*Manas*, which is the highest of all senses, has its seat between the head and the palate. Being situated there, it knows all the sense objects, and tastes and come near it' (Das Gupta 1952). Bhela distinguishes between *manas, citta*, and *buddhi*. Manas is connected with cognition and is situated in the brain. Citta controls various feelings and is located within the heart. Homer's concept of noos and *thymos seems* to find a parallel in Bhela's thinking. Bhela explained the origin of insanity thus: 'the *dosas* (morbid humors) in the brain affect the mind and consequently involve the heart; from the affection of the latter, the understanding is impaired and this leads to madness' (Das Gupta 1952).

The Vedic literature includes metaphysical treatises referred to as *upanishadic* literature, the heart is spoken of as the central point of mental functions-for example, the *Taittiriya upanishad* places the 'mini-person' in the heart; it is the converging point of many channels. The *Aitereya upanishad* has a verse that denotes that heart is the seat of mind. 'The heart sprang up: from the heart proceeded the mind; and from the mind the moon'. The ancient Indian views that the heart is the abode of the mind (with the possible exception of Bhela's view) is similar to those of the ancient Egyptians, the Chinese, and Aristotle.

In the Indian Tantric system of anatomy, which is different from the Ayurvedic school, nerve plexuses are described in detail. One of the plexuses is described as being situated between the eyebrows (mind plexus). To this is attributed the function of the sense-knowledge, and dream-knowledge. The school holds that upper cerebrum is the seat of the soul and describes a connecting structure -jnananadi- between the mind and the soul (Das Gupta 1952). Throughout time, the heart and the brain have in turn been said to be the proud lodgers and controllers of the mysterious faculties of mind. Some of the ancient concepts on the seat of mind and functions have been discussed elsewhere by the author (Venkoba Rao 1971, 1975).

References in the Bhagavad Gita

Mind and its functions

Perhaps for the first time in the history of Indian philosophy, different streams of thought converged into a confluence in the Vedic ritualism of the *Gita, Upanishadic* introspection, *Sankhyan* speculation and yogic meditation.

> *Yogah Karmesu Kausalam.* (Perfection in action is yoga) *Samathvam yogam uchyathi.* (Evenness of mind is yoga)

To these *Gita* adds and accords a supreme place to that master of sentiments - devotion or *bhakti* -the affective component of mental functioning.

This approach of synthesising into one; action, knowledge and feeling is a triumph of Gita over the earlier philosophical attempts and is the forerunner of the modern concept of tripartite mental function, namely, cognition (*jnana*), connation (*karma*) and affect (*ichha* or emotionally tinged desires). This was the classification of major mental faculties offered to modern psychology by the German philosopher Immanuel Kant. Homer had earlier drawn attention to these aspects of personality as noos, *thymos* and *psyche*. A harmonious blending and a concerted action of this trinity of functions is a requisite for the healthy mind. Any breach between them or within them can lead to a pathological split in the mind.

Asocyan anvasocas tvam prajnavadams ca bhasase
gatasun agatasuma ca na 'nusocanti panditah'.

(You grieve for those who should not be grieved for; yet you spell words of wisdom. The wise grieve neither for the living nor for the dead)

Hysteria and schizophrenia in the modern parlance represent the split between and within the mental faculties.

Gita brings out beautifully the process of deterioration of personality -a dementing phenomenon- in a few verses. This is the ladder of doom:

Krodhad bhavati sammohath
Sammohat smrtivibhramah
smrti bhramsad buddhinaso
buddhinasat pranasyati.

(From anger proceeds delusion;
from delusion, confused memory;
from confused memory, the ruin of reason;
from the ruin of reason he perishes)

Interestingly, Sankaracharya describes the converse, namely the construction of personality in his *'Viveka Chudamani'*.

Mental Field

The inaugural interrogative verse of *Gita*, which, incidentally, is the only one from *Dhritarashtra*, is a fine and elegant simile that epitomizes the natural state of the affairs of the human mind and the disturbing forces within it.

dharmaksetre kuruksetre
samaveta yuyutsavah
mamakah pandavas cai'va
kim akurvata samjaya

(Gathered together at Kurukshetra,
the field of religious activities,
what, O Sanjaya,
did my war inclined sons and those of Pandu do?)

The whole of the Gita is in reply to this question. The mind of man can be likened to a veritable battle field- *Manahkshetra.* There is an endless war of forces within the mind between good and evil, divine and demonaic, high and low, *sreyas* and *preyas*, man and beast, light and darkness, virtue and vice as represented in the Mahabharata war by the cousins -*Pandavas* and *Kauravas*. It symbolises what Shakespeare's Brutus calls a state of 'insurrection' in mind. It is for these conflicts, minor and major, that psychotherapy is offered. This constant tussle within the mind was called 'psychomachia' by the ancient Greeks.

Sigmund Freud described the mind as comprising triple terrains of the

conscious, subconscious and unconscious. His discovery of the 'unconscious' (hidden part) has been hailed as a milestone in the history of medical sciences, as significant as the discovery of the circulation of blood by the English physician, William Harvey.

The 20th-century-view on the nature of man can ill-afford to ignore the role of the 'unconscious', notwithstanding the non-Freudians. It is that part of the mind which encages the animalistic and instinctive qualities that press for entry into consciousness and acts as a springboard for motivation of behaviour. This topographical model of mind by Freud represents the battlefield with clash of forces within them.

'The discovery that memories, thoughts and feelings exist outside the primary consciousness is the most important step forward that has occurred in psychology since I have been a student of that science',said William James. 'Within it are held those things that lie in the fringe of the stream of consciousness chiefly at its lower and the non-communicable level'. We all carry the burden of the past -the burdens of the anatomical past, behavioural past and cultural past.

Neuroanatomists tell us that in the human brain the rudiments of animal brain persist. Carl Jung talks about the racial unconscious indicating thereby that we carry over the precipitate of memories of our entire past within our mental realm.

The instinctual urges and suppressed desires rise towards consciousness to be opposed by the downward forces that are influenced by cultural, social, environmental and personal leanings. The unconscious is a necessary component since everything cannot be held in the conscious. Contrary to the views held in the Vedantas and Gita, Freud saw human nature as basically evil, the ultimate destiny lying in its sublimation. Rousseau held that man is good by nature and it is society that corrupts him. The unconscious need not always be the storehouse of evils and the unacceptables. It houses the sparks of goodness as well as divinity. Too often we are unaware of them.

The *Gita* persuades us to recover the gems and flowers which are within us. The sublimating mechanism in Freud's system remains unconscious.

Mind and its nature :

It is difficult to say whether the term 'mind' used in Gita is applicable in the way it is used today. The mind-*buddhi* complex of *Gita* approximate the modern usage of the word, treating the mind as a 'thing' or an entity in the same way as Caraka treats in his *Samhita*. To the mind has been assigned the role of the sense organ in *Gita* and it belongs to the lower order along with the senses, *buddhi* and the body which have their origin in the earth, water, fire, air and ether.

Indriyanam manas ca asmi.
(Of the senses, I am the mind)

In the hierarchy of the derivatives from the lower *prakriti*, mind occupies a place higher than the sense but lower than the intellect or *buddhi*. The personality in Gita as in the Buddhistic writings is compared to a chariot drawn by horses. While the horses represent the sense organs, and *buddhi* the charioteer, the reins denote the mind. This concept has its source in *Kathopanishad*. That the mind is constantly blasted by the sensual desires is highlighted in *Gita*. Freud was not far from this view of *Gita*. The turbulent senses carry the mind away violently.

> *Indriyani pramathini haranti prasabham manah.*
> (Like a boat tossed about on the high seas by a gale, the mind can be uncontrollable)

The difficulty of the control of the mind is brought out in the line:

> *Chanchalam hi manah krischna pramathi balavad dhridam.*
> (The mind is restless, turbulent, strong and stubborn.
> It is as difficult to control as the wind)

Gita advocates the attainment of a state of evenness of mind (*Samathvam*), steadiness (*sthithapragna*) and peace (shanti) comparable to the 'steadiness of a lamp that flickereth not in a windless place'. (*Yathadipo nivathas the naingte.*) An unruffled state of mind is compared to a tortoise with its limbs drawn in. (*Kurmo anagani samharate*). A steady state of mind and sustenance of its peace have been the quest of the philosophies of all lands. The Greeks called this ataraxy, Gita terms it *shanti* and *samatvam*. Osler revived it in his *Aequanimitas*. Venkoba Rao (1980) has dealt with descriptions of the mental sciences in the *Bhagavad Gita*.

Dementia

General paralysis of the insane

Dementia of syphilitic aetiology has been intensively studied and reported from India. It was the western view that neurosyphilis was not as prevalent in the eastern world as among the westerners and this was attributed to the high endemicity of malaria and other fevers in these areas, which acted as a preventive. This notion stands dispelled. It may be recalled that Julius Wagner-Jauregg received the Nobel Prize for 1927 'for his discovery of therapeutic value of malaria innoculation in the treatment of dementia paralytica' (Stevenson 1953). The significant contributions on GPI are from Varma (1952), Venkoba Rao (1958), Venkoba Rao et al (1969, 1972), Verghese and Shanthi (1972) and Narayanan et al (1973). Varma reported on 40 cases of GPI from the Mental Hospital, Ranchi. It is of interest that there was no female paretic in his series. Of 33 cases of GPI reported by Venkoba Rao (1958) and 34 cases reported by Venkoba Rao et al (1972) there was only one female. A review of 240 cases of GPI by Narayanan

et al (1973) included 21 females. In India, GPI appears to be rare among women. Discussing the natural history of GPI in western Europe during the last 170 years, Hare (1959) reported that in every country, when the illness first started, the distribution was almost even; it gradually narrowed down so that it became a male prerogative. Hare suggested that alteration of sexual behaviour consequent on the emancipation of women influenced the sex ratio. Venkoba Rao et al (1972) showed that the symptomatology of GPI could be arranged along a spectrum with neurological and psychiatric poles at either ends. Pure neurological and psychiatric forms are not uncommon though many cases had mixed neuropsychiatric features.

The rarity of the depressive syndrome in patients with GPI was noted by Venkoba Rao et al (1972). Venkoba Rao (1958) found only 2 depressives amongst 33 paretics. The dementing form occurred in nearly 50% of their cases and the grandiose variety was restricted to 4 out of 34 cases. It was long recognised that grandiose forms of GPI were not common. 'All that is grandiose is not paretic' (Venkoba Rao 1958). In an earlier series of 33 cases, less than a third showed grandiose ideas (Venkoba Rao 1958) In his analysis of epidemiological and historical aspects of GPI, Hare (1959) stated that the grandiose symptoms were common over 100 years ago in Europe, but its leading position was gradually taken over by the dementing type. The infrequent presentation of depressive form in the Indian patients is interesting. Depression was uncommon, too, (1.6%) in the series reported by Narayanan et al (1973). The expansive form was common constituting 34.53% and simple demented type ranking second (25.8%). On the other hand, in a report from England, depression formed 27% of the series (Dewhurst 1969). 'Atypical manic picture is relatively rare but depression is more common' (Slater and Roth 1969). Varma (1952) recognised only two clinical varieties of GPI:maniacal (57.5%) and confusional (42.5%). Verghese and Shanti (1972) reported their observation on 18 cases of general paresis. They estimated the incidence of GPI at 0.25% among the total number of consultations over a period of 8 years, which is less than that of 3-5% reported by Venkoba Rao (1958) and 1.1% by Varma (1952). There was a single female patient in their series. A diagnosis was possible on clinical grounds in 50% of their cases, and was confirmed in the entire series by blood and CSF tests. Grandiose ideas were noted in 22.2% of their cases. Mani and Kishore (1964) reported on 20 cases of dementia from the All India Institute of Mental Health (NIMHANS), Bangalore.

Cerebral biopsy was employed as a research and a diagnostic procedure by some to demonstrate treponema pallidum . Venkoba Rao et al (1969) reported on frontal lobe biopsy on 4 subjects diagnosed clinically and serologically proven as GPI. The material from the right frontal lobe was examined under dark ground illumination and by Levaditti staining. The treponema pallidum was seen in two instances. In one patient, left frontal lobe biopsy following a course of antisyphilitic treatment failed to reveal

treponemes, while pre-treatment biopsy from the right side revealed them in abundance. Bruetsch's observation in 1949 on the persistence of treponema pallidum in the brain in a patient after 10 mega units of penicillin is relevant. Cerebral biopsy failed to reveal the treponemes in 12 demented patients (Somasundaram and Sarada Menon 1975). They attributed the absence of treponema pallidum in their material to the possible antisyphilitic treatment the patients might have received earlier.

Other forms of dementia

The importance of cerebral biopsy in the diagnosis of dementia was commented upon by Somasundaram and Sarada Menon (1975). They reported the pathological findings in 12 cases of dementia on whom cerebral biopsy was carried out:

Alzheimer's disease	: 1
Subacute spongiform encephalopathy	: 1
Nonspecific cerebral degeneration	: 1
Post infection dementia	: 2

They did not come across treponema pallidum in their biopsy material. Cases of Alzheimer's disease were reported by Somasundaram (1974).

Thirtyone cases of dementia were encountered among 150 cases aged 60 (or more) that formed the material for the ICMR Task Force Project on the 'problems of the aged seeking psychiatric help'.(Venkoba Rao 1987) There were 102 cases of functional disorders (affective disorders, mania, depression, paraphrenia) and 48 of psycho-organic syndromes (17 acute organic syndrome and 31 dementias). Eleven were termed **senile dementia Alzheimer's type (SDAT) and 20 were of multi infarct variety.** The SDAT cases belonged to a higher age group (mean 71.5) and the inception of illness was insidious. They showed a progressive course with the mean duration of illness (from the index evaluation) being 1.5 years. On the other hand, a relatively earlier age (mean 63 years), an acute or subacute onset, rapid or step ladder course and shorter duration of illness at the time of index evaluation (mean duration 8 months) characterised the multi infarct dementia. Mortality was noticed to be high among the dements. Eleven deaths were noted on follow up evaluation at the end of one year. The Task Force Project has confirmed that dementia is quite common in India and that multiinfarct type outnumbers the SDAT. This pattern is similar to that reported from Japan and disproves the idea that dementing illness is rare in developing countries. Considering the fact that those aged 60 or more, who currently constitute 6% of India's population and number 43 million (1981 census), the incidence of dementia is likely

to increase in the years to come. Neurosyphilitic dementia is still prevalent in India and though much less in frequency continues to be an important differential diagnosis in clinical neuropsychiatry.

A detailed morphological, ultrastructural and immunochemical features of neuronal pathology in a case of Alzheimer's disease has been reported by Shankar et al recently (1988). This is possibly the first detailed study of an authentic case of Alzheimer's disease in India. The authors opine that the features observed by them are identical work to those described in the western patients.

Dementia and other neuropsychiatric manifestations from **cerebral cysticercosis** have been reported in India. Its incidence is higher in the north western parts of India. The clinical picture of neurocysticercosis simulates that of neurotuberculosis and neurosyphilis in the developing world and multiple sclerosis in the West (Venkataraman et al 1977; Srinivasan et al 1977). Vijayan et al (1977, 1979) and Venkataraman et al (1982) reported on the primary psychiatric presentation of neurocysticercosis without signs of intracranial hypertension. This latter finding has been a significant feature in cases with psychiatric changes. Schizophrenic features, manic behaviour, insomnia, hallucinations, paranoid delusions, seizures and intellectual deterioration were observed by them. Kala and Wig(1977) while describing 2 cases of acute organic psychosis marked by disorientation, excitement and irrelevant talk with raised intracranial tension, reported a case of insidious dementia with impaired memory and judgement without raised intracranial tension. Trivedi et al (1983) described a patient who presented primarily with organic psychosis in whom cerebral cysticercosis was diagnosed only on cerebral CT scan . Venkataraman et al (1982) reported on the radioimmuno treatment of generalised cysticercosis of nervous system with iodine131 labelled anticysticercosis antibodies . Other important reports on cerebral cysticercosis are from Ahuja (1978), Chandy and Isaiah (1952), Dinakar et al (1970) and Wadia (1973). Recently, treatment of cerebral cysticercosis with an anthelmintic-praziquantel-has been reported. (Tandon 1983; Ashok Varma et al 1987)

Epilepsy

There has been a considerable literature in India on the psychiatric and psychosocial aspects of epileptic disorders. That epileptics are susceptible to psychiatric disorders has been reported by Bagadia et al (1973) and Abdul Gaffoor and Shantha Kumar (1974). Subsequently, there have been detailed reports on temporal lobe epilepsy (Shukla 1984) and epileptic psychosis.(Fernandez et al 1988 and Swami et al 1976) The occurrance of psychiatric syndromes in epilepsy has been a matter of controversy, some holding the view that the onset of mental changes in epileptics is statistically not any more significant than in the general population.

Attempts have been made by Fernandez et al (1988) to describe the profile of epileptic psychosis. The category of ICD IX is epileptic psychosis (NOS) which implies that atypical psychosis with a likelihood of etiological relationship with epilepsy should be coded under this heading. DSM III APA (1980) overcomes this pitfall. A larger net can be thrown to include other cases too.

There are earlier Indian references on epileptic psychosis. Agnihotri et al (1972) reported seven cases. Neki and Chawla (1975) reported 60 cases and found epileptic psychosis to be characterised by fleeting delusions, unrelated and visual hallucination, apathetic mood and a premorbid personality. The association of psychiatric features with epilepsy of temporal lobe origin has been brought out by some. Shukla et al (1979) report that patients with temporal lobe epilepsy may first present to the psychiatrist. They discuss the neurosis, psychosis, and personality abnormalities among such patients. 79% of their temporal lobe epileptics had psychiatric disturbances, compared to 47% of control group of cases of grand mal epilepsy. This was so notwithstanding the finding that epileptic personality and confusional psychosis occurred more frequently in the controls. Temporal lobe epilepsy is ultimately a diagnosis made on EEG. Although the terms psychomotor epilepsy and temporal lobe epilepsy are used synonymously, this is not justifiable, according to Shukla et al (1979) since nearly 1/3rd of the patients with clinical psychomotor attacks, failed to reveal temporal focus while sizeable proportion of patients with temporal focus (on EEG) presented with purely grand mal seizures. Shukla (1984) has reported on phenomenology, psychiatric manifestations, personality disorders, epileptic personality, behavioural disorder and sexual disturbances in relation to temporal lobe epilepsy.

Shukla et al (1979) found 64% of male temporal lobe epileptics to be impotent compared to 12% of those with grand mal epilepsy. They also found 64% of female temporal lobe epileptics to be hyposexual, while only 8% of grand mal epileptics were so affected. There was a marked decline in sexual interest and performance following the onset of seizures, while sexual functions failed to develop in cases with early onset of the disease. Interestingly in none of these patients was this a leading complaint. Hyposexuality appears to be particularly associated with temporal lobe epilepsy, unattributable either to the psychological impact of seizures or to anticonvulsant medication. Several temporal lobe epileptics develop hyper-sexuality on cessation of seizures following either temporal lobectomy or psychiatric treatment (Shukla et al 1979).

The number of cases with generalised seizures without psychomotor features was high (69%) although EEG focus was demonstrated in temporal lobe. Aura occurred in 60%, the commonest being visual hallucination, fear, vertigo, epigastric sensation, olfactory and gustatory hallucinations. Deja vu and Jamais vu phenomena were infrequent. The auras were pleasant

in 3%. Such auras were reported as the component of seizures in spiritualist Shri Ramkrishna Paramahamsa (Desai 1968). Shukla (1984) noted that phenomenology of temporal lobe seizures in children is different from that in adults. Unusual presentations like episodic and transient pain in abdomen, extreme fear, panic, persistent and intractable night terrors were more frequent in children. A sudden unprovoked outburst of laughter and persistent vomiting have been described in TLE by Shukla et al (1981) and Shukla and Mishra (1981). Neurotic symptoms have also been reported in epilepsy by Virmani and Sawhney (1966), Bagadia et al (1973) and Shukla and Katiyar (1980). The neurotic symptoms were found in 39% of cases of temporal lobe epilepsy in contrast to 16% in the control group of grand mal epilepsy. Shukla and Katiyar (1980) have indicated that patients with temporal lobe epilepsy were 21/2 times more prone to neurosis than patients with grand mal fits. The common neurotic features were neurasthemia, depression, anxiety, hypochondrisis, hysterical and obsessive compulsive features in that order. There is a consensus that schizophrenia occurs several times more often among the temporal lobe epileptics than in other types (Shukla et al 1979 and Shukla and Katiyar 1980). Shukla et al (1979, 1980) found 16% incidence of schizophrenia in temporal lobe epileptics as against 4% in grand mal epilepsy. The psychosis appears 7-14 years after the onset of epilepsy with almost all the features of schizophrenia (marked paranoid and religious colouring and auditory hallucinations). There was no premorbid personality, predisposing to psychosis. The patients with generalised seizures are prone to confusional psychotic state that does not progress to chronic psychosis. The clinical condition characterised by confusion, clouding of consciousness, disorientation and disorganised behaviour is generally precipitated by status epilepticus and lasts for 5-10 days (Shukla et al 1979).

In 564 cases of seizures, reported by Virmani et al (1967) lethargy, depression and anxiety were the presenting symptoms. In 24 patients, even when the seizures were well controlled, episodes of confusion lasting for several days were usually seen following a major seizure. Personality changes were seen in 43 patients and were of the nature of irritability, intolerance, carelessness, decreased efficiency at work, obsessiveness, compulsive behaviour and preoccupation. The authors observed that these patients were different from psychotics for they realised that such feelings were abnormal and they did not identify themselves with the symptoms. Overt paranoid reaction was seen in a woman whose seizures were controlled for over a year.

Inter ictal psychiatric episodes in patients with seizures few and patients did not develop permanent mental disturbances or dementia. In patients presenting with mental confusion, the episodes began, but rarely ended, with a seizure EEG during the episodes was always modified either in the direction of delta dysrhythmia or frequent discharge with the petit mal status type being seen in a few.

Psychosocial and psychiatric aspects of epilepsy were reported by Bagadia et al (1973). In their series of 180 patients studied over a year the incidence of epilepsy was 8% among those attending psychiatric outpatients. Of these 88.4% had grand mal epilepsy; 4.4% grand mal and petit mal; 2.2% psychomotor and 1.8% petit mal epilepsy. All the subjects reported aura and 46% of these were of psychic variety. Forty percent of their patients were found to show psychiatric disturbances-schizophrenia (10.5%) endogenous depression (1.1%) neurotic depression (15.6%) anxiety state (9%) behaviour problems (2.2%). Personality traits were noted in 50% of the patients and consisted of associability, aggressiveness, irritability, restlessness, shyness and overactivity. Bagadia et al (1973) commented upon the association of psychiatric disturbances and emotional difficulties in the epileptic population and also the fact that epileptic patients tend to be handicapped in their education and employment. Interestingly psychic aura was a reason for referral in many instances. These psychic aura were of anxiety, depression, euphoria and deja vu. Twentyfour percent had visceral aura with sensations referred to head and sense organs. Motor aura were reported in 36%.

Psychiatric and psychosocial disturbances in epileptics were documented by Agnihotri et al (1972). All types of psychiatric disturbances ranging from irritability, anxiety, somatic concern and obsessiveness to major psychosis (in 11.8%) and suicidal attempts (in 6.7%) were evident in their 59 cases. Though many of these had centrencephalic epilepsy, 71.5%, who developed psychoses had cortical epilepsy. Their report confirmed the inverse relationship between control of fits and worsening of psychiatric symptoms. In a large majority of their patients, educational, social and occupational adjustment was poor. Psychological tests revealed affective, intellectual, functional disturbances in 66.21%, concentration difficulties in 35.6%, memory disturbances in 32.25%, difficulty with abstraction in 27.1% of simple learning in 20.34% and attention deficit in 10.16%. Rorschach protocols showed a low emotional potential with poor genuine emotional involvement, explosive tendencies and feelings of inadequacy. The patients were impulsive and continued concern with fulfilment of their impulses made them tense and high strung. 70% of the patients functioned at a level below their intellectual potential. The authors suggested that for adequate management of epileptics a proper evaluation of psychiatric status and psychological deficits was imperative.

A relation between epilepsy and crime was reviewed by Somasundaram (1972). Among the 115 criminal mentally ill patients in the Governmental Mental Hospital at Madras, 15 had epilepsy. The author opined that crimes among epileptics posed a problem to the psychiatrists, but in many cases this could be untangled by careful history taking, observation and EEG. He discussed the report of the Royal Commission on Capital punishment (1949-1955) dealing with the relation between crime and epilepsy. Psychiatric disorders occurring in epilepsy could be related (peri-ictal) or

unrelated (inter ictal) in time to the seizures. The inter ictal psychosis occurring in clear consciousness could be further classified as schizophrenia like, schizo-affective or affective in nature. There has been a controversy over the higher prevalence of inter ictal psychiatric illness among epileptics. Although schizophrenia like symptoms have been the subject of many studies, affective symptomatology has also been recognised in relation to epilepsy. Mood disorders can occur peri-ictally but are said to be short-lived and associated with a low level of consciousness and diffuse EEG slowing. Mood disorders occurring inter ictally in a setting of clear consciousness resemble functional psychiatric disorders. Psychiatric symptoms classifiable on the basis of the degree of consciousness are as follows (Bruens, 1974):1. Psychosis with disturbances of consciousness 2. Psychosis with normal consciousness (a) short-lived, less than three weeks and (b) long lasting.

Depressive symptomatology in epilepsy has been reported in Indian literature. On the other hand hypomania and maniacal episodes are rarely associated with epilepsy in the west. Toone et al (1981) could find only 3% with bipolar features in population of 69% with a combined diagnosis of epilepsy and psychosis. Maniacal episodes were observed in 4.7% in a population of 536 patients with epilepsy reported by Bagadia et al (1973). In a series of 150 cases of epileptic psychosis Satyanarayanaswamy et al (1986) found 6% to be maniacal. Pathological elevation of mood was observed in a significant sub-population of 60 cases of epileptic psychosis studied by Antony Fernandez et al (1988). These authors observed grandiose delusions to be the second most common type of delusions.

Fernandez et al (1988) reviewing 60 cases of epileptic psychosis during the period 1980-85 from NIMHANS, Bangalore, observed that the most common presentations of psychiatric symptomatology were unclassifiable psychosis and paranoid hallucinatory state. The brief psychiatric episodes tended to be marked by pressure of speech, inappropriate affect, generalised epilepsy and several previous episodes. The authors classified psychosis into 5 descriptive groups and a miscellaneous group. Paranoid hallucinatory states were marked by predominant delusions and/or hallucinations, schizophrenic forms (non paranoid hallucinatory psychosis) were marked by inappropriate affective or formal thought disorder. Grand mal probands had affective disorder or irritability with or without grandiose delusions. Depressive patients with depressed affect had other associated thought contents and fell in the miscellaneous groups. There were disturbances in psychomotor activity and irrelevant talk with no clear-cut features for grouping into any type of psychosis. The authors do not subscribe to the view which implicates temporal lobe epilepsy to explain psychiatric symptomatology. In their series, only 3 of 10 EEGs showed temporal focus. They report that grand mal seizures are more often associated with psychiatric state. However, chronic paranoid hallucinatory state accounted for the largest group consistent with findings of Slater et

al (1963). Schizophrenic forms of psychosis were found only in 4 out of 60. In their study of 150 cases of epileptic psychosis Satyanarayanaswamy et al (1986) arrived at the ratio of epilepsy to epileptic psychosis as 23:1 (150 cases out of 3449 epileptics). With the breakdown of the figure into acute and chronic epileptic psychosis separately the ratios arrived at were 1:54 and 1:40 respectively. This agrees with the figure of 1:42 of Bruens (1971) and is at variance with that of Bartlett (1957), whose ratio was 1:89. Under the category of epileptic psychosis they included a number of remitting confusional psychotic episodes, post ictal or inter ictal as acute psychotic episodes while prolonged psychotic states without any clinical discernible relationship with the seizures were defined as chronic psychosis. In their series, 62% of patients suffered grand mal epilepsy and 33% temporal lobe epilepsy. This runs counter to the report wherein psychotic states stem from TLE. The unspecified psychotics formed 40% of their material.

There is a view that grand mal epilepsy causing depression and suicide behaviour is relatively uncommon and this is explained on the basis that grand mal fits are 'anti-depressant' in their effect acting as natural ECTs. Some Indian studies do not testify to the higher incidence of depression or suicide in epileptics (Bagadia et al 1973; Venkoba Rao et al 1974).

Brain tumours and mental symptoms

The incidence of psychiatric symptoms in patients with intracranial neoplasms have been estimated variously by different workers. Verghese (1964) reported on a midline tumour, in the vicinity of the third ventricle, pressing upon the hypothalamic area. The brain biopsy showed a glioma. This was diagnosed as schizophrenic reaction prior to investigation. Remington and Robert (1962) made a 30 year survey at Syracuse Psychiatric Hospital and found that the incidence of psychosis due to brain tumours was 0.2% as against the usual incidence of 2.3% in the State Mental Hospital. Verghese (1964) while reviewing the cases in the department of psychiatry, Vellore for the year 1962, estimated an incidence of tumours at 0.35%. This low figure is attributable to the preliminary screening of all the cases in the department of neurology and neurosurgery at Vellore. In a survey of 70 cases of frontal lobe tumours over a ten year period in the department of neurology and neurosurgery, Vellore, Verghese and Chandy (1960) found that 41.4% of them showed psychiatric symptoms. The figures offered by others have been 84% (Denny Brown 1951), 50% (Kolodny) and 58.2% (Nickolsky). It is a dictum in psychiatric training to be on the look out for an organic basis whenever the psychiatric syndromes failed to conform to the expected clinical pattern. Though mental symptoms as manifestations of brain tumours are generally recognisable, their localising value is poor (Venkoba Rao 1986).

Psychiatric syndromes, especially schizophrenia and catatonic features, were reported by Shah and Desai (1960). Autopsy showed such brain lesions

like acute cerebral abscess and infarction in their cases. Virmani et al (1967) reported on psychiatric symptoms occurring in certain cases of space occupying lesions, infections like meningitis and encephalitis. 5 of 7 cases of tuberculosis meningitis presented as psychiatric problems. Psychiatric symptoms were observed in 12 of 72 cases of encephalitis: lethargy, confusion, disorientation, anxiety, depression, euphoria, aggressiveness and memory disturbances. Electroconvulsive therapy in cases of brain tumours was deemed risky although it was argued that it should not be so, since convulsions do occur from intracranial neoplasms. ECTs have been used successfully in the treatment of a patient with frontal lobe tumour who later developed schizophrenic symptoms.(Doongaji and Saraf 1966)

Cerebrovascular disorders

A study involving 50 stroke patients in respect of psychiatric disturbances was reported by Haroon (1986).

The patients were interviewed for a period ranging from 4 to 90 days following the stroke. The duration of post stroke period was not significantly related to the severity of psychiatric disturbances. Several prestroke and other factors of pathogenesis of stroke were found to be related to poststroke psychiatric disturbances. Haroon found association of right hemispherical lesions with depression thereby supporting the findings of Folstein et al (1977). The psychiatric symptoms in the study were rated on a self-designed scale. Male sex and the presence of past history of stroke were related to emotional withdrawal. Hypertension was related to hostility. It is important to recognise the depressive syndromes associated with stroke since they are amenable to antidepressant pharmacotherapy and cognitive measures.

Brainstem hemorrhages cause affective disturbances by interfering with the adrenergic, serotonergic and dopamine pathways from the nuclei of origin projecting on to diencephalon fore-brain structures. Subarachnoid hemorrhages from leaking posterior communicating artery aneurysm cause depression because of the contiguity with hypothalamus. The present author had under his care a patient with two episodes of subarachnoid hemorrhage from anterior communicating artery aneurysm who developed severe depression with two serious attempts at suicide. His depression is attributable to the involvement of neighbouring basal-frontal limbic system (Venkoba Rao 1986).

Subacute sclerosing panencephalitis

Subacute progressive encephalitis was first reported in psychiatric literature in India by Mehta et al (1959) who reviewed 27 cases from the literature, adding their own case. Subacute progressive encephalitis was defined as 'a neuropsychiatric syndrome characterised by mental changes,

variable neurological manifestations referable to wide-spread involvement of central nervous system, an unrelenting course of weeks or months ending in death; minimal or no change in CSF, non-specific changes in EEG, diffuse focal change in the brain with or without inclusion bodies'. Later the illness was variously described as 'inclusion encephalitis' Dawson (1934) 'subacute encephalitis' (Clarkin and Miller 1952) and 'cytomegalic inclusion encephalitis' (Campbell et al 1952).

Mehta et al's case was a boy of 16, who had treatment for petit mal epilepsy with barbiturates prior to admission into the psychiatry ward of K.E.M. Hospital, Bombay with a provisional diagnosis of barbiturate ataxia. The leading complaint was attacks of 'falling down' of three months' duration. A bright student though he was, he failed in the examination for no apparent reason and found it difficult to solve arithmetic problems, at which he was good until then. The attacks of falling down momentarily were occurring once or twice a day. The boy was telling his parents that he was mimicking the acting of a drunkard whom he had witnessed in a movie. Gradually the attacks worsened with the boy sustaining injuries. Petit mal epilepsy was diagnosed and he was put on anticonvulsants. He became apathetic and his facial expression turned dull and idiotic. 'He walked as if he was drunk'. The drugs were continued but the ataxia worsened. There were generalised movements with extension of the trunk, flexion of shoulders, elbows, wrists, hips and knees. Serial EEG showed marked deterioration suggesting generalised cortical damage. Throughout the graph, there were paroxysms starting with spikes, high voltage discharge lasting for about 1/5th of a second followed by high voltage flat topped cycles 0.2 cps, which had a frontal basis. This was followed by wave discharge at 3 cps. A subsequent graph showed a total absence of alpha activity with delta waves at varying frequency of 1-2 cps either flat topped or saw toothed. The patient became deluded, and hallucinated. 'Many doctors are coming, taking away all the patients from the ward'... My clothes are burning. All the doctors are also burning... Please turn me into a woman.' A brain biopsy was refused. He was discharged in a poor state.

During recent years and with the advancement of the understanding of the disease there has been a good sprinkling of reports on the subject in Indian literature. Subacute sclerosing panencephalitis (SSPE) is now known to be an infectious disease of the nervous system from a persistent infection with measles virus. Although there has been a drop in its incidence in the west consequent to widespread use of measles vaccination, SSPE continues to be frequent in India. A large series has been reported by Singhal et al (1974). Earlier Mani et al (1964) reported on 4 cases of subacute panencephalitis in childhood.

The currently accepted criteria for the diagnosis are as follows:

a) Classical clinical picture

b) Classical EEG findings including slow, bizarre, generalised periodic complexes
c) Elevated CSF measles antibody titer
d) Elevated CSF immunoglobulin levels and
e) Classical histopathologic changes.

The severity of SSPE is graded as follows:
Grade 1: Psychiatric changes only
Grade 2: Recurrent myoclonic jerks
a) Occasional
b) Repeated falls
Grade 3: Decerebrate posturing and
Grade 4: Vegetative state.

Eight percent of cases reported by Thakare et al (1987) fell under grade 1, 57% in grade 2 (a) or 2 (b) and 35% in grade 3. It is understandable that many cases in earlier stages are mistaken for psychiatric illness and treated accordingly. Hysteria is a popular misdiagnosis.

Singhal et al (1974) found positive Lange curve in 12 of their 39 cases (31%). Immunoglobulin studies have been reported recently in cases of SSPE. Thakare et al (1987) reported on the clinical picture, EEG changes and measles virus antibody titres along with immunoglobulin in the CSF in their 24 cases. In their youngest case the onset was at 21/2 years and in the oldest in the 26th year. 27% had a definite history of measles. Mental regression was noted in 33.3%, periodic myoclonus in 92.5% and maculopathy in 8.3% in their material. The EEG showed recurrent periodic complexes in 95% and in 79.1% on first admission. Antibodies to measles virus were detected in low titres in 50% of CSF samples and in 16 serum samples. The CSF IgG was raised in 87% and CSF albumin raised in 8% of cases. The CSF total protein was elevated in 52% and was mainly contributed to by IgG. These authors felt that absence of CSF antibody is not sufficient to exclude a diagnose of SSPE. The clinical picture, EEG, immunoglobulins and whenever possible antibody titers should all be taken in totality for a diagnosis wherever histological verification is not possible.

Gilles de la Tourette's disease

A case of Gilles de la Tourette's disease was published by Chakraborty in 1962, when reports on three of its kind had appeared in Britain. Her patient was a boy of 16 from a east Bengal family with no significant family history. He was the eldest of 7 with normal birth and infancy. He walked and talked at the expected ages. When he was 21/2 years, he suddenly woke up one night, crying and shouting 'Tiger, Tiger'. During the subsequent month, he remained rather ill, not taking food, fretting and crying all the time. From then on his behaviour changed, he would not mix or play with other children and did not talk to anyone. Schooling became impossible and

gradually his speech became monosyllabic, with such words like: 'Khabo'(i.e. 'want to eat' etc.). He would remain totally withdrawn to himself, playing, sitting or walking around alone. From the age of 15, he became disturbed and restless and began clutching parts of his body doubling himself up and shouting incessantly. He was making a loud noise, which was like an imitation of tiger's call and was followed by plain shouts continuously, interrupted only by pauses for breathing. Though he had abnormal posture and the meaningless motor act, tics were absent. This case, with an initial diagnosis of childhood schizophrenia or early infantile autism, developed Tourette's disease later. The obsessive compulsive features were marked. In the other cases referred to in the literature schizophrenia was a later development. The boy was administered analytically oriented psychotherapy and chlorpromazine intramuscularly, with no benefit.

The second case of Gilles de la Tourette's disease in India was reported by Sarojabai (1966). The patient had the classical symptoms of muscular spasms, vocal utterances of barking or stuttering, obsessional neurotic features of stamping with the foot. There was a positive familial history of mental retardation and mental illness, and epilepsy. EEG showed mild dysrhythmia not suggesting epilepsy. 'Marked improvement' was observed with lithium therapy.The authenticity of the two cases of Gilles de la Tourette's syndrome referred to above has been disputed. The case of Chakrabarty had fits resembling myoclonus (Singer 1970) and the one reported by Sarojabai was a case of schizophrenia and failed to fulfil the diagnostic criteria of the disease. Other cases have been described by Prabakaran (1970), Jeste et al (1973) and Agarwal and Sitholey (1978).

Abnormalities in biologic amine metabolism in the syndrome has been reported by Sayeed and Shanbogue (1980). Gilles de la Tourette in a girl with a history of rheumatic fever and of facial tics in her father was reported by Kaul et al (1988). The CT Scan showed cortical atrophy but with intact basal ganglia. The clinical response to haloperidol was satisfactory with decreased frequency and severity of tics and resumption of sphincter control. An improvement in the EEG also occurred.

Psychosurgery

The overlap of psychiatric and neurosurgical practice earlier in India is evidenced when it is noted the Superintendents of State Mental Hospitals and the directors of Private Psychiatric hospitals were performing standard bilateral frontal leucotomy, transorbital leucotomy and also cingulumotomy. Among the earlier generation of psychiatrists credited with such psychosurgical practice were Govindasamy and Rao 1944; Davies et al 1954, Mujawar 1954.

Govindasamy and Rao (1944) published the first series of leucotomy in

India. Cingulumotomy for drug addiction was initiated and popularised in India by Balasubramanian et al (1974).

The earliest case of cingulumotomy in pethidine dependency in India was reported by Venkoba Rao 1971. The patient was a 32 year old dental surgeon, who was dependent on pethidine for over 10 years. He attempted suicide thrice. He was a 'mainliner' administering himself 800-1000 mg of the drug intravenously. In view of the suicidal attempts and the difficulty in producing abstinence, he was subjected to cingulumotomy by Dr. V.Balasubramanian on 7th February 1970, in General Hospital, Madras. The follow up was possible for a period of 10 months during which the patient remained drug-free.

The decision to submit the patient to psychosurgery then was influenced by the advice of Busch (1957) 'when severe and disturbing mental symptoms threaten to disintegrate a more or less an intact personality and every other less destructive therapy has been tried in vain, psychosurgery is the fully justified. Faute de mieu, in the time of little or no understanding of the underlying pathophysiology'. Subsequently such surgical procedures were employed for other dependent states like alchoholism. There have been quite a few reports on psychosurgical procedures in other psychiatric illnesses.

The series reported by Venkoba Rao and Rawlin Chinnian (1974) comprised 22 patients (18 men and 4 women) in the age range of 18 and 50 with diagnoses of various psychiatric disorders. Obsessive compulsive neurosis contributed to 7, schizophrenia 5, opiate dependency 3, depression 2, aggressive psychopathy 1, hyperkinetic syndrome 1 and conversion reaction 1. The psychosurgical procedures conducted were bilateral cingulumotomy (15), basofrontal tractotomy 2, bilateral cingulumotomy and basofrontal tractotomy 1, prefrontal leucotomy 1 and amygdalotomy 1. The followup was conducted for a period of 6 months to 3 years among the cases of obsessive compulsive neurosis. The evaluation of improvement was on the basis evolved by Sykes and Tredgold (1964).One patient completely recovered, three improved with residual symptoms, two were unchanged and one worsened. Both the cases of refractory depression have been maintaining remission following basofrontal tracatomy.

Ramamurthi et al (1980) reported on 'functional neurosurgery' in depressive psychosis, obsessive compulsive neurosis and drug addiction. They have offered the followup of their 30 cases ranging from 1-7 years and recommend that in certain intractable cases of depression and obsessive compulsive neurosis precise stereotactic techniques of basofrontal tractotomy and cingulumotomy provide relief.

Neuropsychiatry of HIV Infection

Considering the urgency of the situation, the Indian Council of Medical

Research constituted a Task Force on HIV infection in 1985. The Task Force reviewed available information on the prevalence of HIV infection and recommended steps for establishing a suitable infrastructure for conducting clinical and serological surveillance for HIV infection in India and monitoring high risk groups for HIV infection. ICMR's National Institute of Virology (NIV) Pune and the Centre for Advanced Research in Virology, Christian Medical College, Vellore started screening high risk groups (sexually promiscuous men and women, homosexuals, drug abusers and person receiving repeated transfusions) for HIV antibodies using the available ELISA test. The first evidence of HIV infection in India was obtained in March 1986 when serum from 10 female prostitutes from the vigilance home in Madras showed presence of HIV antibodies by ELISA and Western Blot tests. Later NIV, Pune detected HIV antibodies in the first two patients of AIDS in the country - one following blood transfusion and the other following factor 8 infusion in USA. Following this, the ICMR Task Force recommended that a nation wide serosurveillance programme be initiated to screen persons with symptoms and signs suggestive of AIDS related complex (ARC), ADC and asymptomatic persons belonging to the high risk groups.

The details of the serosurveillance programme for HIV infection in India have been offered in the ICMR Bulletin, December 1987. 56,934 persons from high risk groups had been screened and 145 seropositive individuals detected. Surveillance data indicate that in India, prevalence of HIV infection even among the high risk groups was low and that heterosexual promiscuity is a major mode of transmission in the country. Transmission of HIV from spouse to spouse, infected mother to infant and through blood transfusion has been documented. The write-up in the ICMR Bulletin suggested that these data are to be constantly reveiwed so as to permit the incorporation of appropriate steps,namely screening of blood donors at appropriate time. It was suggested that the followup of seropositve individuals would provide information on course and outcome of HIV infection in India.

AIDS, ARC and ADC in India

Until recently, the AIDS cases reported from India were from among female prostitutes, foreigners living in India or Indians who had received blood transfusion abroad. A Bombay based 56 year old businessman, who developed AIDS subsequent to blood transfusion during cardiac surgery in US, was the first Indian victim of AIDS.(Lele, Parekh and Wadia 1986) A couple of years later, a 25 year old microbiologist at Hyderabad succumbed to AIDS. He too had blood transfusion in US (Indian Express, 8th August 1986). As on 28th July 1986, 18 cases of AIDS from India were described, all but 3 cases were from Tamil Nadu (Indian Express, 28th July 1986). Recently, AIDS deaths among Indians, who acquired the virus 'indigenously' have been reported - one from Vellore (Indian Express, July

20, 1988) and other from Bombay. According to the recently published information, there are 33 confirmed cases of AIDS syndrome in the country. There have been 19 deaths during the last 3 years of which 13 were Indians. 39 AIDS surveillance centres have been set up by Government of India and so far 1,50,000 people have been screened. There are 4 referral centres, two at New Delhi, one in Pune and one in Vellore (ICMR, Director General's Report 1986-87).

Neuropsychiatric and psychosocial aspects of HIV infection in India have been reported by Venkoba Rao (1988) and by Jacob John et al (1988). Besides symptoms of depression and suicidal behaviour, cases with schizophreniform symptoms have been observed. A careful psychological examination showed cerebral involvement. This suggests that depressive and schizophreniform symptomatology are consequent to brain damage. Cognitive disturbances like poor concentration and memory defect appeared even in the absence of gross neuropsychiatric symptomatology. In an appreciable number of cases associated sexually transmitted diseases like neurosyphilis are present but in the cases under discussion the symptomatology is attributable to HIV infection (Venkoba Rao 1988). Jacob John et al (1988) have narrated their experience and the organisation of psychosocial unit in association with the national AIDS reference and surveillance centres of the ICMR at Vellore. Presently, a project is in progress in ICMR Centre for Advanced Research on 'Health and Behaviour', Government Rajaji Hospital, Madurai, on HIV infected patients with a view to study 'psychiatric, neurological.psychosocial and behavioural aspects'.

Neuropsychiatry of AIDS and AIDS related problems

Five male patients with psychiatric symptoms associated with the fear of having contracted AIDS have been reported in India (Jacob et al 1987). They were negative for ELISA test and the clinical features included anxious, neurotic premorbid personality, tendency to have low extraversion and high neuroticism score on the Eysenck Personality Questionnaire, history of promiscuous heterosexual contact and symptoms and signs of anxiety state. These authors prefer to call this clinical state 'AIDS phobia'.

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Neuroradiology

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The doyen of neurosurgery in India, B. Ramamurthi, narrowly missed the opportunity of performing an open carotid angiogram in 1946. In the summer of 1949, he introduced the technique in Newcastle-upon-Tyne, England, having learnt it from Rowbotham at Manchester. When he returned, to start neurosurgery in Madras, there were formidable challenges and limitations. He had to work with the all-powerful general surgeons at the medical college and hospital. They decreed that he could perform his tests and operations only after they had finished their work for the day. The craniograph sanctioned by the government could not be put to use by him for 2 years as there was no x-ray tube on the machine! The bureaucrat placing the order had overlooked the need for this component.

The timely arrival of Mahadevan Pillai as radiologist to the Barnard Radiology Institute at the hospital helped Ramamurthi in investigating his patients radiologically. The outbreak of the Second World War had compelled Pillai to return to India after qualifying in radiology in England. He contributed greatly to the recognition and advancement of neuroradiology as a discipline. His profound knowledge of clinical medicine and excellent technical skills in radiology made his colleagues seek his advice on radiological methods and interpretation. Ramamurthi found him an enthusiastic colleague. At that time plain x-rays formed tha mainstay in the diagnosis of space occupying lesions. Sellar changes, bone erosion, hyperostosis and pineal shifts were looked for eagerly. In 1952, Pillai and Ramamurthi embarked on percutaneous direct carotid angiography as a routine diagnostic procedure. Ramamurthi recalls with nostalgia how he used to wheel the patients with stereotactic frame fixed on their heads from his ward to the radiology department to the amazement of onlookers in the long corridors. Gradually pneumoencephalography, ventriculography and myelography were introduced. His association with such giants among European neuroradiologists as JWD Bull, Pendergrass, Lindgren and Seldinger helped Mahadevan Pillai pioneer several techniques in our country. Apart from being an astute radiologist he was a great innovator and with the help of a local technician he designed a manual changer (to hold cassettes in series with springs for serial angiography) costing just Rs.160. In a similar manner connecting tubings, needle positioners etc.

were locally fabricated and used for angiography. He obtained the Seldinger percutaneous puncture needle and long rolls of catheter tubing from Lysholm's radiology department in Sweden and carried out the first transfemoral carotid angiography at Madras. He enjoyed teaching the technique of catheterisation to his students. Like many other clinicians interested in neuroradiology, Krishnamoorthy Srinivas, whilst in training in neurology,worked with Sydney P. Traub and was soon performing PEG, angiography and myelography independently. In London he worked with James Ambrose who helped him sharpen his angiographic techniques. On his return to Madras, he put these to good use.

During this period, at Vellore the aggressive zeal of Jacob Chandy to establish neurosurgery and neuroradiology was complemented by the enthusiasm of eminent radiologists like Scudder, Patterson and Johnson.

In Bombay, R. G. Ginde, Homi Dastur and J. N. Sidhva developed neuroradiology from 1955 onwards. Schoenander skull tables were installed at the Sir Jamsetjee Jejeebhoy (JJH) and King Edward Memorial Hospitals (KEMH) and cerebral angiography was started on a regular basis by Sidhva (JJH) and Homi Dastur (KEM) using serial film changers. P. E. Billimoria started catheter angiography at the JJH in 1960 and performed vertebral angiography through this route. K. V. Chaubal, retired professor of orthopaedic surgery, Topiwala National Medical College, recalls Billimoria's unequivocal demonstration in 1963 of hemistenosis of the lumbar canal in a patient complaining of unilateral sciatica.

In 1958 Ginde recognised the skills of D. S. Dadhich in radiology and arranged his visit to the Montreal Neurological Institute for training under Donald McRae. At the instance of Prakash Tandon, Dadhich sailed to Oslo to work with Frimandahl and Amundson at the Ulleval Hospital. In 1961, Dadhich went to Lindgren at Stockholm and later worked with Wickvlom at Gothenberg before returning to Bombay by the end of the year. By this time the Bombay Hospital was equipped with a Schonander skull table, tilting table for myelography and a serial changer. Dadhich quickly put the equipment to use and performed the first transfemoral vertebral angiogram at the Bombay Hospital.

Ginde (JJH) and Homi Dastur (KEMH) occluded carotid-cavernous fistulae by floating muscle grafts through external carotid arteriotomies - perhaps the first interventional neuroradiological procedures to be performed in this country. Homi Dastur (KEMH) studied hydromyelia by air myelography from 1969 onwards and was able to demonstrate the collapse of the cervical spinal cord on auto-tomography.

In 1960 Sidhva (along with Erik Lindgren, Ziddes des Plantes, Fischgold and others) was appointed on the Problem Commission on Neuroradiology of the World Federation of Neurology. Sidhva was the only Asian member. For his pioneering work on positive contrast cisternography, Sidhva was awarded the Sarat Kumar Gold Medal of the Indian Radiological Association in 1970.

In 1959, the techniques of fractional pneumoencephalography, myodil ventriculography and carotid angiography were simultaneously introduced at the Tirath Ram Shah Hospital, Delhi and at the K.G. Medical College at Lucknow. These conventional diagnostic procedures were established at the All India Institute of Medical Sciences (AIIMS), New Delhi by 1963.

Around 1960, Lt. General Prataprao specialised in neuroradiology at Guy's Hospital, London and he became the architect of neuroradiology in the Armed Forces Medical Services. His interest in neuroradiological evaluation of epilepsy and stroke with detailed clinical correlation won him the Sir J.C. Bose Oration and a Gold Medal.

The demands of neurosurgeons for precise diagnostic support helped the development of neuroradiology as a discipline. Ganguly, Varadarajan, Shyam Sharma, Goulatia and later Arya, Meera and Vasundhara are prominent among those devoting themselves fully to this speciality. Varadarajan was a close associate of Ramamurthi and contributed to several techniques in neuroradiology. With undiminished energy he continues to publish his clinical experiences. The rich contributions of Shyam Sharma on craniovertebral junction anomalies received wide attention in our country and Goulatia's work on the empty sella and disappearing lesions on computerised tomography added greatly to clinical management.

Gajaraj, the architect of modern neuroradiology at Madras had his training at the Royal Victoria Infirmary and Newcastle General Hospital. Bruce, Klaus Bron and John Feist guided him. In 1970, he was appointed Director of Barnard Institute of Radiology. He created a separate section of neuroradiology,starting with the appointment of a lecturer and then upgrading the post to that of a reader and then professor. He set up nuclear imaging with Rajagopalan's help and studied CSF circulation using Ytterbium DTPA.

Sneh Bhargava opened new vistas for neurodiagnosis in India with the installation of the first computerised tomographic scanner at the AIIMS in 1978. Pneumoencephalography was soon rendered obsolete. The studies at AIIMS threw new light on tuberculosis of the central nervous system and cysticercosis. With the availability of digital subtraction angiography unit. another whole body C.T. scanner and transcranial sonography the AIIMS has achieved the status of the centre of excellence in neuroradiology.

Mahadevan Pillai laid the foundations of a fully equipped neuroradiology department at the start of the National Institute of Mental Health and Neurosciences (NIMHANS) at Bangalore. After a brief stint at Zambia, he returned to Trivandrum and organised the department of radiology at Sree Chitra Tirunal Institute in 1977 and shaped the careers of many youngsters in neuroradiology. His intense interest in imaging and

knowledge in clinical neurology was a tremendous help to the young clinicians and the radiologists alike. As an administrator he gave full liberty to the youngsters to attempt and establish special procedures such as magnification angiography, stereoscopic angiography, air-myelography and spinal angiography. Unforgettable is his borrowing a new connecting tube from me for angiography at the age of 73, when he was a consultant to a nursing home.

By 1977, magnification and subtraction angiography became the order of the day at Sree Chitra Tirunal Institute, Trivandrum. Demonstration of collapse of syringomyelic cord in 1978 was an exciting experience. At the time when myodil ventriculography was generally in vogue, water-soluble contrast medium was used here in more than 800 patients. With the availability of image intensifier, arterial catheters, and the injection pump, percutaneous transfemoral pan-cerebral angiography became a routine.

Cooperation and mutual understanding between the surgical team and neuroradiologists gave birth to the frontier area of neurointervention. Free flow muscle embolization was introduced for the treatment of large and inaccessible arteriovenous malformations. After preliminary animal experiments with the use of liquid polymer embolic agents, first hand experience was gained in superselective catheterisation and embolization of cerebral and spinal arteriovenous malformations with isobutyl 2-cyanoacrylate. Techniques using coaxial microcatheters for detaching balloons and coils in carotid-cavernous fistulae and aneurysms of the carotid were perfected. Therapeutic embolisation is currently being carried out at the Sree Chitra Tirunal Institute, Trivandrum by the author; King Edward Memorial Hospital, Bombay by Anil P. Karapurkar and Ravi Ramakantan; National Institute of Mental Health and Neurological Sciences, Bangalore by B. Y. T. Arya and All India Institute of Medical Sciences, New Delhi by Goulatia and Misra. Arteriovenous malformations, arteriovenous fistulae, selected aneurysms and vascular tumours in the cranium and spine are being treated thus at each of these centres.

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Neurosurgery in India

Ram G. Ginde *

'Workers are here today and gone tomorrow, but the cause of science and the relief of human suffering will continue to exist'.

Wilder Penfield

We have assembled here today to rejoice in the twentieth anniversary celebrations of the Department of Neurology and Neurosurgery of the Government Medical Colleges and the General Hospital, Madras and to witness the inauguration of this fine Institute of Neurology, built up by my dear friend and colleague, B. Ramamurthi, with the help, loyal cooperation and hard work put up by himself and a dedicated group of his associates for nearly two decades, the encouragement received by him from his former teachers and well wishers as well as the generous support given to him by the Government of Tamil Nadu (Madras). It is a red letter day in his long and distinguished career.

I am happy to be here to express my great appreciation of his achievements and to congratulate him and his colleagues for the realization of their aim of creating this Institute of Neurology in Madras. I am sure, this is just a beginning and only an early milestone in the long and checkered career this institution is likely to play in the cause of neurology and neurosurgery in India.

On this solemn and momentous occasion, it seems appropriate to review the position of neurosurgery in India during the last 20 years. Brief notes and small articles have appeared in Indian and western journals and a comprehensive article on 'Emergence of neurosurgery in India' by Harvey Gass appeared in the Journal of Neurosurgery in 1966. Some discrepancies seem to have crept into these inadvertently. An opportunity has now presented itself to review the position of neurosurgery in India in the proper perspective and present its factual appraisal. As has been said by Sir Winston Churchill, 'Without a sense of history no man can understand the

* Reproduction of an address given by him on the occasion of the 20th Anniversary of the Department of Neurosurgery General Hospital, Madras and inauguration of the Institute of Neurology, Madras.

problems of our time.' In attempting this sketch care has been taken to be as objective and impersonal as possible with malice or bitterness towards none and charity and goodwill towards all.

Background

As is well known, trepanation was one of the earliest surgical procedures, practiced more than 5000 years ago, in the neolithic period, long before the existence of written records of history. Since those times, neurological surgery has evolved slowly and progressed very gradually, at times haltingly or even remaining dormant for a while, again to pick up lost ground by trial and error. In the middle ages, after the Renaissance, with the revival of modern scientific medicine, advances were made in the clinical, diagnostic and therapeutic fields. A real beginning was made in the latter part of the last century. Guest lecture delivered by the late Dr. Ram G. Ginde at the 20th anniversary celebrations of the Departments of Neurology and Neurosurgery, Madras Medical College and Madras General Hospital, 15 December 1970. During the more recent decades we see a staggering rate of progress. The story of its development is a fascinating saga of human pursuit and endeavour in the cause of science and relief of human suffering and has been well documented in the excellent monographs on the subject by Sachs, Horrax and Walker. Shortage of time precludes referring even casually to some of the most important landmarks on this occasion except to draw attention to the fact that the early pioneers who were attracted to neurosurgery in India, as in the rest of the world, have been general surgeons . They and their pupils, who took up to this speciality and are practicing it as their career have been influenced by some of the most illustrious and leading authorities in this field throughout the world.

Modern scientific medicine, called allopathic medicine at times, came to India with the establishment of the British rule in the first half of the last century. The graduates of our early medical colleges, now more than five quarter-centuries old, were fortunate in getting their postgraduate training in England. There, they worked under some of the most eminent physicians and surgeons of the time. Upon their return, while still practising as general surgeons and making surgery safe under the very trying local conditions they courageously undertook operations for diseases (including tumours) affecting the nervous system too.

Early pioneers of neurosurgery in India

I would like to specially mention and pay my humble tributes to the most commendable and courageous efforts made by surgeons like the late A.P. Bacha, G.V. Deshmukh, R.N. Cooper and A.V. Baliga (my teachers) in Bombay; N.S. Narasimhan, C.V. Vishwanatha Menon and U. Mohan Rao in Madras (who happily are with us and are gracing this occasion by their

presence), Lt. Col, F.J. Anderson and Provat Sanyal in Calcutta, Col. V.R. Mirajkar and Baldev Singh at Lahore and Balkrishna Rao of Mysore (now at the All India Institute of Medical Sciences, New Delhi). As is to be expected, the first batch of surgeons to train in this speciality and practice it exclusively have also come from these regions.

Emergence of neurosurgery as an independant speciality

Although neurosurgery was being performed with gradually increasing interest by general surgeons (who still carried the load of general surgery) in Bombay since 1940, the credit for starting it as an independent speciality goes to Jacob Chandy of Vellore, who after completing his training in Canada and the United States, started a separate department at the Christian Medical College and Hospital at Vellore in the second quarter of 1949 with 12 beds spread in the various medical and surgical wards. B.Ramamurthi soon followed at the Government General Hospital in Madras, in the fall of the same year. It seems he had to work for a while as a general surgeon till a separate and an independent chair for neurosurgery was created in 1950. The twentieth anniversay is being celebrated today. A passing reference may be made here to the efforts of the late S. T. Narasimhan, who after a brief visit abroad started a private neurosurgical clinic in this city in 1948 and later set up an EEG laboratory at the Government General Hospital in Madras in 1950.

In Bombay, neurosurgical work was started from the beginning of 1951, again as part of general surgery. More than 80% of the allotted 25 beds were occupied by neurosurgical cases within the first 6 months. After a considerable struggle, a separate and independent department of neurology and neurosurgery was opened in the fall of 1953.

With only three qualified neurosurgeons for the whole country till 1956-57, the work load at all these centres rapidly increased both in quality and in quantity. further developments occurred according to the response and adaption to local environmental factors as a result of the presence or lack of encouragement, cooperation and support. Suffice it to recall here the remark made by the great scientist and Nobel Laureate, the late Sir C.V. Raman in his lecture at my college in 1932, with his inimitable humour, 'In our vast subcontinent there seems to be more of brain in the south, more of brawn in the east', remarks which have proved to be almost prophetic with the passage of time. For those interested in medical conditions existing in the early fifties, I would like to refer to the candid, very constructive and helpful report of the late Alan Gregg, Vice-president of the Rockefeller Foundation, made after visiting all the then existing medical colleges and research institutes, and talking to the men working in them for over 3 months.

Development of the speciality in different parts of the country

The departments in Vellore, Madras and Bombay gradually started

showing an increasing output of work and created interest for the speciality in some of the resident staff. The bed capacity increased and better diagnostic and operating facilities were provided. Training programmes were initiated. Simultaneously, following close on their heels as it were, newer departments were started in different parts of the country. To get a clearer picture of the course of these developments, it seems better to consider them in the different zones, starting with the south, which had taken the lead.

The Southern Zone

Here, the pride of place must be given to the Christian Medical College and Hospital at Vellore where the first department of its kind was started in April-May 1949 with the appointment of Jacob Chandy as an Associate Professor of Neurosurgery. (He became professor in 1954.) In the earlier years, he had as his close associate Baldev Singh, the neurologist. The credit for the reputation and fame that Vellore has achieved as the leading institute of neurological sciences is due to their vision, tenacity of purpose and hard work coupled with the cooperation that Chandy was able to get from his devoted colleagues in the department and the institution, the State and the Central Governments as well as from the Christian missions in the west.

It was here that the first residency training programme was started in 1954. The first recognized University course for M.S. and later for M.Ch. was begun in 1958 and so far 12 persons have qualified. I am very happy that the quiet, soft spoken, amiable and efficient K.V. Mathai, who is now the head of the department after the retirement of Chandy after over 20 years of solid work, was the first person who had his entire training and qualified as a neurosurgeon in India.

The first neurology training programme was initiated in 1966 and 2 persons have qualified for the doctorate in neurology. Vellore also has other firsts to its credit. The first full time department of Neurochemistry was started here with B.K. Bachawat as its head and so far 9 persons from other universities have obtained their Ph.D. from it. It was in 1957, that a new wing with offices and laboratory facilities was opened by W.C. Penfield, O.M., F.R.S. of Canada. This later became the Department of Neurological Sciences. At present, it has the largest number of medical and paramedical personnel, the best equipment, facilities for diagnosis (including Echoencephalograph, EMG and isotope head scanner, over and above the conventional neuroradiological equipment and EEG Machine), a well equipped library and the best training facilities for graduate students,

including facilities for experimental neurosurgery. It also has the added advantage of annual visits and participation in the training programme by one of the members of the Congress of Neurological Surgeons of America, who spends at least 6 weeks at the institution.

B. Ramamurthi in Madras, who in the earlier years was associated with Balasubramanian, Arjundas, and the late S.T.Narasinhan, has also achieved an almost equal success with much less financial and other support, has overcome some of the deficiencies, has made a headway and now built up an Institute of Neurology, the first of its kind in India. (Another institute, the Bangur Institute of Neurology has come up later at Calcutta.) Mention may be made of some of the highlights of this institute in Madras. The EEG Department was opened in October 1950. A separate head injury unit was started in 1967. Situated as it is within the precincts of the Government Medical College and Hospital, let us hope that it will continue to do its specialised work in collaboration and cooperation with the parent institutions.

From these two original centres in the south, neuro-surgery spread to Stanley Medical College, Madras in 1962, with P.Narendran in charge; to Madurai in 1963 with M. Natarajan at the helm. The latter in this short span, even before the department is adequately staffed and equipped, has succeded in initiating a postgraduate training programme with one of the candidates already obtaining the M.Ch. degree. In 1968 another unit was started as Thanjavur with R. Narayanan in charge.

In the state of Mysore (now Karnataka), a beginning was made at Bangalore at the All India Institute of Mental Health by the late Govindaswamy in the early fifties. A formal neurosurgical department was started in the Mental Hospital in 1959 by R.M. Varma, who had his training under Mr. Alexander at Bristol, U.K. He has been able to develop an independent department of neurology and neurosurgery with the latest diagnostic and operating room facilities, at the same time keeping a close liaison with the Institute of Mental Health. He has as his associate Mani, the neurologist. I believe, a training programme for the M.Ch. degree has also been started.

In Kerala, the first neurosurgical unit was started at Trivandrum in 1966 with Bahuleyan and Sambasivan and another one at Calicut with Rajan in 1969.

Eastern Zone

While the senior general surgeons were operating occasionally on

neurosurgical cases, a small neurological unit with facilities for EEG was working at the S.S.K.M. Hospital with T.K. Ghosh and the late N.N. Das in charge. In 1955, Herbert Kraus of Vienna came to Calcutta at the invitation of B. C. Roy,the Chief Minister of the Government of West Bengal and developed neurosurgery at this hospital. R.N. Chatterjee and Asoke Bagchi, who trained under him, have now set up a well organized department at the Institute of Postgraudate Medicine and Research and the Sir Nilratan Sircar Medical College respectively. Chatterjee has been joined by R.N. Roy.

Since then the Bangur Institute of Neurology, has come up and has started functioning from June 1970. Full fledged work is likely to start from January 1971. It is hoped that all neurological and neurosurgical work in that region will be concentrated at this Institute.

In recent years, a centre at Ranchi (Bihar) is being developed by R. Prasad and Jaiswal and another at Bhubaneshwar (Orissa) by Sanathan Rath.

Central zone

The development of neurosurgery in Andhra Pradesh may now be considered, as this seems to have been influenced early in its development by the neighbouring States. The first neurosurgical unit in this region was started at the King George Hospital, at Vizag, (now called Vishakhapattanam) in 1956 by S. Balaparameshwara Rao. He was trained by Ramamurthi in Madras. He has developed it into a well established unit. During this period, B. Dayanand Rao, the present head of the Department and additional Director-General of Meedical Services of Andhra Pradesh, returned after his training under Mr. Rowbotham at Newcastle-upon-Tyne and started the neurosurgical department at the Osmania Medical College and Hospital at Hyderabad in 1957. He seems to have brought with him the interest of his teacher in head injuries. He was the first to shoulder the total responsibility of all head injury cases in the hospital at Hyderabad in 1957. He has been joined by Veera Raghava Reddy as Professor of Neurology since 1964 and both of them are working in close cooperation with the Psychiatric Department headed by Raghuram Reddy. Since 1969, under their combined efforts, assisted also by K. Rubia Rao, Professor of Radiology, a postgraduate training programme for M.S. degree of the Osmania University has been started. A third centre came into existence between 1964-67 at Kurnool under K.V. Chalapathy Rao, who had trained at Hyderabad and Vellore. In 1969, a fourth centre has been started at Guntur Medical College, with M.V. Subramaniam

as Professor. He has been trained at Hyderabad. Except at Hyderabad, there are no qualified assistants in neurosurgery.

Northern zone

In the north, neurology and neurosurgery started in 1956 with the arrival of Baldev Singh from Vellore at the Tirath Ram Shah Charitable Hospital. It was due to him and Col. V.R. Mirajkar that I had the opportunity to do some neurosurgical work there for a few months. Col. A.C. Ray of the Army Medical Centre also helped Baldev Singh in the initial stages. Soon however, Victor M. Rao, arrived from U.K. after his training with Mr. Murray Falconer and started regular neurosurgical work in 1958-59. He was also attached to the Irwin Hospital where in the capacity of a Junior Honorary Surgeon, he was able to operate once a week with great difficulty.

In 1962-63, a second neurosurgical unit came into being at the G.B. Pant Hospital at Delhi with Arjun Sehgal as neurosurgeon and Janaki, who was formerly at Vellore, as neurologist. In the following year 1963-64, Pathak, who was working as a general surgeon at the Willingdon Hospital, started doing neurosurgery after observing work in Bombay and some experience gained at Vellore. He has also been to Canada for a short period, but, it seems, he has not had any formal training in the speciality.

The All India Institute of Medical Sciences whose foundation stone was laid in 1946-47, had set up a committee of experts in various basic sciences and clinical disciplines in 1951, of which I happened to be one of the members. The institute was built up gradually at first with the basic sciences for the undergraduates, then the main clinical departments. Due to his special interest, neurophysiology was being developed at the Institute by Prof. B.K. Anand since its inception in 1957. Neuroanatomy (with L. Chacko and N.H. Keswani) and neurochemistry were also started simultaneously. In 1963, James Austin, a visiting Professor of Neurology from the United States started the neurology unit. Vimala Virmani took over from him. The regular departments of neurology and neurosurgery came into existence only in March 1965 with the appointment of Baldev Singh as Professor in neurology and P.N. Tandon as Professor of neurosurgery. After his training in Canada and Norway, Tandon had earlier started a neurosurgery unit at Lucknow in 1961. Vimala Virmani continues as Assistant Neurologist and Ajit Banerjee, who had his training at Vellore, was appointed as Assistant Neurosurgeon in 1966. Postgraduate training in neurology and neurosurgery was begun soon after-

wards and the first two batches have already passed after completing their training. Possessing practically all the required equipment medical and paramedical staff, secretarial assistance, reference library, facilities for research and continuous in-service residency training programme, this institution has come upto the expectation of its founders and other observers, as one of the best in the country for training undergraduate and postgraduate students in practically all the specialities, perhaps next to the Christian Medical College and Hospital at Vellore. I predict that these two institutions and the institute of neurology here in Madras, are likely to remain at the forefront as the main training centres in neurological sciences for quite some years.

Another neurosurgery unit came into existence at the Safdarjang Hospital, New Delhi in 1967 with H.S. Ahaluwalia as Neurosurgeon and Nigam as a neurologist. This institution has the special advantage of having a neuropathology department and the Indian brain tumor registry under the able hands of Professor Sriramchari, who with his industry, genial personality and obliging nature has endeared himself to all the neurosurgeons who seek his advice and guidance. He has also been training neuropathologists. In 1965, one more neurosurgical unit was started at the Military Hospital in New Delhi with Major R.S. Rana at the helm.

However, in New Delhi, the last five years have seen some turmoil with its attendant repercussions. R. M. Varma was appointed Professor. Varma has since returned to his own institution in Bangalore. During Varma's tenure Mehta was appointed as an Associate Professor of Neurosurgery. Sehgal with no other option, has plunged into private practice and he has been doing neurosurgery mainly at the Holy Family and Sir Gangaram Hospital. He has been closely associated with S.S. Pant, a qualified neurologist as the latter also has had no opporunity of getting a position in a teaching institution. Victor M. Rao has left India and it is said that he may not return. Baldev Singh has formally retred but continues to carry on his research activities as an emeritus Professor and a National Scientist. S.N. Pathak has been appointed in his place as Professor of Neurology. At the Safdarjang Hospital, M. Gourie-Devi has been appointed as Professor of Neurology and Nigam has entered private practice. Recently, he left India and has gone to the United States. Major Rana has resigned from military service and has joined the fray of private practice, doing most of his neurosurgery at the Tirath Ram Shah Charitable Hospital.

Apart from Delhi, one of the earliest neurosurgical centres in the northern region is the one at Lucknow, where between 1958-61

some neurosurgery was being done at the Military Hospital by Lt. Col. A.C. Ray. Col. Ray has now joined administration and Col. Mohinder Singh, who was formerly at Poona, is doing neurosurgery at the Military Hospital. About that time, a neurology service was started at the King George Medical College, in the Department of Medicine headed by N.N. Gupta. P.N. Tandon joined as a neurosurgeon in 1961, in the Department of Surgery headed by C.B. Singh who was doing some spinal surgery. (This is a factual error. Professor S. C. Misra was the head of the department of surgery. Professor R. V. Singh was the other professor in the same department. In the early 1950s, Dr. Pritam Das satarted some neurosurgery at this institution but he did not pursue it. - Referee's comment by Dr. P. N. Tandon.) The first chair for neurosurgery was created in 1963 again as a part and parcel of the Department of Surgery and the same arrangement continues even now. The post fell vacant in 1965 when Tandon moved to All India Institute of Medical Sciences, in Delhi. Some work was carried on in the meantime by G. Newton, who was appointed Reader after he had his neurosurgical training at Vellore. In 1967 V.S. Dave, who had trained under Wilder Penfield and his team in Montreal and had subsequently worked for four and half years as an Honorary Assistant Professor of Neurosurgery at the Grant Medical College and Sir Jamsetjee Jejeebhoy Hospital in Bombay, was invited to this chair. Now, he has a separate neurosurgical wing with attached neuroradiological facilities and operating room set up. He also has a fully trained neuropathologist in K.M. Wahal. There is a good animal house with facilities for experimental work. The neurology service however still continues to be run by the Professor of Medicine. Dave has initiated a postgraduate training programme for the M.S. degree in neurosurgery of the Lucknow University.

In the Punjab-Haryana sector, D.R. Gulati, after his formal training in Canada started the neurosurgical department in 1962, as an Assistant Professor at the Institute of Postgraduate Medicine and Research at Chandigarh. He became Professor of Neurosurgery in 1968. The neurology service was started simultaneously, initially by Vimala Virmani but the post fell vacant after she moved to Delhi in 1964. There has been no neurologist so far. (Recently two assistant neurologists have been appointed.) Inspite of these deficiencies, a postgraduate training programme has been started and one candidate has got his M.Ch. 2 years ago. At the Christian Medical College and Hospital at Ludhiana some neurosurgery is also being done by Namboodripad, a Vellore-trained neurosurgeon.

Smaller centres also sprang up in this region. M.G. Sarin, who had some 15 to 18 months training at Vellore started a unit at S.M.S.Hospital at Jaipur (Rajasthan) in 1961-62. Since then, he has spent sometime in U.K. and is now a full-time Professor. There is no assistant neurosurgeon, nor is there a counterpart in neurology. The centre has yet to develop fully.

Perhaps due to the interest of Balkrishna Rao (then Professor of Surgery at Gwalior) in neurosurgery, Dharkar was deputed for training to Vellore in the early fifties. He has been doing some neurosurgery while still carrying on the load of general surgery. There is no neurologist and his department has not been able to function as yet in a regular way. The sixth department in this region was started at the Banaras Hindu University at Varanasi (U.P.) in 1963. S .K. Mukherjee, who had worked for several years in a neurosurgical unit in U.K. under Valentine Logue, and subsequently completed his postgraduate degree (M.S. General surgery) under Homi M. Dastur in Bombay was appointed as a reader. Because of lack of facilities, and absence of neurologist till 1967, the progress of this unit seems to be rather slow. Katian, a selftrained neurologist has since been appointed as a reader. At Indore (M.P.), there is a unit of neurology headed by A.C. Jain under the Department of Medicine at the Mahatma Gandhi Medical College and Maharaja Yeshwantrao Holkar Hospital, but there is no neurosurgeon.

Western Zone

The western zone, where neurosurgery has taken roots much earlier, is considered last because of its differing ideological environment and historical background. Traditionally, it has been a hot bed of politics. To quote a few examples it was in Bombay that the late Lokmanya Tilak had proclaimed way back in 1903, 'Swarajya is my birth right and I shall have it'. The late Sardar Vallabbhai Patel under Gandhiji's direction had started the non-cooperation movement at Bardoli (Gujarat) in 1923. Later, Gandhiji himself had started the salt march at Dandi (also in Gujarat) in 1931 and finally gave the Quit India call to the British Government in Bombay in 1942. It was in Bombay that the first medical college in the country staffed entirely by Indians belonging to the independent medical profession (Seth Gordhandas Sunderdas Medical College) was started in 1925-26. The repercussions of these political activities have unfortunately permeated and polluted the medical atmosphere too.

Although regular neurosurgery was started in Bombay in January 1951 at the Seth Gordhandas Sunderdas Medical College and King Edward VII Memorial Hospital, it was not until October 1953 that the Department of Neurology and Neurosurgery was at last opened after considerable struggle with a separate ward of 40 beds and an independent operation theatre. Neuroradiology was done on the then existing x-ray machines. Inspite of increasing amount of work that was being done under very trying circumstances the Department of Neurosurgery was temporarily closed about the middle of 1956 due to many reasons which though very pertinent and important have not been referred to because of their local and very narrow interest. It was revived in 1957 with the appointment of Homi M. Dastur (who had trained for four years with Wyllie McKissock in U.K.) as Assistant Professor. Two years later he became a Professor. About the

same time Anil D. Desai was attached to the neurosurgical unit as Honorary Assistant Neurologist. The tall, dignified and soft spoken E.P. Bharucha, a British trained neurologist, who also had a year with Denny Brown at Harvard in U,S.A., was already in charge of the Neurology Unit since its inception in 1953. He was joined by V.P. Mondkar (whom he had trained) as Honorary Assistant Neurologist. Subsequently, Mondkar has been to U.K. at the Institute of Neurology, Queen Square for over a year and has spent a few months under Ludo Van Bogaert at Brussels. In 1964, U.S. Vengsarkar, a Vellore trained Neurosurgeon was appointed as Assistant Neurosurgeon under Dastur. However, due to some differences and difficulties that he experienced, he went abroad and spent over a year and a half, as a resident at St. Vincent's Hospital in New York. After his return he has joined Sheth Vadilal Sarabhai Hospital at Ahmedabad as Assistant Neurosurgeon. S.K. Pandya, who had some neurosurgical experience while doing his M.S. (General surgery) under Gajendra Sinh, was appointed as Assistant Neurosurgeon under Dastur in 1967 and was confirmed in 1969. These departments have eventually made a steady progress during these 12-13 years, with a neurosurgical setup, separate offices, operating room block with facilities for stereotaxic surgery also. Recently an Echo-encephalograph has been added. D.H. Deshpande has joined as Neuropathologist after some training in Bombay (under Ilona Bubellis, a visiting Neuropathologist from the United States in 1964-65) and then in U.K. at the Institute of Neurology, London, under Professor Blackwood. EEG facilities have been in existence almost from the very beginning to which EMG was added a few years ago. Over the last three years, an Epilepsy Research Project has been undertaken. Training for M.S. (Neurosurgery) of the Bombay University has at last been started with requirements and training programme quite different from all the other previously mentioned centres perhaps more suited to the local genius and approval of the medical faculty of the University.

At the Grant Medical College and the Sir Jamsetjee Jejeebhoy Group of Hospitals, Bombay, one of the three oldest medical colleges in the country, neurological work was started as part of general medicine by Menino DeSouza, after his return from his training in U.K. in 1949-50. In 1957, N.H. Wadia, who had worked for several years under the late Lord Brain, was appointed as Honorary Assistant Physician in DeSouza's unit where 5 to 6 beds were earmarked for neurology. S.J. Irani, who also had training in neurology in U.K. was also attached as Honorary Assistant Physician to the hospital about the same time. J.N. Sidhva, who had trained in neuroradiology with James Bull at the Institute of Neurology in London was appointed as Honorary Assistant Radiologist in the middle of 1957. In the 1950s, Shantilal J. Mehta, Professor of Surgery, was keen on developing neurosurgery. He encouraged his Assistant Surgeon, Gajendra Sinh, to specialise in this branch. Gajendra Sinh therefore went to Vellore and worked with Jacob Chandy. In 1959, separate neurology and neurosurgery units were started. These were headed by Wadia and Sinh

respectively. A Schoenander skull table and 90-90 myelography table were installed shortly afterwards. In the beginning of 1962, another unit of neurosurgery with 30 beds was added making a total of 60 beds for neurosurgery and 30 beds for neurology, all housed together in one of the wings of the newly built hospital building. In the latter half of the same year, S.N. Bhagwati (who had part of his training in Bombay and then four years with Wylie McKissock in London and a year with Luis Amador in Chicago) and V.S. Dave, who had three years training in Canada, were appointed as Honorary Assistant Neurosurgeons. In 1963, a new operation theatre block exclusively for neurosurgery was opened with recovery rooms next to the nursing station. B.S. Singhal, who had his training in neurology under R.E.Kelly and S. Levin, then at Maida Vale Hospital in London, with special interest in EEG was appointed Honorary Assistant Neurologist. The Neuropathology Unit of the I.C.M.R. under D.K. Dastur was shifted from the Tata Memorial Hospital to the premises of the Grant Medical College. It has steadily grown and deals with neurological and neurosurgical material referred from the Neurology and Neurosurgery services, from the Department of Paediatrics and Plastic Surgery as well as from other hospitals. D. K. Dastur has also been guiding students for M.Sc. and Ph.D. in Biochemistry.

With the laudable objects of improving the quality of work, giving timely assistance, training specialists for other medical colleges in the state and elsewhere, encouraging research, to absorb trained Indian medical men returning from abroad for gainful employment in the speciality, to get some substantial aid by way of equipment and starting a proper training programme with exchange of personnel, a Directorate of Neurology was started at the Grant Medical College and Sir Jamsetjee Jejeebboy's Hospital by the Government of Maharashtra in January 1964. Unfortunately, it met with strong opposition from its inception and has recently been abolished.

In 1965, R.D. Variava, trained under Geoffrey Knight in U.K. worked for a few months as a Pool Officer at the J. J. Hospital and has since been in private practice in neurosurgery in Poona. In 1967, Dave left the J.J. Hospital after accepting the post of Professor of Neurosurgery in Lucknow. In 1970 S.B. Yodh, who had several years of training in neurosurgery in Toronto and then in Boston at the Harvard Medical School under William Sweet, has been appointed as Honorary Assistant Neurosurgeon and C. Vas, a U.K. trained Neurologist under the late Hugh Garland of Leeds with special interest in EEG has been appointed as additional Honorary Assistant Neurologist. EMG is done through the Department of Plastic Surgery.

At the Topiwala National Medical College,(which was upgraded for the graduate course in medicine after independence in 1947) S. Patrao, one of the senior honorary general surgeons, had started operating occasionally for lumbar discs, spinal cord tumours and tics in the early fifties. V.G. Daftary, who was working in his unit as Honorary Assistant Surgeon, returned in 1959-60 after spending two years in neurosurgery under Rowbotham of Newcastle-upon-Tyne. P.M. Dalal, who was appointed as

a full time Professor in Medicine in 1958, went to Boston for his training in Neurology as a Rockefeller Fellow in 1960-62 under Professor Raymond Adams and Miller Fisher. He brought with him the interest of his teachers in cerebrovascular disorders and was appointed Professor of Medicine and Neurology in 1963 with 16 independant beds for neurology. Since 1969, after another year abroad as a visiting Professor, he resigned from the fulltime post, and is working as Honorary Neurologist. He has entered private practice. There is no neurosurgery unit as yet. Daftary still heads one of the units of general surgery and he is officially in charge of 7 neurosurgical beds. However, he is filling more and more of his general surgical beds with neurosurgical cases. There is no assistant either for neurology or neurosurgery. Neuroradiology was done by S.G. Daftary one of the Honorary Assistant Radiologists till 1969, when G.R. Jankharia, a British trained Neurradiologist under Phillip Sheldon at Oxford and David Edwards in London, was appointed as Honorary Neuroradiologist. K.K. Ahuja, one of the Assistant Professors of Pathology had returned after spending a year in New York in Neuropathology but soon left for Calcutta and has joined a private hospital. There was an EEG machine run by the Psychiatric Department but no EEG work is being done in the Department since 1967. The new hospital attached to the College is nearing completion. It may be possible for both neurology and neurosurgery to make a little more rapid progress when it is commissioned.

Neurosurgical work for private patients in Bombay was started at the Bacha Memorial Nursing Home and Parsee General Hospital in 1951, thereafter at the Breach Candy and the Bombay Hospitals in 1954. The work load and the bed capacity at the Bombay Hospital increased with the provision of increasing facilities with the result that by 1959 a separate unit of 20 beds for patients in very low income group and an additional 12 to 15 beds for private patients with separate neuroradiological set up consisting of a Schoenander skull table, automatic serial changer for angiography, 90-90 table for myelography and an independent operation theatre exclusively for neurosurgery were established. Neuroradiology was done by D.S. Dadhich, who had his training under Donald McRae in Canada and then for over a year under Freemandahl and Amundsen in Norway. Neuropathology was done routinely in the Department of Pathology. In 1962, the EEG Department was started under the supervision of B.S. Singhal, who was appointed as neurologist to the hospital. Within the next 2 to 3 years, practically all the neurosurgeons and most of the neurologists who had Honorary attachments in teaching hospitals were on the staff of the Bombay Hospital.

In Poona, R.D. Variava has been been doing private practice in neurosurgery since 1966 in some of the nursing homes. He is not attached to the Byramjee Jejeebhoy Medical College. Since the last 4 months, S.D. Dighe, who had earlier trained under Daftary in Bombay, has returned from U.K. after working with Mr. Dutton of Preston while doing his

Fellowship of the Royal College of Surgeons. He has also started private practice as a neurosurgeon. Some neurosurgery is done at the Armed Forces Medical College and its affiliated hospitals by Col. Virendra Mohan (who was formerly at Lucknow). A few years ago, Azariah, a well qualified neurosurgeon trained abroad, tried to develop neurosurgery at the Wanless Hospital at Miraj but he soon left it and, I believe, has settled in New Zealand. N.A. Siddiqui, Professor of Surgery, at the Mayo Hospital, Nagpur, who had 18 months training in Bombay and two years in U.K. under Mr. Wyllie McKissock was doing some neurosurgery at the Sassoon Hospital, Poona, even with very limited facilities, in his capacity as Assistant Professor of Surgery. But, he too has been very unfortunate in not getting any encouragement or opportunity of working either in the existing neurosurgical units in Bombay or developing it independently either at Poona or at Nagpur, where he has virtually been incarcerated. Thus, apart from the three units in Bombay, which are still not fully developed, no neurosurgical or neurological work is being done in any of the remaining 7 medical colleges in the state.In the neighbouring state of Gujarat, which was formerly part of the bilingual Bombay Presidency, neurological work was begun by M.B. Patel, who had some training under Bharucha in Bombay. He is the Honorary Physician to the Civil Hospital, Ahmedabad, since 1961. About the middle of 1964, P.R. Thakore, who had his training in U.K. under Valentine Logue, was appointed as Professor of Neurosurgery and Patel became Honorary Neurologist. The department of Neurosurgery was however first opened at the Sheth Vadilal Sarabhai Hospital where B.J. Damany, who had one and a half years training in Bombay and then spent four years at the Mount Sinai Hospital under Robert Sidney Gross, was appointed as a Neurosurgeon in April 1963. He too, had to work for some months in a general surgical unit. In January 1964, a completely independent Department of Neurosurgery was opened with separate beds and operation theatre. Soon afterwards, P.C. Chandani, who had his training in Bombay for a few years and then spent 2 years in Norway under Professor K. Kristiansen, and who had set up private practice in Ahmedabad, after a brief sojourn in Bombay after his return, was appointed as Honorary Assistant Neurosurgeon. Within a year or so, however, he left for the United States and seems to have settled there. Damany continues as the fulltime Professor and head of the department. He has been joined by U.S. Vengsarkar, as Assistant Neurosurgeon since 1968. The institution is now part of the School for Postgraduate Medicine and Research, attached to the Gujarat University. H.D. Joshi, an Honorary Physician is in charge of the Neurology beds in addition to those of general medicine.

Summary

To summarize, during the last 20 years the number of neurosurgery centres has increased from the original three centres at Vellore, Madras and Bombay to 32 units distributed in different parts of the country. The

statewide distribution is as follows: Tamil Nadu (5), Andhra Pradesh (4), New Delhi (4), Maharashtra (4), Uttar Pradesh (3), West Bengal and Punjab-Haryana region (2 each), and a single unit, still in the early stages of development in the states of Mysore, Bihar, Orissa, Rajasthan, Madhya Pradesh and Gujarat. There are no units so far, in the states of Jammu and Kashmir, Assam, Meghalaya, Himachal Pradesh, Tripura, Manipur, Goa and other centrally administered territories.

Of all these centres, only three have developed fully: the Christian Medical College and Hospital at Vellore, the All India Institute of Medical Sciences, New Delhi and the Institute of Neurology in Madras. These three institutions are adequately equipped to enable all types of neuro diagnostic investigations to be carried out and to cope up with all varieties of neurological and neurosurgical problems. They are also adequately staffed with medical and paramedical personnel to ensure timely and efficient treatment to be given even to serious and emergency cases at short notice and to provide proper after care and followup. There is proper record keeping, satisfactory secretarial assistance, a good reference library with sufficient books and periodicals. There is a continuous well organized in-service graduate training programme for candidates who are selected after proper screening. This covers the theoretical aspects in the main and allied subjects and ensures a very satisfactory practical approach to clinical neurology and familiarity with bed side, diagnostic and operative procedures. There are regular bed side ward rounds, seminars, group discussions and actual performance of Technical and diagnostic procedures including different types of operations under the supervision and guidance of the senior members of the staff. At All India Institute of Medical Sciences, New Delhi, a dissertation or thesis and a more detailed study in one of the aspects of the speciality is also compulsory. The other centres at Bangalore, Bombay, Calcutta, Chandigarh, Delhi, Hyderabad and Lucknow are likely to develop fully in the next few years.

Specialist Training

A word about the specialists' training. There are as is well known varying standards in the different medical degrees of the various Universities in India. There is no conformity as regard the basic requirements, equipment, staff, duration and nature of the training programme. It is necessary to have some basic minimum standards in keeping with the nature of the speciality. These have been formulated and laid down in the recent report on Postgraduate Medical Education published by the Medical Council of India in 1966. But they are not strictly adhered to. Selection of candidates should be made based on aptitude and capacity to do sustained hard work as well as on the previous career and performance. A continuous in service training should be absolutely essential. In my humble opinion, in the present setting of the general medical education in India, where standards are gradually deteriorating, there should be no specialist without a prior

postgraduate qualification in any of the specialities, much more so in a speciality like neurosurgery. Otherwise, we may soon have, not only neurologists or neurosurgeons without general postgraduate training in medicine and surgery but also neuroradiologists, neuropathologists etc. without basic qualifications in their respective specialities. The final certification may however be left either to the universities or specialist national organizations.

Research

Regarding research, again it is so essential not only to have well equipped and adequately staffed departments with sufficient scope and accommodation but continues and devoted work of all the workers with a team spirit and loyal cooperation even on the day to day problems facing them. Many a time, this alone even in the absence of adequate equipment, leads to a break through and is likely to result in producing worthwhile contributions to research. In its absence, the efforts of a single individual no matter how skilful, hard and sustained, are likely to prove almost futile, specially in a clinical speciality like neurosurgery. To quote the late Sir Edward Archibald, 'Carrying on research single handed in modern medicine is like Christopher Columbus sailing in a birch canoe and expecting to reach the North Pole'.

Present state of neurosurgery in India

There are now about 58 qualified neurosurgeons in the country and almost an equal number of neurologists and a few neuroradiologists, neuropathologists, neurochemists and neurophysiologists. As with the medical colleges, speciality departments are springing up like mushrooms without adequate staff and equipment and even postgraduate degrees have been introduced in some of the institutions which are still deficient in these. These events do not forbode well for the speciality, and are likely to affect the standard of performance of the specialists even after possessing the degrees and lower the prestige of the Indian neurosurgeons in international bodies.

Inspite of there being well qualified and experienced specialists in practically all the branches of medicine and surgery including neurosurgery in India, one witnesses ministers, V.I.Ps and people in affluent circumstances rushing abroad for operations and even for consultations of flimsy grounds. I beg to submit here that there is something basically wrong in our philosophy or outlook. Either the specialists are inexperienced or cannot instill confidence in these persons and deliver the goods or, the hospitals are ill equipped and poorly run or that they are just not good enough for these people, who perhaps feel that they are the only ones who are entitled to these privileges of going abroad for medical help which are denied to the average Indian. Even if half the amount that is spent on

foreign trips by these people on medical grounds alone, could be spent on improving the medical institutions in the country, it would help many of our institutions to be properly equipped not only to give the necessary treatment for these elite but would indirectly also be able to give better care to the average Indian, who unfortunately has no option at present but to endure his inevitable fate out of sheer desperation and helplessness.

There are well qualified, skilled and experienced surgeons in the country but the conditions of their work in most institutions are deplorably poor. It is extremely ignorant, insultingly cynical and most unfair to expect good results from even well trained men under the present existing conditions. It is a sad commentary to see that many highly qualified Indians after their training prefer to settle down abroad or those that have returned and seen the conditions of work are forced to leave the country for want of gainful employment and due to lack of adequate facilities in many of the ill-equipped institutions. Yet one hears and reads so often, about the national brain drain. In this connection, I can do no better than to quote a few excerpts from the report of Alan Gregg, 'Every action or inaction that sets quantity above quality of medical education invites corruption, quackery and incompetence as your best offering for those in need of medical care'. 'If a government seriously underpays the teachers of the doctors of the future, it will deserve the charge of criminal negligence' and, 'Indian legislators can neglect, ignore or override the importance of recruiting enough devoted and well trained teachers for the future. But they do so in perfect certainty of having ample time to regret their choice, for it will take a long time to correct such inexcusable improvidence'.

The future

It is necessary or rather essential that large scale assistance should be made available by the Central and State Governments, philanthropic institutions and trusts, people in affluent circumstances and the talents of the scientists and technocrats be harnessed for improving the standard of medical care, medical education and research. Even if adequate funds are not available, there should be no difficulty in introducing and supporting full time work at all teaching institutions even in the Honorary capacity providing facilities for paying and private patients and allowing the medical men to earn an honourable and respectable living while devoting all their time in the cause of science and relief of human suffering, from a mutually agreed moiety of the income collected from paying patients. It is a great pity, however, that due to vagaries of different traits of human nature based on traditions, bureaucracy, vested interests, political influences, corruption at all levels and above all, because of lack of real national fervour and concern for fellow men that such contrasting conditions are noticed even to casual observers from abroad in this unfortunate over-populated, multiracial, multireligious, multilingual, economically poor still largely illiterate and backward country of ours. I

would like to end this resume with some excerpts from Wattman's Medical Education in the western civilisation. To quote 'in history one learns of, reads of eras of calamity. Unhappy man so many countless time has mustered his forces and endured incredible hardships in his study and labour for a better future. When brighter days do come at last, one would think that history might take a rest in this respect. But, no! Each time dark shadowing clouds again appear, the whole structure falls and man has once more to face the same infinite toll to reinstate that which is lost. The hard won golden ages eludes poor man and in the unbroken flow of life itself all things pass, swept away again'.

I am grateful to many of my colleagues particularly to Mathai, Ramamurthi, Tandon, Bagchi, Chatterjee, Ghosh, Dayanand Rao, Damany and others for their help in supplying me with some of the information gathered in this review. I once again congratulate Ramamurthi and his colleagues for bringing up this fine Institute of Neurology in Madras. Let me hope that in keeping with the very ancient saying,'By wisdom is a house built, by understanding is it established and by knowledge shall its chambers be filled'. Ramamurthi and his colleagues will continue to strive to maintain and enhance its reputation and leave a tradition for posterity. I wish them all strength, good luck and God speed. Finally, I would like to close this review with a sublime thought so beautifully expressed by Sir William Osler in his Minerva Medica written in 1908 'Where the worshippers are most devoted, not mark you, where they are most numerous, where the clouds of incense rise highest, there must my chief temple be and to it from all quarters will the faithful flock.

Neurosurgery

Vijay K. Kak

Introduction.

The development of neurosurgery in India during the past 40 years has almost paralleled the achievements of the country in "40 years of freedom" India is a virtual subcontinent itself, extending from 7.5oN to 37oN latitude and 68oE to 97.5oE longitude, with an area of 3.3 million km2. However, there was no trained neurosurgeon nor any department of neurosurgery at the time of independence in 1947. Neurosurgery was being performed by a few Indian general surgeons at that time. These included A.P. Bacha, G.V. Deshmukh, R.N. Cooper, A.V. Baliga, A.E. De Sa and S. Patrao S J Mehta at Bombay; Col. F.J. Anderson, P.C. Sanyal, U.P. Mukherjee and Col.N.C. Chatterjee at Calcutta; Col. V.R. Mirajkar and Col. A.C. Roy at Delhi; N.S. Narasimhan, C.P. Vishwanatha Menon and U. Mohan Rao at Madras and B.N. Balakrishna Rao at Bangalore and Gwalior (Bagchi 1987, Ginde 1970, Karapurkar and Pandya 1983).

Karapurkar and Pandya (1983) tracing the development of neurosurgery in ancient India refer to transplantation of the head of an elephant on Ganesha (an Indian deity), trepanation and removal of an intracranial mass by Jivaka (physician to Lord Buddha) and the neurosurgical accomplishments of Sushruta, the master surgeon, documented in the Sushruta Samhita.

Modern neurosurgery was started in India in 1949 by Jacob Chandy at Vellore, followed soon thereafter by B. Ramamurthi at Madras (1950) and R.G. Ginde at Bombay (1951). Salient details of the development of neurosurgery in India are detailed below region by region. The names of states are as at the present time.

For additional information, the reader is referred to the publication entitled Profiles of research in neurosciences in India (Reddy et al 1984) and their more recent review of current status of clinical neurosciences (Reddy et al 1988). The emergence of neurosurgery in India, as seen through western eyes, can be studied in Harvey Gass' paper (1967).

Development of modern neurosurgery

Southern Region

Tamil Nadu:

The first department of neurology and neurosurgery was started by Jacob

Chandy in April 1949 at the **Christian Medical College and Hospital, Vellore,** with beds spread in various medical, surgical and paediatric wards. Initially Chandy had to work all by himself as a neurologist, radiologist, pathologist and neurosurgeon. An early assistant, P. Isiah worked with him for three years before opting for obstetrics and gynaecology. In 1951 Baldev Singh having read Chandy's publications in medical and lay journals, came over from Amritsar to join him. A neurology clinic was started twice a week. 404 new patients were seen during the first year, 143 of them being admitted. 131 operations were performed that year. An EEG laboratory was officially opened in December, 1952. Construction of a 36 bed ward for neurology and neurosurgery was started in 1951, and was inaugurated by Rajkumari Amrit Kaur on 20.2.1954. Three days later, Wilder Penfield laid the cornerstone of the new neurology block, which was inaugurated by Sushila Nayar on 7.1.1963 (Pandya 1982c).

Trainees from other centres started joining the team, R.N. Roy from Calcutta (1955), Gajendra Sinh from Bombay (1956) and R.S. Dharker from Gwalior (1956) being some of the earlier ones. The postgraduate training course in neurosurgery was started in 1958 with K.V. Mathai as the first trainee for M.Ch. (Neurosurgery). He was followed by M.G. Sarin (1958), Jacob Abraham (1959), K.N. Nambudripad (1960), K.V. Chalapathi Rao (1961), U.S. Vengsarkar (1961), Col. Mahendra Singh (1961), A.K. Banerji (1962), Goodwin Newton (1962), Sanathan Rath (1963), M. Sambasivan (1964), J.K. Sharma (1965), Ramesh Chandra (1965), K.V. Devadiga (1966), I. Dinakar (1966), N.D. Vaishya (1968), D.K. Panda (1970), K. Satyanarayana (1970), P. Sreekumar (1971), T. Surya Rao (1971), Mathew Chandy (1972), S.K. Ramachandran Nair (1972), S.R. Dharker (1973), S.M. Panda (1973), T.N. Shadangi (1974) and A. Marthanda Pillai (1974) during the first 25 years of this department (Anonymous 1974). The credit for the reputation and fame that the department of neurological sciences at Vellore has achieved is due to the vision, tenacity of purpose and hard work coupled with the coöperation that Chandy was able to secure from his devoted colleagues in the department and the institution, the state and central governments as well as from Christian missions in the West.

Chandy retired in June, 1970 and was succeeded by K.V. Mathai as head of the department of neurological sciences. The position was taken over by Jacob Abraham in April, 1973.

Following on the heels of the department at Vellore was that at the **Madras Medical College and Government General Hospital, Madras** with the joining of B. Ramamurthi in October, 1950. He had to start from scratch, developing goodwill, confidence of colleagues and patients and all the physical requirements of a neurosurgical department. In 1948, S.T. Narasimhan had started a private neurosurgical clinic in Madras. He later joined Ramamurthi in the Medical College Hospital. Angiography became

possible only in 1952 when a trained radiologist, K.M. Pillai, joined them. Ramamurthi was made in-charge of an independent unit with 4 beds! It was hard work all the way - coming early, departing late, writing case notes, filling indent forms, and attending to outpatients, dressings and roentgenographic tests. After eighteen months, he was given 10 beds, an operation day and two house surgeons who were changed every month. In 1953, the traditional ether induction of anaesthesia gave way to the use of thiopental sodium and muscle relaxants. In 1956, on the advice of Wilder Penfield, Ramamurthi overcame the idea of leaving Madras to join the All India Institute of Medical Sciences (AIIMS), New Delhi. Gradually he built up his team and was able to attract trainees like S. Balaparameswara Rao (1955) and M. Natarajan (1959). V. Balasubramaniam was the first candidate from his department to obtain the degree of M.Ch. (Neurosurgery). Other trainees included P. Narendran, S. Kalayanaraman, R. Narayanan, T.S. Kanaka, P.B. Ramanujam, R. Govindan, A.K. Sait and K. Logamuthukrishnan (Pandya 1982a).

In 1965, Ramamurthi obtained Rs.2,00,000 from a trust towards the establishment of an Institute of Neurology at the Madras Medical College, the first of its kind in India. Ramamurthi was the first Director of the Institute of Neurology, Madras. He retired in January, 1978, and has been heading the Dr. A. Lakshmipathy Neurosurgical Centre at Madras since February, 1978. Ramamurthi was succeeded by P. Narendran at the Institute of Neurology, Madras. S. Kalayanaraman is the current occupant of the post.

From these two original centres in the south, neurosurgery spread to **Stanely Medical College, Madras** in 1962 with P. Narendran, to Madurai in 1963 with M. Natarajan and to **Thanjavur** with R. Narayanan in 1967. Narayanan stayed at Thanjavur upto 1972, when he was transfered, to be reposted there in August, 1981.

The department of neurosurgery was started at the **Government Erskine Hospital** (now **Government Rajaji Hospital), Madurai** by M. Natarajan in September, 1963. He started the department with 30 beds, sharing the operation theatre with general surgeons, and without any qualified assistants (Athiappan, 1987). A postgraduate training programme was started in the year 1967, with D. Balakrishnan as the first trainee. He later started the department of neurosurgery in the **Medical College, Coimbatore,** in November, 1979, and was appointed professor.

Karnataka:

In the state of Mysore, a beginning was made at the **All India Institute of Mental Health, Bangalore,** by Govindaswamy in the early fifties. A formal neurosurgical department was started in the **Mental Hospital**

(later **National Institute of Mental Health and Neurosciences), Bangalore,** in 1959 by R.M. Varma. He was able to develop an independent department of neurology and neurosurgery, keeping a close liaison with the Institute of Mental Health. His sustained efforts culminated in the formation of the National Institute of Mental Health and Neurosciences (NIMHANS), with Varma as its Director. Upon his retirement, he was succeeded by G.N. Narayana Reddy. The Institute houses all the major and ancillary disciplines related to neurological sciences. The present faculty includes B.S. Das, K.S. Narayana Swamy, B.A. Chandra Mouli, N.V.S. Murthy and A.S. Hegde.

St. John's Medical College, Bangalore also has a neurosurgery department. In addition, neurosurgical facilities are available at **Kasturba Medical College, Manipal,** and at **Mangalore**.

Kerala

During the thirties, general surgeons managing head injuries and depressed fractures included A.E. John and Poduval. During this period Somervelle at Neyyoor was doing some neurosurgery. A **Medical College** was established at **Trivandrum** in 1951, and Col. D.K. Sabhesan, K.K. George, R. Kesavan Nair, K. Sivarajan and Mathew Verghese were performing neurosurgery while doing general surgery. K. Bahuleyan joined as assistant profesor of orthopaedics and started doing full-time neurosurgery. He soon left and joined the armed forces. The department of neurosurgery was started by M. Sambasivan in 1966, after his training at Vellore. Two years later, neurosurgery was started by C.A. Rajan at Medical College, Calicut and by K.M. John at **Kottayam Medical College, Kottayam.** Rajan is currently the professor of neurosurgery at Kottayam, P. Sanal Kumar is heading the department at Calicut and K. Bhavadasan is at **Medical College, Alleppey.**

The **Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum,** was founded to commemorate the 60th birthday of the Maharaja of Travancore in 1972. Neurosurgery at this Institute was started by George Mathews, who later left for the U.S.A. D. Rout, trained at Postgraduate Institute of Medical Education and Research (PGI), Chandigarh, joined in 1979, and is currently heading this Department of Neurosurgery. Neurosurgery in the private sector has developed at Cochin with P. Sreekumar, S.M. Pillai, K.M. John, A.N. Subba Rao and Sojan Ipe (Sambasivan 1989).

Andhra Pradesh

The earlier neurosurgical operations at King George Hospital, Vizag, were performed by B. Tirumal Rao, an E.N.T. surgeon, and M.V. Ramanamurti, a professor of surgery, and at Osmania General Hospital, Hyderabad, by

M.G. Kini, C.L. Modi and K. Ramesh Pai, all general surgeons. Planned neurosurgical operations were performed by John Potter, a British surgeon based at the Military Hospital, Secunderabad, during 1946-47 (Pai 1985).

The development of neurosurgery in Andhra Pradesh was influenced by the development of this speciality in its neighbouring states. The first neurosurgical unit in this region was started at the **King George Hospital, Vizag (now called Vishakhapatnam),** in April, 1956 by S. Balaparameswara Rao who had been trained at Madras. A year later, B. Dayananda Rao, having finished his training at Newcastle, started the neurosurgery department at the **Osmania Medical College at Hyderabad.** Both these pioneers worked hard to develop their respective units into full fledged departments. A third centre came into existence at **Kurnool Medical College** in April, 1964 under K.V. Chelapathy Rao, who had been trained at Hyderabad and Vellore. A fourth centre was started at **Guntur Medical College** in 1969 with a Hyderabad trained neurosurgeon, M.V. Subrahmaniam. Except at Hyderabad where M.V.R. Reddy had joined as professor of neurology in 1964, there were no qualified assistants in neurosurgery nor any neurologists at other centres.

Subsequently neurosurgical units were started at every medical college in the state - **Gandhi Medical College, Hyderabad,** in 1971 by Raja Reddy and at Warangal by K.I. Askari in 1973. Radha Krishna Reddy started the centre at **Kakinada** and **Tirupathi**. All medical colleges in the state have neurosurgery departments now. The neurosurgery department at **Nizam's Orthopaedic Hospital, Hyderabad,** was started by S. Balaparameswara Rao in June, 1976.

Postgraduate training in neurosurgery was started at Osmania Medical College by B. Dayananda Rao in 1969 and at Gandhi Medical College, Hyderabad by D. Raja Reddy in 1976. At the present time, neurosurgical training facilities are also available at Andhra Medical College, Vishakhapatnam and Nizam's Institute of Medical Sciences, Hyderabad (Raja Reddy 1989).

Western Region

Maharashtra

Prior to start of neurosurgery as a separate discipline, Shantilal J. Mehta at the Grant Medical College, Bombay, A.P. Bacha, G.V. Deshmukh, R.N. Cooper, A.V. Baliga and Arthur E. De Sa at the Seth G.S. Medical College, Bombay and S. Patrao at the Topiwala National Medical College, Bombay, were practising neurosurgery as well while doing general surgery (Ginde 1970).

The first specialised department of neurosurgery, and the third in the

country, was started at the **Seth G.S. Medical College and King Edward Memorial Hospital, Bombay,** by Ram G. Ginde in April 1951. Initially Ginde's patients were housed in a general surgery ward. He carried out all neuroradiological tests himself and performed 2-3 operations every week.

However, it was not until October, 1953 that the department of neurology and neurosurgery was opened with a separate ward of 40 beds and a separate operation theatre. As the terms under which Ginde was asked to work at these institutions were not satisfactory, he resigned in 1956. He was appointed as a consultant neurosurgeon at the Breach Candy Hospital, Bombay, and shortly thereafter as honorary neurosurgeon at the Bombay Hospital, Bombay, at R.N. Cooper's recommendation (Pandya 1982b).

The neurology and neurosurgery department at the K.E.M. Hospital was revived with the appointment of H.M. Dastur as assistant professor in June, 1957. About the same time Anil Desai was attached to the neurosurgical unit as assistant neurologist. Dastur was provided just one house surgeon and had to fend for himself for regular beds, investigation facilities and operation theatres. In 1964, U.S. Vengsarkar, a Vellore trained neurosurgeon, was appointed under Dastur. However, he soon went abroad for a year and a half and joined the Sheth V.S. Hospital at Ahmedabad on his return. S.K. Pandya was appointed as assistant neurosurgeon in 1967 and currently heads the department. The department has now a bed strength of 45, 3 operation theatres and its own neuroradiology department. The present staff includes R. D. Nagpal, A. P. Karapurkar, Atul Goel and Santosh Prabhu.

The historically older **Grant Medical College and Sir J.J. Hospital, Bombay,** lagged behind their sister institutions in Parel. Gajendra Sinh, after his training at Vellore, started the department of neurosurgery in 1958 with one house surgeon. V.S. Dave, trained at Montreal, joined him in 1962. Ginde joined in 1961 to form the second unit and S.N. Bhagwati a year later. The department has now a bed strength of 45 and 3 operation theatres. The present staff includes M.J. Virani, K.N. Turel, and V.R. Parikh.

The third neurosurgical department in Bombay was started by V.G. Daftary at the **Topiwala National Medical College and B.Y.L. Nair Hospital** in 1971. Daftary, a renowned general surgeon, had received neurosurgical training at Newcastle. His was the only unit in the city then which took on the total care of a head injury patient by a neurosurgeon. Daftary retired in 1977. U.S. Vengsarkar now heads the department and is assisted by V.G. Panchal.

The fourth teaching department of neurosurgery was created at the

Lokmanya Tilak Medical College and Hospital, Sion, Bombay, by B.J. Damany and P.S. Ramani in 1975. The unit was upgraded to a full department in 1977 with Damany as the professor of neurosurgery. During the early years, they had patients scattered all over the hospital and were permitted to operate only when the theatres were free. The department now has a bed strength of 16.

In addition, the larger private hospitals in Bombay have their own neurosurgical units. Neurosurgical work for private patients in Bombay was started at the Bacha Memorial Nursing Home and Parsi General Hospital in 1951, followed by the Breach Candy and Bombay Hospitals in 1954. The Bombay Hospital increased its facilities so that by 1959 there was a unit of 20 beds for the very low income group patients and an additional 12-15 beds for private patients. The neurosurgery unit at the Bombay Hospital was founded by Ginde, at the Jaslok Hospital by Gajendra Sinh, at the H.N. Hospital by Vengsarkar and Damany, at the Nanavati Hospital by Daftary, at the Bhatia General Hospital by Gajendra Sinh and at the Sushrusha Hospital by Ramani (Ginde 1970, Pandya 1986).

In Poona (Pune), R.D. Variava had been practising neurosurgery since 1966 without any attachment at the medical college. S.D. Dighe also started neurosurgery practice in 1970. Earlier, Azariah, a qualified neurosurgeon, had tried to develop neurosurgery at the Wanless Hospital at Miraj but he soon left and settled abroad. N.A. Siddiqui, who had been trained for 18 months in Bombay and 2 years in U.K., started doing some neurosurgery at the Sassoon Hospital, Poona, in his capacity as assistant professor of surgery. However, he did not get any encouragement, opportunity or facilities for developing the speciality either at Poona or at Nagpur, where he worked as professor of surgery at the Mayo Hospital (Ginde 1970).A viable department of neurosurgery at the B.J. Medical College and Sassoon Hospital in Pune was started by the late Shankar D. Gokhale. It is now headed by Bafna.

Gujarat

Neurological work in Gujarat was started by M.B. Patel, who was trained at Bombay, at the **Civil Hospital, Ahmedabad,** in 1961. About the middle of 1964 P.R. Thakore, who was trained in U.K., was appointed professor of neurosurgery. However, the first department of neurosurgery in the state was opened in April, 1963 at the **Sheth V.S. Hospital, Ahmedabad,** where B.J. Damany, trained at Bombay and the U.S.A., was appointed as a neurosurgeon. He had to work for some months in a general surgical unit. An independent department of neurosurgery was opened in January, 1964. Soon afterwards, P.C. Chandani, trained at Bombay and Norway, was also appointed as a neurosurgeon but he left within a year. Damany continued as professor of neurosurgery, and was joined by U.S. Vengsarkar in 1968, who later on left to join the department of neurosurgery at the B.Y.L. Nair Hospital, Bombay (Ginde 1970).

Neurosurgery at Baroda was started in a private hospital by C.D. Patel in 1976. Pradeep Pethe has established neurosurgery at Surat.

Rajasthan

M.G. Sarin, after finishing his neurosurgical training at Vellore in 1961, joined the **S.M.S. Medical College, Jaipur,** as lecturer in neurosurgery. Later he spent a year in U.K., and was appointed professor of neurosurgery. He retired in 1977. S.R. Dharkar, trained at Vellore, joined the department in 1975, and currently heads it. A postgraduate training course in neurosurgery has been started since 1985. The department has 60 beds and a new building named as the Bangur Medical Research Centre (Dharkar 1986).

Recently, lecturers in neurosurgery have been appointed in **Medical College at Udaipur and Ajmer.**

Eastern Region

West Bengal

In the early forties Col. F.J. Anderson and P.C. Sanyal, both professors of surgery at the Calcutta Medical College, U.P. Mukherjee of the Carmichael Medical College, Calcutta, and Col. N.C. Chatterjee of the Residency General Hospital, Calcutta, were occasionally operating on patients needing neurosurgery.

In September 1951, T.K. Ghosh set up the nucleus of the first neurological unit at the **P.G. Hospital (present S.S.K.M. Hospital), Calcutta.** A combined department of neurology and neurosurgery was opened at the P.G. Hospital, Calcutta, in February, 1955, and Herbert Krause of Vienna was invited to become its first director. R.N. Chatterjee and A.K. Bagchi joined Krause as neurosurgeons and T.K. Ghosh as neurologist. Krause left India in 1956 and the onus of further development of the speciality fell on the three successors. R.N. Roy joined the department in 1958 after completing his neurosurgical training at Vellore. Following further training in Vienna and Edinburgh, Roy was appointed assistant professor in 1956.

The same year, A.K. Bagchi left the department and joined **Nilaratan Sarkar Medical College, Calcutta,** to open the second such department in the state of West Bengal. B.G. Chakraborty was appointed as a lecturer to help Bagchi.

The beginning of microneurosurgery was established there following the visit of H.W. Pia and E. Grote. A.K. Bagchi retired in 1984 and the department is currently headed by A.K. Ray.

D. Roychoudhury, after working in the department of neurosurgery at the

P.G. Hospital, Calcutta, from 1960 to 1968, left to join the **National Medical College, Calcutta,** to open the third neurosurgical department.

The combined department of neurology at the Institute of Postgraduate Medical Education and Research, S.S.K.M. Hospital, Calcutta, was split into independent department of neurology (headed by T.K. Ghosh) and neurosurgery (headed by R.N. Chatterjee) in 1966.

The fourth neurosurgical department came up at the **Calcutta Medical College with** the joining of B.G. Chakraborty and N.A. Wasek. The **Bangur Institute of Neurology** was founded in 1970, adjacent to the main Institute of Postgraduate Medical Education and Research campus, to establish an institute of neurological sciences. R.N. Roy took over charge of the department of neurosurgery following the retirement of R.N. Chatterjee in 1974. A postgraduate teaching course was started in the year 1977. M.K. Bhattacharya and S.N. Banerjee joined the department of neurosurgery in 1981. The Bangur Institute of Neurology developed into a full fledged neurosciences centre during the tenure of R.N. Roy. Following his retirement in 1986, Bhattacharya took over charge of the department of neurosurgery, which also has S.N. Banerjee, P. Saha and I. Roy (Bagchi 1987, Bhattacharya 1987).

Assam

The first state in north-east India to have a neurosurgeon, after West Bengal, is Assam. B.C. Kakati, after his training at Vellore, set up a skeletal department of neurosurgery at the **Medical College, Guwahati.** Recently K.V. Mathai, after his retirement from Vellore, has set up a private neurosurgical practice based on a CT scan centre at Guwahati. He has been joined by Zakir Hussain who was trained at Vellore. Zakir Hussain has recently been appointed assistant professor of neurosurgery at Medical College, Guwahati.

Orissa

Orissa had Sanathan Rath as its first neurosurgeon at the **S.C.B. Medical College,** Cuttack, which he joined in December, 1966 following his training at Vellore. A regular postgraduate training course was started in 1980. The department has gradually expanded with the joining of B.N. Acharya, S.C. Mohanty, B.C. Tripathy and B. Lenka.

More recently smaller neurosurgical centres have been opened at the **Medical College at Burla and Behrampore.**

Bihar

The first neurosurgical unit in Bihar was established by R. Prasad at

Ranchi. He was trained in England. The centre is now headed by H.P. Narayan. Patna, the capital city of Bihar has three neurosurgeons - H.R.P. Varma, trained in England, Ramesh Chandra, trained in Vellore and R.P. Chowdhury who has joined Varma at the **Prince of Wales Medical College, Patna.**

Northern Region

Delhi

Neurology and neurosurgery started in the north in 1956 with the arrival of Baldev Singh from Vellore at the **Tirath Ram Shah Charitable Hospital, New Delhi.** In the initial stages Baldev Singh was helped by Col. V.R. Mirajkar, Col. A.C. Ray and R.G. Ginde. Regular neurosurgical work started in 1958 with the joining of Victor Rao, who was trained in England. He was also attached to the Irwin Hospital, New Delhi, where he was able to operate once a week with great difficulty.

A second neurosurgical unit was started at the **G.B. Pant Hospital, New Delhi,** in 1962 with Arjun Sehgal as neurosurgeon and S. Janaki as a neurologist. In the following year L.R. Pathak, who was worked as a general surgeon at the Willingdon Hospital, New Delhi, started doing neurosurgery after a period of observation in Bombay and some experience gained at Vellore.

The neurology unit at the **All India Institute of Medical Sciences (AIIMS), New Delhi,** was started by James Austin, a visiting professor of neurology from the U.S.A., in 1963. This unit was continued by Vimla Virmani. However, regular departments of neurology and neurosurgery came into existence in March, 1965 with the joining of Baldev Singh as professor of neurology and P.N. Tandon as professor of neurosurgery. P.N. Tandon, who after his training at Montreal and Oslo had earlier started a neurosurgical unit at Lucknow in 1961, was soon joined by A.K. Banerji who was trained at Vellore. A postgraduate course in neurosurgery was started in 1966. This department made rapid progress in the fields of patient care, training and research. Constant efforts made to broaden the horizons of neurosurgery by collaborating with other allied disciplines led to the recognition of the need for developing a comprehensive neurosciences centre at the Institute. The proposal was approved by the Government of India in 1975, and various parts of the building of the centre began to be occupied from February 1983 onwards. Brahm Prakash, who was trained at the Institute, joined its faculty and worked till July 1980 when he left to take over as professor of neurosurgery at G.B. Pant Hospital, New Delhi. The other faculty members at present at the AIIMS include R. Bhatia, V.S. Mehta, A.K. Mahapatra and Sanjiv Bhatia (Ginde 1970, Tandon 1988).

In the meantime, another neurosurgical unit was started at the

Safdarjang Hospital, New Delhi, with the husband-wife team of H.S. Ahluwalia and J.J. Ahluwalia as neurosurgeons. However, they left after a few years and the department is currently manned by R.K. Navalakha and Laxman Das both of whom were trained at the AIIMS, New Delhi.

Arjun Sehgal left the G.B. Pant Hospital, New Delhi where R.M. Varma of Bangalore was appointed as professor of neurosurgery in 1967. Varma, who was joined by D.S. Mehta, returned to Bangalore in 1968 and Mehta resigned to start neurosurgical practice at Amritsar. Sushil Kumar and D.N. Pal joined in 1979. Brahm Prakash joined as professor of neurosurgery in July, 1980 and has built up a well equipped department. They have since been joined by A.K. Singh and Ajay Sharma. A postgraduate training course has also been started. This department was the first in the country to start using laser and CUSA, and has been doing excellent microneurosurgical work (Prakash 1988a).

The department of neurosurgery at **Ram Manohar Lohia Hospital (formerly Willingdon Hospital), New Delhi,** is currently staffed by S.P. Agarwal and Karam Chand who were both trained at the AIIMS, New Delhi.

In the private sector, Victor Rao left India in the early seventies. Delhi has a number of private hospitals were good neurosurgical facilities are available. Arjun Sehgal, H.N. Agarwal, S.K. Sogani and Col. V.S. Madan are working at Sir Ganga Ram Hospital, New Delhi. K.K. Joshi, trained at P.G.I., Chandigarh, formerly also worked at Sir Ganga Ram Hospital, New Delhi, but has recently moved over to the Holy Family Hospital, New Delhi. Jawahar Dar and J.K. Sharma are practising at the Mool Chand Hospital in Delhi.

Uttar Pradesh

Apart from Delhi, one of the earliest neurosurgical centres in the northern region was the one at the **King George's Medical College, Lucknow,** where P.N. Tandon had joined in August, 1961 following his training at Oslo and Montreal. The post of professor of neurosurgery, created in 1963, fell vacant in early 1965 when Tandon moved to the AIIMS, New Delhi. Some work was carried out in the meantime by G. Newton, who had joined there after being trained at Vellore. In November, 1967, V.S. Dave, who was trained at Montreal and had worked for four and a half years at Bombay, joined as professor of neurosurgery. The department slowly increased its activities and a postgraduate training programme was also started (Newton and Prakash 1972). Dave retired in 1988. Apart from Newton, the present staff includes I.N. Vajpeyi, Mazhar Hussain and I.C. Premsagar.

Another department of neurosurgery has very recently been started at the

Sanjay Gandhi Postgraduate Institute of Medical Sciences at Lucknow. The Institute, meant for superspecialities only, is nearing completion of its first phase of construction. D.K. Chhabra and V.K. Jain have joined the department of neurosurgery. The second neurosurgical centre in the state of U.P. was started in 1962 when K.C. Mukherjee joined the **Institute of Medical Sciences, Banaras Hindu University, Varanasi,** after completing his training in England and under H.M. Dastur at Bombay. During the initial years, he attended to out-patients and performed a few emergency neurosurgical procedures. The joining of S. Mohanty as lecturer in neurosurgery in June, 1975, after his training at AIIMS, New Delhi, gave the much needed boost to the department. The bed strength increased from 8 to 19 in 1978. Mukherjee retired in September, 1977. A postgraduate training course was started in 1976. S.C. Tandon joined as lecturer in 1979 (Mohanty 1984).

Another smaller neurosurgical unit has been functioning at the **J.L.N. Medical College, Aligarh Muslim University, Aligarh.** Narendra Kumar had been working as the sole neurosurgeon until 1988 when V.K. Srivastava joined him. Recently the government of U.P. had appointed lecturers in neurosurgery in Medical College at Allahabad, Agra, Kanpur, Meerut and Gorakhpur.

Chandigarh:

The **Postgraduate Institute of Medical Education and Research (P.G.I.), Chandigarh,** was created as an institute of national importance in 1962. Neurosurgery was started at Chandigarh at the General Hospital, Sector 16, in 1961 and later at the P.G.I. in January, 1962 with the joining of D.R. Gulati as assistant professor following his training at Montreal. Initially he worked single handed and looked after both neurology and neurosurgery with a total of 47 beds. Vimla Virmani helped him in neurology during 1965-66 and Ved Sachdev in neurosurgery during 1966-68. Neuroradiological investigations were started by J.S. Sodhi in 1962. An EEG machine was acquired in 1966. The division of neurology was separated from neurosurgery in 1968. Twelve beds in the emergency ward were allocated to neurosurgery in 1978. The postgraduate training course in neurosurgery was started in 1966, with Ved Sachdev as the first trainee. He left for the U.S.A. in 1968. V.K. Kak, after his training at Belfast, joined the department in 1969. Successive faculty members of this department include K.C. Pani, D. Rout, K.S. Mann, V.K. Khosla, S.N. Mathuriya, B.S. Sharma, S.M. Rohatgi and Ashis Pathak. Pani left early for the U.S.A. Mann, who had been trained at London, left 4 years after joining and moved to Hong Kong. Rout and Rohatgi have joined the faculty of Sri Chitra Tirunal Institute of Medical Sciences and Technology at Trivandrum. Gulati retired in 1983 and Kak took over as head of this department.

Punjab

Ludhiana in Punjab has neurosurgical facilities at three private medical institutions. N. Nambudripad, a neurosurgeon trained at Vellore, had been working at the **Christian Medical College** (CMC) since 1962. He was joined by Lajpat Rai and T.N. Shadangi. The latter left the C.M.C. to join as neurosurgeon at a private cancer hospital in the city. The Dayanand Medical College appointed B.K. Pansey, trained at P.G.I., Chandigarh, as assistant professor in 1983.

Haryana

The neighbouring state of Haryana has a department of neurosurgery at the **Medical College, Rohtak.** J.K. Sharma worked in this department for a short time in the early seventies. However, regular work started with the joining of N.K. Sharma, in 1981, and Sanjeev Dua a little later.

Jammu and Kashmir

The **Sher-e-Kashmir Institute of Medical Sciences, Srinagar,** started a department of neurosurgery with M.A. Wani, R.K. Peshen and M.L. Babu. Peshen has since left for Saudi Arabia. R. Sexena worked here for a short time before leaving for Gorakhpur.

Madhya Pradesh

The development of neurosurgery in M.P. has lagged behind considerably. Until recently, the only neurosurgical centre was at the **G.R. Medical College, Gwalior.** B.N. Balakrishna Rao, a professor of surgery, was doing some neurosurgery during the early period. S.R. Dharkar, who was deputed for training in neurosurgery at Vellore in 1956, joined this centre on his return. He was joined by N.D. Vaishya, another Vellore trained neurosurgeon, in March 1970. Only very recently, lecturers in neurosurgery have been recruited for the **Medical College at Bhopal, Indore and Jabalpur.** It is planned to develop a full fledged department at Bhopal.

Neurosurgical facilities are also available at the steel plant at Bhilai.

Indian contributions to neurosurgery

An attempt will now be made to give a brief resume of some of the important contributions made by Indian neurosurgeons. Admittedly there would be an element of overlap in this regard with some of the other chapters of this book. The object of the present review is to highlight those conditions which present to the neurosurgeon requiring surgical intervention or those which are more common in the Indian population than in other less populated and economically affluent nations.

Congenital Anomalies

An analysis of 23 hospital-based studies of all live births and still births showed a mean major malformation rate of 20.2 per 1000 births, ranging from 8.6 in Bombay to 36.0 in Chandigarh and 37.9 in Pondicherry where autopsy rates are very high. The mean neural tube defects were 2.41 per 1000 births. There were only 3 hospital-based surveys of live births with a mean of 18.9 major malformations and 3.33 neural tube defects per 1000 births. Only 2 studies have examined newborns in the general population. The mean major malformation rate was 30.15 and neural tube defects 2.35 per 1000 births. The prevalence of anencephaly and spina bifida is high in Punjab, Delhi and Rajasthan as compared to that in the southern and eastern states, and is as high as in Ireland (ICMR 1984).

Sethi et al (1962) described their experiences of 5 congenital central nervous system (CNS) malformations in 1350 patients attending the neurology out-patient service. Prakash et al (1976) reported on intracranial congenital malformations presenting in adults.

Encephalocoeles

Anterior encephalocoeles are seen in unusually large numbers in Uttar Pradesh, Delhi, Punjab and Haryana. Tandon (1966) reported on 30 such cases seen during 31/2 years at Lucknow. He continued to see patients with anterior encephalocoeles at Delhi (Tandon 1970, 1973). Dayanand Rao (1969) discussed the anatomical basis for a two stage surgical procedure for repair of these encephalocoeles. Tandon has now introduced a single stage operative procedure for repair of the encephalocoele and correction of craniofacial deformity. Kak and Gulati (1973) have reported the familial occurrence of anterior encephalocoele, the first in the literature. Kak (1980) reported on his experience of 20 cases of frontoethmoidal meningoencephalocoeles.

Hydrocephalus

Despite all advances, the management of hydrocephalus continues to be a perennial problem. It is not uncommon in India. Since the majority of neurosurgical centres drain vast geographic areas with varied terrain, these children more often than not reach late for treatment. Of the 708 cases of hydrocephalus treated at Madras between 1950 and 1969, only 275 were less than 6 months of age and 90 children were above 3 years of age when first seen (Ramamurthi 1970a) Iyer et al (1960) wrote about the anatomical findings in three children with hydrocephalus. Pandya reviewed congenital fourth ventricular outlet block (1974a) and Chiari malformations in childhood (1984a). Till the late 1960s, the therapy of hydrocephalus was crude and the results unpredictable. Roy Chowdhury (1969) reported 'arrest' of hydrocephalus in 72% of 36 patients treated with

oral glycerol. The prohibitive cost of Pudenz and Holter shunts was beyond the reach of most patients. The Denver shunt was a little cheaper, but it was only after the development of an inexpensive silastic shunt by Upadhyaya, that an effective mode of therapy became available. Recently another indigenous shunt system (Chhabra shunt) has been developed. The management of hydrocephalus has been discussed by Balasubramaniam et al (1967) and Pandya (1984b). A case of unilateral hydrocephalus secondary to obstruction of one foramen of Monro was reported by Bhagwati (1964). The problems associated with the management of multicystic hydrocephalus have been discussed by Pandya et al (1974b). Sambasivan and Sanal Kumar (1984) and Rapgay et al (1987) used real time ultrasound through the anterior fontanelle for the diagnosis of hydrocephalus. Raja Reddy and Laxmi (1985) reported on the intellectual development in shunted hydrocephalic children.

Prolonged survival following shunt surgery has resulted in the development of certain uncommon complications. Cases of 'shunt nephritis' following ventriculoatrial shunt have been reported from Chandigarh (Pereira et al 1987) and Vellore (Singh and Chandy 1987). The development of pericardial effusion following an atrial shunt was reported by Dev (1979). Complications reported following ventriculoperitoneal shunt include subdural abscess (Sharma and Kak 1987), subdural abscess following colonic perforation (Sharma and Kak 1988), umbilical CSF fistula (Pansey 1987) and spontaneous extrusion of the peritoneal catheter through the intact abdominal wall (Sridhar et al 1988).

Spina Bifida

All varieties of spina bifida are seen in this country. However, lack of proper facilities at most rural and over urban centres result in a delayed referral of cases. Patients with occult spinal dysraphism are seen at all ages, and in a large proportion deformities of the feet, trophic ulcers, paraparesis and urinary incontinence have already developed by the time they seek treatment. The variety of dysraphic states do not vary from those seen elsewhere (Rao and Dinakar 1971, Dinakar et al 1980, Babu et al 1980).

Infants with meningomyelocoele, with or without hydrocephalus, present a greater difficulty in management. Several infants have already developed infection due to delayed referral. The scarcity of rehabilitation facilities makes the management of survivors even more difficult. A variety of factors, other than medical, influence the decision of the neurosurgeon regarding surgery in some of these cases. Pani et al (1972) described a dorsolumbar meningomyelocoele associated with non-capsulated lymphoid, fatty, cartilagenous and bony tissue.

Craniosynostosis

All varieties of craniosynostosis are encountered in India. However, delayed

referral results in the development of gross deformities and visual impairment. Earlier reports on craniosynostosis include those by Ramamurthi (1966) and Bagchi (1967). For the past several years, the author has been performing extensive fronto-temporo-orbital craniectomies for these children with good cosmetic results. Karapurkar and Goleria (1986) have devised a new technique of stack grafts for reconstructing the lateral walls and advancing the orbits in cases with coronal synostosis.

Arachnoid Cysts

Dastur and Mukherjee (1962) reported 3 cases of primary arachnoid cysts of the brain presenting with raised intracranial pressure. They could demonstrate that these were associated with absence of nervous tissue. Sethi (1970) presented his experience of 5 cases of primary arachnoid cysts. We have come across 33 patients with primary intracranial arachnoid cysts, out of which 21 were infratentorial (Tripathy et al 1988).

Spinal arachnoid cysts have been encountered at extradural as well as intradural locations. The publication of Dastur (1963) on the radiological appearance of spinal extradural arachnoid cysts was the first detailed report on the subject. Spinal extradural cysts have also been reported by Mathew et al (1970) and Rath et al (1976). In contrast 7 intradural and 3 extradural spinal arachnoid cysts have been seen in the author's department (Singh et al 1988).

Craniovertebral anomalies

There are unusually common in India. Congenital atlantoaxial dislocation and its clinical presentations were highlighted by Wadia (1960,1967) and Bharucha and Dastur (1964). These have been followed by published reports from all parts of the country (Srinivasan et al 1967, Chatterjee et al 1973, Singh et al 1974, Jawalkar et al 1983, Bhattacharya 1983, Hegde et al 1983, Sharma and Rout 1983, Shukla et al 1984). A case of atlantoaxial dislocation has been reported in a child with achondroplasia (Gulati and Rout 1974). Pandya has reviewed atlantoaxial dislocations in detail (1972), and John Hilton's contributions on the disease (1970).

The surgical management of craniovertebral anomalies has evolved over the past quarter of a century. Following a few early fatalities attributed to haematomyelia during posterior decompression (Dastur et al 1965), Sinh pioneered the anterolateral approach to the atlantoaxial joints. He performed fusion after reduction by traction. His report on 71 operated cases of congenital atlantoaxial dislocation constituted the Presidential Address delivered in December 1975 (Sinh 1976). We have been treating these patients with traction followed by posterior fusion with or without decompression with good results (Chopra et al 1988). More recently the transoral approach is being used, wherever indicated.

Infections and Infestations

Tubercular Infections

Intracranial Tuberculomas

Tubercular infection of the nervous system, in the form of a tuberculoma, tubercular abscess or tubercular meningitis, was common in India during the fifties and sixties. The report by Reddy (1951a) of four tuberculomas (among 38 intracranial tumours studied at autopsy) was the first on the subject. Subsequently Chandy and Isaiah (1952a) reported 8 cases, Ramamurthi (1956) reported 35 cases and Bagchi (1961) reported 16 cases. Dastur and Desai (1965) compared 107 brain tuberculomas with an equal number of gliomas, and Mathai and Chandy (1967) reported 143 cases. Dastur (1972a) has reviewed published literature on tuberculomas of the brain.

Bagchi and Pain (1970) found a total of 320 tuberculomas reported in the Indian literature between 1951 and 1967. Ramamurthi (1973) found 316 tuberculomas in a series of 1789 intracranial tumours. The mode of presentation of intracranial tuberculosis as abscesses, cysts, granulomas, tumours en plaque and mimicking a meningioma with meningeal involvement were described by Natarajan (1974a). Mathai reported 197 intracranial tuberculomas in 1978, and described the difficulties in diagnosis in 1979. Lalitha and Dastur (1980a) in a study over 26 years (1953-1978), found that the incidence of tuberculomas in the CNS in children was highest during the period 1967-1971. It was also observed that there was a decline in the number of tuberculomas of the brain during the 12 year period from 1966 to 1978, particularly in the paediatric age group. Its incidence fell from 30.5% of all intracranial space occupying lesions in 1963 and 21.5% in 1968 to 17.6% in 1972 and 12.3% in 1974 (Dastur 1980, Dastur et al 1968, Lalitha and Dastur 1980a). Ramamurthi (1973) also reported a similar reduction at Madras from 20% in 1960 to 14% in 1970. However, for an unexplained reason, the incidence of tuberculomas in the north - Delhi 4.8% and Chandigarh 8% - has been lower than the rest of the country, though the incidence of tubercular meningitis is the same as the rest of the country (Tandon and Pathak 1973).

With the installation of the first CT scanner at Delhi, Bhargava and Tandon (1980) studied 55 cases of tubercular meningitis and demonstrated hitherto undetected microtuberculomas. CT scan has now become the investigation of choice for the diagnosis and follow-up of tuberculomas (Vengsarkar et al 1986).

Surgical excision of tuberculomas in the pre-streptomycin and isoniazid era was often disastrous. Tubercular meningitis usually followed surgery and resulted in high mortality and morbidity. With the advent of

antitubercular drugs, total excision of tuberculomas again came in vogue (Bhagwati 1986). The observation that intracranial tuberculomas, with a concomitant lesion in the lung or a miliary involvement, also regressed on treatment with strepromycin and isoniazid, led to the development of medical management of smaller tuberculomas or those involving the motor or speech areas of the brain in the fifties and sixties (Ramamurthi and Natarajan 1960, Ramamurthi 1973, Pandya 1982d, Bhagwati 1985). Excision, however, continued to be the principal mode of therapy till the advent of newer bactericidal drugs like rifampicin and pyrizinamide. A three drug regime of isoniazid, rifampicin and pyrizimamide has proved to be very effective in the management of most tuberculomas (Bhargava and Tandon 1980, Pandya 1982d, Kalyanaraman 1983, Tandon and Bhargava 1985.

Perplexing variations in the behaviour of these lesions have been described. Sinh et al (1968) described 6 unusual variants, including caseous liquefaction. Dastur and Desai (1965) reported liquefaction identical with pus formation, in 8 out of 114 tuberculomas. Pandya et al (1982), reporting a case showing partial caseous liquefaction in solid brain stem tuberculoma being treated with antitubercular drugs while two cerebral tuberculoma regressed, discussed the role of humoral factors and thrombosis of arterioles in such an occurrence.

Tandon et al (1970) attempted to develop an experimental model of human tuberculoma in guinea pigs and monkeys. Unprotected, unimmunised animals reacted with generalised meningitis. The lesion was localised to the site of inoculation in BCG vaccinated or drug protected animals. Intracerebral infection in the latter groups resulted in well circumscribed focal abscesses. Typical tubercular granulomas were not encountered.

Tubercular Abscess

Tubercular abscesses are rare. Devadiga et al (1969) described 2 cases of tubercular abscess of the brain. Dinakar et al (1971) reported a tubercular abscess in the cerebellum. Ramamurthi et al (1981) reported 2 cases - one in the cerebellum and the other in fronto-temporal region. The diagnosis may be missed unless pus is examined for acid fast bacilli.

Tubercular Meningitis (Surgical Aspects)

Tubercular meningitis continues to be prevalent all over India and its manifestations may mimic almost any neurological disorder affecting the CNS (Tandon and Pathak 1973). Raised intracranial pressure tends to adversely effect the course of this disease. In the acute stage raised intracranial pressure is more likely to be due to cerebral oedema of inflammatory, allergic or vascular origin with a small ventricular system. In the subacute and chronic stages of the disease, dilatation of ventricles

due to impaired CSF circulation leads to raised intracranial pressure (Dastur and Udani 1966, Dastur et al 1972, Thomas et al 1977). Encouraging results following insertion of a ventriculoatrial shunt have been reported by Bhagwati and Singhal (1970), Bhagwati (1971), Satyanarayan and Taori (1972), Reddy et al (1974) and Singhal et al (1975). Beneficial effects of shunt surgery in patients with tubercular meningitis and hydrocephalus have been the experience of most neurosurgeons. The problems of shunt surgery in tubercular meningitis have been reviewed by Bhagwati (1982). Following the use of intrathecal hyaluronidase as an adjuvant in the treatment of tubercular meningitis by Gourie-Devi and Satish (1980), Bhagwati and George (1986) conducted a randomized trial to compare the effects of intrathecal hyaluronidase with the insertion of a ventriculoperitoneal shunt in the management of children suffering from tubercular meningitis with hydrocephalus. They reported that intrathecal hyaluronidase leads to an improvement in sensorium in most cases, but does not offer any particular advantage over shunt insertion in terms of specific neurological deficit or overall functional improvement. Pandya (1987) has critically analysed the justification of short term chemotherapy in tubercular meningitis.

Spinal Tuberculomas

Spinal tuberculomas are more uncommon than their intracranial counterpart. Dastur (1972b) in his review of spinal tuberculomas described arachnoiditis, subdural granulomas and extradural granulomas. Intramedullary tuberculomas have been reported by Sarin and Chandy (1961), Natarajan et al (1962), Rao and Subrahmanyam (1962), Dastur and Shah (1968), Chandrasome (1976) and Bagchi (1983). Epidural spinal tuberculoma may occur either with evidence of overt osseous involvement of the vertebral body or the neural arches or without any evidence of bony involvement when they present as 'spinal tumour syndrome' (Kak et al 1972). Ginde and Banker (1954) described a case of epidural tuberculoma. 4 cases were reported by Rao et al (1965), 5 cases by Mathai and Chandy (1967), 8 cases by Dastur (1969) and one case each by Dinakar et al (1974) and Inba Sekaran et al (1985). A case of spinal dural tubercular granuloma with abscess has been reported by Kumar et al (1985).

Atlanto-axial tuberculosis

Pandya (1971) described the clinical, radiological and pathological features of tubercular atlanto-axial dislocations, confirming that the entire atlanto-axial bone and ligement complex is affected by the disease process. The management of tubercular atlanto-axial dislocation has been outlined by Karapurkar (1988), Singh et al (1988) and by Khosla and Kak (1989).

Pyogenic Infections

Brain Abscesses

Brain abscess still remains the commonest surgically treatable pyogenic

infection of the nervous system in India. One of the earliest publications on the subject was by Ramamurthi and Narasimhan (1957a). Subsequent series were reported by Bagchi (1965), Yadav and Bhatia (1968), Kalyanaraman et al (1970), Mathai (91971), Balakrishnan and Natarajan (91971a) and Bhatia et al (1973). Bagchi (1965), Ramamurthi and Ramanujam (1973) found middle ear and paranasal sinus infections as the commonest cause of brain abscess. Otogenic brain abscesses formed the single largest group in 220 cases at AIIMS, New Delhi (Bhatia et al 1981) and 213 cases at PGI, Chandigarh (Kumar et al 1981). Temporal lobe has been reported to be the commonest site of brain abscesses by Bagchi (1978), Bhatia et al (1981) and Sharma et al (1988). Abscesses at uncommon locations like thalamus and brainstem have been reported by Tandon and Das (1974), Panchal et al (1974) and Nair (1977).

Late referral of patients to our neurosurgical departments is the main cause of poor prognosis (Ramamurthi and Ramanujam 1973). The majority of patients have impairment of consciousness when first referred to a neurosurgical department (Bhatia et al 1973, Dharkar et al 1978, Sharma et al 1988). Factors affecting mortality in brain abscess have been analysed by Bhatia et al (1981a), Kak (1986) and Sharma et al (1988). Late referral, altered sensorium, signs of raised intracranial pressure and/or meningitis, and emergence of resistant strains proved to be bad prognostic features. Abscess associated with congenital cyanotic heart disease carried a higher mortality (Bhatia et al 1976, Sharma et al 1988). Primary excision of the abscess carried 13.5% mortality. 18% mortality was noted after aspiration and subsequent excision. 33% mortality was seeb after aspiration alone (Sharma et al 1988). 16% mortality was reported by Bhatia et al (1981) after primary excision.

The role of anaerobic organisms and appropriate chemotherapy has been reported from Bangalore and Chandigarh. Chandramukhi et al (1980), in a study of 50 cases, isolated anaerobic organisms as the sole causative agents in 34% of cases. In 28% these were mixed with other organisms. The commonest organisms isolated were anaerobic streptococci and B. fragilis. Most of these patients had otogenic brain abscesses. Ayyagari et al (1983,1985) studied a total of 77 patients of brain abscess. Anaerobes were isolated in 74% of these cases. They were the sole organisms isolated in 25% of cases and were mixed with aerobes in 49%. Gram negative anaerobic cocci were the commonest organisms. Thirty of these abscesses (39%) were otogenic in origin. Associated meningitis due to anaerobic bacteria was found in 4 cases.

Spinal abscesses

Pyogenic spinal abscesses are uncommon. Gulati et al (1972), from P.G.I., Chandigarh, reported 11 cases of spinal suppuration. There were 6

epidural, one subdural and 4 intramedullary abscesses. Later from the same department, Khosla and Kak (1983) reported on 10 cases of spinal intramedullary abscesses. Six patients showed excellent recovery and another showed mild improvement following surgery. Renhen et al (1977) had also reported a case of spinal epidural abscess.

Syphilitic Infections

Nagpal et al (1979) reported on two cases of cerebral gumma. Both had presented with clinical features of raised intracranial pressure and were surgically explored. Syphilitic infections of the nervous system have become uncommon now.

Leprosy of nervous system

Facial nerve involvement in leprosy has been reported by Antia et al (1966) and Dastur et al (1966). Indira et al (1969) reported 4 cases with leprotic granulomatous lesions involving the fifth, ninth and twelfth cranial nerves and roots of the cauda equina.

It is quite common to find hypertrophic neuropathy causing severe pain and/or neurological deficit in leprotic affections of peripheral nerves. Bose (1964) and Bagchi (1983) reported good results after splitting the nerve sheaths. Khosla et al (1988) reported the results of surgery on 13 nerves in 12 patients. Intraneural abscess was found in 5 nerves, granulomas in 2 and gross thickening in 6 nerves. Very good results were obtained in all patients following surgery which included drainage of abscess, removal of granuloma or neurolysis, combined with anterior transposition of the ulnar nerve (9 cases).

Fungal Infections

Fungal infections of the central nervous system are being recognised more frequently in India, possibly because of greater awareness of their presentations.

Aspergillosis

A solitary case of cerebral aspergillosis from India was reported by Chitnis and Deshpande in 1967. Balasubramaniam et al (1971) described a case of aspergillus granuloma who presented with proptosis and raised intracranial pressure. Another case of aspergillus granuloma (in a series of 11 cases of fungal infections of CNS) was reported by Kak et al in 1972. Deshpande et al (1975) reported 9 cases of CNS aspergillosis (in a series of 20 cases of CNS mycotic infections) seen during a 5 year period. Three cases had chronic granulomas involving the optic nerve, brain and spinal cord, another 3 had diffuse cerebritis and the rest had suppurative

cerebritis with other systemic disease. Banerjee et al (1977) described 8 cases of cerebral aspergillosis pointing out the differentiating features between cases diagnosed at surgery and autopsy. Mohandas et al (1978) reported 4 cases of CNS aspergillosis, Malik et al (1985) 4 cases and Mehta et al (1985) 8 cases of aspergillus granulomas.

We have had an experience of 62 cases of cerebral aspergillosis out of a total of 75 cases of fungal infections of the brain. Twenty eight cases presented as slowly growing intracranial mass lesions of whom 10 had similar lesions in paranasal sinuses or orbit. Twenty nine cases had an acute fatal neurological illness and autopsy showed acute disseminated aspergillosis. Additional clinical patterns were cerebral abscess (2 cases), postoperative infection (1 case) and subarachnoid haemorrhage following rupture of fungal aneurysm (2 cases) (Kak et al 1989). None of our patients were immunosuppressed. This was also the experience of Mehta et al (1985). A case of fungal aneurysm had also been reported by Ahuja et al (1978).

Cryptococcosis

Bagchi (1983) reported that 18 cases of cerebral cryptococcosis had been reported from India (Krainer et al 1946, Balakrishna Rao and Lilauwala 1952, Ramamurthi and Anguli 1954a, Sriramachari et al 1961, Chhetri et al 1967, Rao et al 1968, Devadiga et al 1968, Mittal et al 1969, Reddy et al 1969). Since then Raja Reddy (1971) has described one case, Kak et al (1972) 7 cases, Malik et al (1985) one case and Mehta et al (1985) 4 cases.

The lesions may simulate a brain or spinal cord neoplasm, cause extradural spinal compression (Rao et al 1970) or present as meningitis. The prognosis has improved following the availability of Amphotericin B and 5-fluorocytosine.

Chromoblastomycosis

Bagchi et al (1962) reported the first Indian case of cerebral chromoblastomycosis (Cl. trichoides). The patient had presented with findings suggesting a right parietal neoplasm. Dastur et al (1966) reported another case of left parietal granuloma from which Cl.trichoides was cultured. Balasubramaniam et al (1971) reported one and Kak et al (1972) two such cases. Sandhyamani et al (1981) reported two cases of chromoblastomycosis who had presented as cerebral abscesses.

Mucormycosis

Cerebral mucormycosis was first reported in India by Shivde et al (1969) in a patient who had diabetic ketosis. Deshpande and Desai (1976) reported 4 cases of mucormycosis in patients suffering from renal failure. All cases

at autopsy showed haemorrhagic infarction of the orbital surface of frontal lobes. Two cases of mucormycoses were reported by Malik et al (1985) and one by Mehta et al (1985).

Nocardiosis

Nocardia species belong to the group of pseudomyecetes. Natarajan et al (1974) reported a case of nocardial extradural spinal granuloma causing spinal cord compression. Surgery was followed by complete recovery. Recently we had the experience of 2 brain abscesses from which N. asteroides was cultured. One of these patients had received a renal transplant 5 years earlier (Kundra and Kak 1988a).

Actinomycosis

Actinomyces are also not true fungi. Actinomycotic infection of the CNS is uncommon. Mehta et al (1985) reported an actinomycotic cerebellar abscess in a patient who had been operated for a pyogenic cerebellar abscess two months earlier. They postulated possible entry of the organisms through the surgical wound. Khosla et al (1984) reported a solid actinomycotic granuloma in an elderly man with CT findings resembling a meningioma. The solid nature of the lesion as well as the CT scan findings were the first such described in the literature.

Parasitic Infections

Cysticercosis

Campbell and Thompson encountered a case of multiple cysticercus cellulosae in Andhra Pradesh in 1907, but the brain was not examined during autopsy. According to them cysticercosis was first referred to in 1912 by Thirumurthi who mentioned that only three cases had been reported from India. In 1912, Krishnaswamy too reported cerebral cysticercosis in a south Indian worker. Subsequent reports from India were by Minchin (1937), Menon and Veliath (1940), McRobert (1944) and Subrahmaniam (1946). Most of these cases were from the states of Andhra Pradesh and Tamil Nadu. More recently the infestation has been reported from all over India through the publications of Raman et al (1950), Reddy (1951b), Chandy and Isiah (1952), Singh and Jolly (1957), Banerjee (1958), Singh et al (1963), Reddy et al (1964), Ramamurthi and Balasubramaniam (1970), Dinakar et al (1970), Natarajan and Balakrishnan (1970), Balasubramaniam et al (1971), Bhaskaran (1973), Raja Reddy et al (1973), Mani et al (1974), Ahuja et al (1978), Venkataraman et al (1979), Vijayan et al (1979), Srinivas et al (1980) and Chopra et al (1981).

Cysticercosis is the result of infection of the central nervous system by the larval stage of the intestinal tapeworm Taenia solium. It is predominantly a disease of the developing nations and is endemic in India. The incidence

of cerebral cysticercosis was reported to be 1.25% of all intracranial space occupying lesions (ICSOL) at Madras (Ramamurthi and Balasubramaniam 1970) and 2.5% at Delhi (Wani et al 1981). At the same time, 2% cases of focal epilepsy at Delhi (Wani et al 1981) and 2.2% of all epileptics at Bangalore (Mani et al 1974) were attributed to this disease.

The clinical presentation of cysticercosis in India is at variance from that reported from other countries. We have a higher incidence of raised intracranial pressure and focal neurological deficits (Tandon 1983). Cases of intramedullary spinal cysticercosis have been reported by Singh et al (1955), Mehta et al (1971), Roy et al (1976), Natarajan et al (1976), Sharma et al (1987) and Murthy et al (1988). Sawhney et al (1976) described a case of cysticercosis with pseudohypertrophic myopathy. Dinakar et al (1979) also described a case of cysticercosis resembling myopathy.

The radiological appearance of cysticercosis have been reviewed by Bhargava (1983). In earlier reports, Govinda Reddy and Ramamurthi (1953) and Balaparameswar Rao (1970) described the ventriculographic features of cerebral cysticercosis. The diagnosis of cysticercosis has been revolutionised with the availability of the CT scan. CT findings in cysticercosis have been described by Bhargava and Tandon (1983), Kak (1986b,1987a) and Suri et al (1989). Mahajan et al (1974) evaluated cysticercus and adult worm antigens in serodiagnosis of cysticercosis. They also compared indirect haemagglutination and complement fixation tests in its diagnosis (1975). Chandramukhi (1980) obtained 25% positivity through complement fixation tests for cysticercus antibodies. Studies at several centres are currently in progress with the ELISA technique for serodiagnosis (Suryanarayana et al 1987).

The management of cysticercosis in the earlier days consisted of antioedema measures, steroids, anticonvulsants and surgical procedures like bitemporal decompression, removal of the 'mass lesion' and various shunt procedures. Although specific chemotherapy in the form of praziquantel became available in the early eighties, its cost and lack of easy availability precluded its routine use in Indian patients, especially those with a meagre source of income (Ahuja 1985, Singhal et al 1985, Verma et al 1987). More recently we have used albendazole in the management of neurocysticercosis with good result (Kak 1987b, Pathak et al 1988). Surgery for intraventricular cysts is very rewarding (Wani et al 1981, Inbasekaran et al 1985, Kak 1987 a,b). Patients presenting with focal mass lesions generally do well following excision of the lesions. Patients with obstructive hydrocephalus respond well to the insertion of a ventriculoatrial or ventriculoperitoneal shunt. Results of surgery, in the form of bilateral subtemporal decompression and/or a thecoperitoneal shunt, in patients with diffuse parenchymatous lesions, have not been uniformly satisfactory (Ramamurthi and Balasubramaniam 1970, Wani et al 1981). For such cases the author has been performing a frontal

lobectomy on the non-dominant hemisphere with good results (Kak 1987a,b). The procedure tides over the acute problem of raised intracranial pressure, saves vision and provides time for specific chemotherapy.

Ecchinococcosis

Hydatid disease has a lower endemicity in India. It is more common in Kurnool district of Andhra Pradesh, Madurai district of Tamil Nadu and the state of Punjab. Balasubramaniam et al (1970) found only 6 cases of hydatidosis in 3000 patients with ICSOL, Raja Reddy et al (1972) found 4 out of 1000 ICSOL and Bagchi (1983) found 2 hydatid cysts presenting as ICSOL. Virani et al (1982) reported a patient presenting with clinical features suggestive of posterior fossa space occupying lesion. Investigations and surgery showed multiple secondary hydatid cysts from a primary cyst in the left ventricle of the heart. Inbasekaran and Natarajan (1986) described a posterior fossa hydatid cyst.

Intradiploic ecchinococcosis has been reported by Kanaka et al (1970) and Balakrishnan and Natarajan (1973). Vasal et al (1978) reported a case of hydatid cyst of the skull presenting with a jugular foramen syndrome.

Spinal hydatid cysts have been reported by Das (1957), Chitkara (1957), Vengsarkar and Abraham (1965), Maini and Mittal (1967), Balasubramaniam et al (1970), Natarajan (1974) and Bagchi (1983).

The reviewer has come across 10 hydatid cysts of the brain and 3 spinal hydatid cysts. These include a case of infected intradural hydatid cyst at the foramen magnum (Mathuriya et al 1985) and another with multiple intracranial hydatid cysts in both supratentorial as well as infratentorial compartments (Mathuriya et al 1987). The diagnosis of ecchinococcosis has become easier with the availability of the CT scan (Raja Reddy et al 1984).

Dracunculosis

Guinea worm (dracunculus medinensis) is a parasite seen in some parts of south India. Neurological deficit may follow intimate involvement of the worm with peripheral nerves and consequent inflammatory thickening of the nerve sheath (Balasubramaniam and Ramamurthi 1963). The first case of quadriplegia due to an extradural guinea worm abscess was reported by Donaldson et al (1961) from Miraj in Maharashtra. Similar cases have subsequently been reported by Reddy and Valli (1967), Lodha et al (1972) and Dinakar et al (1977).

Visceral Larva Migrans

Indira et al (1969) reported a case of microfilaria associated with cerebral tuberculoma. Another case of a nematode larva producing severe

encephalpathy was reported from Chandigarh (Kapur et al 1976). The larva was demonstrated in the brain biopsy. The patient later made a complete recovery. They suggested that the clinical features were due to an allergic reaction to the parasite.

Protozoal Infections

Gastointestinal infestation due to Entamoeba histolytica is common in India. It causes ulcerative lesions in the colon from where the parasite may enter the liver and occasionally the lungs. Involvement of the brain is extremely rare. Pan and Ghosh (1971) described 2 cases of primary amoebic meningo-encephalitis. Two cases of amoebic brain abscess have been described by Ahuja and Deshpande (1963) and Raja Reddy et al (1974). Banerjee et al (1983) described 4 cases of secondary cerebral amoebiasis at autopsy in a 10 year period. Extensive, almost confluent and multiple lesions were seen in brains of 3 cases who had neurological features. A case of primary amoebic meningoencephalitis due to soil amoeba has been described by Bhatia et al (1979).

Malarial affections of the brain were very common in India, but had declined with control of mosquitoes. With the emergence of DDT resistance in mosquitoes, the incidence of cerebral malaria is again rising due to the parasite P.falciparum. Untreated the disease is fatal. Softening of various parts of the brain develops in patients who survive with timely appropriate therapy. Banerjee et al (1986) compared the pathological findings in brains of 6 fatal cases of human cerebral malaria with those in experimental cerebral malaria in mice. They found demyelination to be a very important lesion in fatal human cases. They also studied the role of immune complexes in cerebral malaria (Gupta et al 1988).

There are occasional reports of toxoplasmosis from this country. The infestation may cause hydrocephalus in children.

Intracranial Neoplasms

Chandy on joining at Vellore was told by Kutumbiah, an eminent profesor of medicine there, that he had seen only three brain tumours in 30 years and all these were at autopsy. Chandy soon found a patient in the medical ward being treated for 'syphilitic pachymeningitis' who had bilateral papilloedema and signs suggesting a frontal lobe tumour. A right frontal glioma was found at surgery. Two more tumours were found that week (Pandya 1982c). During the early period, intracranial tumours were being diagnosed by neurosurgeons at a late stage, thereby resulting in a higher morbidity and mortality. The pioneers soon effected improvements and a large number of publications started to appear beginning with the Presidential address of Ginde in 1955 on his personal experience of 68 consecutive verified intracranial tumours during the period 1951 to 1954

(Ginde 1955). In 1965, Bagchi presented his experience of 63 ICSOL in infancy and childhood seen during a period of 9 years. In successive publications from Vellore, Sambasivan et al (1966) reported clinical features and results of surgery in 80 cases of acoustic neurinoma, Chandra et al (1967) analysed 482 cases of intracranial gliomas treated between 1950 and 1966, and Rath et al (1967) described 1225 neoplasms out of 1492 ICSOL. Around the same time Dastur (1967) analysed 1000 ICSOL seen during a period of about 13 years of which 768 (76.8%) were neoplasms. Recounting their experiences with ICSOL over 20 years at Madras, Ramamurthi (1970) stated that the proportion of patients with loss of vision at the time of presentation fell from 60% in the first two years to 8% in the last 2 years. There was 1249 tumours among 1559 ICSOL.

As mentioned elsewhere, the high incidence of tuberculomas in ICSOL seen during the early period has gradually declined. The types of tumours seen in India and their incidence are no different from those in the rest of the world, with the exception of the state of Kerala from where a higher percentage of pineal tumours have been reported (Sambasivan 1972). More recent analyses of intracranial neoplasms have been reported by Chandy (1974), Lalitha and Dastur (1980b), Malik et al (1980), Mohanta and Rath (1981) and Rohatgi et al (1985). For a survey on current neurooncology, the proceedings of the national seminar on neurooncology are recommended (Deshpande et al 1981). From his experience of 36 cases, Nagpal (1983b) strongly advocated surgery for brain stem masses to exclude a benign lesion.

The diagnosis of intracranial neoplasms has been made easy with the availability of CT scan. Attempts were made to evaluate its reliability in the histological diagnosis of ICSOL. Mehta et al (1983) reported an overall accuracy of 90.3% in a series of 300 cases, but there were some areas of difficulties. Pillai and Sambasivan (1985) could correlate the CT morphology with histological types in 25 acoustic neurinomas. Experiences with the use of microsurgery have been reported by Prakash et al (1977), laser and CUSA by Prakash (1986) and operative sonography by Chidambaram et al (1986).

Abraham and Chandy (1963) for the first time introduced the use of ventriculoatrial shunt in the management of posterior fossa tumours, which still continue to present to the Indian neurosurgeons at a very late stage. Reviewing their experiences in 328 posterior fossa tumours of whom 142 had a shunt, Lodha et al (1981) confirmed the beneficial effect of precraniotomy shunt in reducing mortality, improving the patient's clinical condition and permitting a smoother postoperative course. However, the possibility of tension pneumocephalus developing following posterior fossa surgery in the sitting position in the presence of a functioning shunt was described by Sharma and Kak (1988b).

The effect of levamisole on cell mediated immune status of brain tumour patients was studied by Sharma et al (1985), who found it to be of no immunostimulant value. Bhagwati and Parulekar (1987) tried heterologous skin grafting in patients with malignant gliomas with encouraging results. Bhagwati also found good results with the use of LAK cells in malignant gliomas (Sankhla and Bhagwati 1988).

Pituitary adenomas and craniopharyngiomas are encountered in fair numbers, usually in advanced stages (Ramamurthi 1960, Bagchi 1971, Kanaka et al 1971, Prakash et al 1974, Jawahar et al 1985, Sambasivan and Pillai 1986). Giant pituitary adenomas are still seen. There is perhaps a greater occurrence of haemorrhagic adenomas (Ramamurthi and Anguli 1954b, Dastur and Pandya 1971, Kundra and Kak 1988b). Ramamurthi (1986) has well discussed the management of large pituitary adenomas. With the development of endocrinological facilities and availability of CT scan, an increasing number of microadenomas of the pituitary are being diagnosed though the bulk of tumours are macroadenomas with extrasellar extensions. Transsphenoidal surgery is now being performed at most neurosurgical centres in the country (Banerji et al 1986).

Indian reports of uncommon intracranial tumours include a glioma of the hypophysis (Ginde and Iyer 1954), an epidermoid tumor producing bilateral frontal lobotomies (Dastur 1954), spontaneous infiltration of the dura and skull by an ependymoma (Iyer and Monteiro 1955), medulloepithelioma of the eye (Gulati and Jain 1963), diffuse cerebellar hypertrophy (Dastur and Deshpande 1966, Dastur et al 1975), extrusion of a piece of clivus chordoma through a lumbar puncture needle (Pandya and Sinh 1967), teratoma in a 5 week old infant (Chandrasoma 1975), gangliocytoma of the pituitary with acromegaly (Pathak et al 1985) and gliosarcoma with cartilage formation (Banerjee et al 1989).

Cerebrovascular Disease

It was generally believed that subarachnoid haemorrhage (SAH) and intracranial aneurysms were less common in India than in the west and in Japan (Ramamurthi 1969, 1970b). This assumption stemmed from an analysis of records of 6949 inpatients from 1951 to 1964 at Madras, wherein 62 aneurysms and 36 arteriovenous malformations (AVM) were found (Ramamurthi 1965a). Mathai and Chandy (1965) in an analysis of 10410 admissions during a 15 year period found only 47 SAH in which there were 10 AVM and 7 ruptured aneurysms. During the same period 35 AVM and 15 aneurysms in all were treated. In the early seventies, a relatively higher incidence of aneurysms was reported by Sambasivan from Trivandrum. To find answers to these questions, the Indian Council of Medical Research (ICMR) undertook a multicentric hospital-based study during 1972-75 on the epidemicology of SAH. The clinical study was conducted at Bombay, Calcutta, Chandigarh, Delhi, Madras and Trivandrum, and the patho-

logical study at Chandigarh and Delhi. A total of 661 patients with SAH/aneurysm/AVM were admitted during this period - the minimum (34) at Delhi and the maximum (195) at Trivandrum. Among 491 fully investigated patients, SAH was due to an aneurysm in 36.7%, AVM in 7.1% and hypertensive intracerebral haemorrhage in 9.4%. The study revealed that once SAH is proved, the incidence of saccular aneurysms and AVM as the etiological factor is no different from that anywhere else in the world. The apparently lower incidence of intracranial aneurysms reported earlier may be due to non-referal of patients with SAH to neurosurgical centres. Since the conclusion of the study a larger number of patients with SAH are being refered for investigations. In a pathological study of 404 unselected autopsies there were 3 aneurysms, one AVM and 6 hypertensive intracerebral haematomas. This incidence is certainly less than reports from the west. The incidence of anomalies of the circle of Willis was similar to that reported from other parts of the world where aneurysms are reported to be more frequent (ICMR 1987).

In an earlier study on circle of Willis from 357 brains of unselected autopsies, Raja Reddy et al (1972) did not find any aneurysm. The nature and type of anomalies found were comparable to similar studies in the western literature. Devadiga (1974) carried out a prospective study to determine the incidence of SAH at Manipal over 2 years. The incidence was 1.5 per 1000 hospital admissions and comparable to reports in the western literature.

Surgery for intracranial vascular lesions had been advocated by Ramamurthi (1958) and Ramamurthi and Natarajan (1961). However, individual experiences at various centres were limited because of small numbers of cases. Enthusiasm for microsurgery increased following microneurosurgical courses held at Bombay, Calcutta and New Delhi by Pia and Grote in 1978 (Pia and Grote 1979). Surgery for intracranial aneurysms and AVM is being performed at several centres now. Sambasivan et al (1984) analysed 1000 cases of SAH over a period of 16 years and found 337 aneurysms and 61 AVM. Rout at SCTIMST, Trivandrum, is also doing excellent surgery for intracranial aneurysms and AVM. Mandalam et al (1985) reported on CT evaluation of 26 intracranial aneurysms. Rao et al (1988) reported good results with percutaneous superselective transcatheter embolisation using isobutyl 2-cyanoacrylate in cerebral AVM.

Recently results of treatment in 120 cases of intracranial aneurysms were described by Prakash (1988b) from Delhi, 90 cases by Krishnadas et al (1988) from Vellore, 130 cases by Kak et al (1988) from Chandigarh and 67 anterior communicating and 9 distal anterior cerebral aneurysms from Trivandrum (Nair et al 1988, Chand et al 1988).
Cerebral venous thrombosis and dural sinus thrombosis probably occurs more frequently in India than in the west. Reviewing 80 cases seen over

a period of 16 years, Nagpal (1983a) concluded that anaemia and malnutrition also play an important part in the pathogenesis of cerebral venous thrombosis. A significant number of these patients require surgery for a large mass effect, deteriorating consciousness, anisocoria, bradycardia or uncal herniation.

Abraham at Vellore has had a continuing interest in haemodynamics in relation to brain and spinal cord. He has reviewed the epidemiology of stroke patients, his experimental model of focal ischaemia, and experimental and clinical data of omental transposition in the management of ischaemic brain disease and paraplegia in his Presidential address (Abraham 1985).

Stereotactic Surgery

Prior to the introduction of present day type of stereotactic surgery in India, some neurosurgeons were using 'free hand' techniques to place lesions mainly in patients of Parkinson's disease. Thus chemopallidectomy using a 'free hand' technique and injection of alcohol was being practised in Madras by Dr. Chinthan Narliar in the Startley Medical College and at Vellore in 1957-58 where they acquired the Bertrand stereotaxic guide in 1960 and began treating Parkinsonism and epilepsy (Mathai and Taori 1972). From 1987 the CT compatible BRW instrument is being used and biopsy of deep seated lesions and bilateral amygdalotomy are being done (Rajshekhar et al 1987).

A Similar "free hand" method was being used at Bangalore involving the use of a "topomatter" and radiological control for performaing chemopallidotomy by percutaneous introductions of the needle through the foramen avale (Verma 1965). Their experience in the treatment of Parkinsonism was presented by Varma and Sunderrajan (1980). The Laitinen apparatus was acquired later.

While 'free hand' techniques gave good results, they lacked the flexibility of a stereotactic apparatus and could not attack different targets for different indications.

The McKinney's apparatus was in use at Bombay since 1962 for the treatment of Parkinsonism. It was replaced by the Leksell apparatus in 1964 and surgery for Parkinsonism and other extrapyramidal disorders as well as psychosurgery are being done. Earlier diathermy lesions were made but the current preference is for cryogenic lesions (Bhagwati 1969).

Sehgal of New Delhi devised his own instrument for stereotactic surgery for Parkinsonism. This is being used at other centres as well.

Stereotactic surgery was started at Madras in 1959 with an early model of Cooper's chemopallidectomy machine, mainly for the treatment of Parkinsonism and other involuntary movements (Balasubramaniam and Ramamurthi 1965).

The Leksell instrument was acquired in 1963 and Mr. Walsh of Atkinson Morley Hospital, London, spent one month at Madras demonstrating his technique of management of Parkinsonism. Lesions were made by thermocoagulation. After some experience, younger patients with bilateral disease were managed by simultaneous bilateral stereotactic lesions (Kalyanaraman and Ramamurthi 1966) or by using two machines simultaneously (Kalyanaraman and Ramamurthi 1970b). Gradually the spectrum of conditions being treated by stereotactic procedures widened. Patients with cerebral palsy were treated for spasticity by lesions in the dentate nucleus (Kanaka 1972) - a new introduction. Lesions were also made in the pulvinar and CM nucleus of thalamus (Kanaka and Balasubramaniam 1971, 1974). Encouraged by the results of dentatectomy, chronic cerebellar stimulation was introduced (Kanaka 1987). The development of sedative neurosurgery at Madras was the zenith of their entire work on stereotactic surgery. Amygdalotomy soon became very popular, and was also started at Vellore and Bombay. The observation that amygdalotomy had a good effect on co-existing seizures led to its use in the treatment of grandmal seizures (Ramamurthi et al 1970, Kalyanaraman 1980). Failures of amygdalotomy led to the development of hypothalamotomy and later the two procedures were compared (Balasubramaniam and Kanaka 1973).

Psychosurgery, though not very popular at many centres in India, was also taken up at Madras. Sedative neurosurgery and leucotomies were performed (Kalyanaraman and Ramamurthi 1973, Balasubramaniam and Kanaka 1975). Cingulumotomy for drug addiction (alcohol, pethidine, morphine) was started in 1970, with very good results (Balasubramaniam et al 1973).

In addition stereotactic surgery is being done in several private institutions at Madras using the Leksell, Sano or Sehgal apparatus.

Stereotactic surgery was started at the PGI, Chandigarh, in 1974 with the McKinney instrument. The Leksell machine was obtained in 1980. A wide variety of patients are being treated by stereotactic procedures including stereotactic biopsies for deep seated tumours (Chhang et al 1987).

At the All India Institute of Medical Sciences, New Delhi, stereotaxy was started in 1977 with the Leksell machine. Their experiences have been presented at various meetings (Bhatia 1986, Bhatia et al 1986).

The Leksell machine is also used at Trivandrum. Stereotactic biopsy is being done at Varanasi with Sehgal's apparatus. At Patna stereotactic surgery is being done using a head frame and a Rand-Wells palidothalamotomy guide. A Leksell's machine has recently been obtained at Srinagar. A summary of stereotactic procedures being done at various centres in India is given in table I (Balasubramaniam 1988).

Table I: Stereotactic Surgery in India

Centre	*Year of Starting Stereotatic Surgery*	*Machines used*	*Diseases*
1. BANGALORE	1962	Freehand Laitinen	P
2. BOMBAY	N.A.	McKinney Laksell	P, D, Psy:A
3. CHANDIGARH	1974	McKinney Leksell	P, D, PN, E, B
4. CUTTACK	1970	McKinney	P
5. HYDERABAD	N.A.	Wells	P
6. MADRAS	1962	Cooper's Leksell Seghal Sano	P, D, PN, CP, E, Psy : A, C, H, L
7. NEW DELHI (a)	1977	Leksell	P, B, Psy : Occasional
(b)	N.A.	Sehgal	P
8. PATNA	N.A.	Rand-Wells Guide	P, D, PN, B
9. SRINAGAR	N.A.	Leksell	N.A.
10. TRIVANDRUM	N.A.	Leksell	P, Psy: A,
11. VARANASI	N.A.	N.A.	B
12. VELLORE	1957	Freehand Bertrand BRW-CT	P, Psy : A, B

P : PARKINSONISM
D : DYSKINESIAS
PSY : A–AMYGDALOTOMY
C–CINGULOMOTOMY
H–HYPOTHALAMOTOMY
L–LEUCOTOMY

Cp : CEREBRAL PALSY
B : BIOPSY
E : EPILEPSY
PN : PAIN
N.A. : NOT AVAILABLE

Recently the tempo of stereotactic surgery has come down due to the advent of CT, MRI and microsurgery (Balasubramaniam 1984).

Craniocerebral Trauma

Trauma to the brain is as much a major health and social problem in India as in western countries. Most head injuries are still treated by general surgeons. The first head injury unit staffed by neurosurgeons was set up by B. Dayanand Rao at Hyderabad in 1957. Since then, head injury units and services have been set up by B. Ramamurthi at Madras, by P.N. Tandon at New Delhi, by Asoke Bagchi at Calcutta and by D.R. Gulati at Chandigarh. At other places only complicated cases are referred to the neurosurgeons. However, the nature and extent of injuries is fast changing due to rapid urbanisation and industrialisation and the need of trauma care centres is being felt badly (Bagchi 1984). The first combined accident and trauma services (CATS) is being given shape for the city of Delhi.

An idea of the workload of trauma patients can be had from the report of Kalyanaraman et al (1972) who had 2000 cases of head injuries treated as inpatients during a period of 33 months and Pathak et al (1972) who reported on 2190 patients during a two year period. During the earlier period Chatterjee and Sarkar (91965) analysed 360 cases of head injuries and Rao et al (1967) analysed 271 deaths (8.5%) out of 3184 cases seen during 1959-1964. They suggested that mortality and morbidity could be improved by management in neurosurgical units.

Several studies have attempted to analyse factors affecting outcome in head injuries under Indian circumstances (Jain and Kankanady 1969, Kalyanaraman and Ramamurthi 1970, Tandon 1986). Mahapatra et al (1985) reported 20 survivors out of 62 head injury patients with bilateral decerebration.

Several neurosurgeons including Ramamurthi (1965) and Sambasivan (1977) have highlighted the problems of head injuries in India. In an attempt to find a good dural substitute, Gulati et al (1974) used gold and silver foil in experimentally created dural defects. Gold foil was found better than silver foil for the purpose, but both can be used. Rao et al (1974) evaluated the use of 'stellon', dental acrylic manufactured in India, to cover experimentally produced skull defects. They found it a useful cranioplastic material.A unique type of crushing injury to the head has been described from the thickly populated agricultural areas of north Indian states of Punjab, Haryana, Uttar Pradesh and Bihar. The head gets compressed between the frame and the beam of the 'kohlu' (sugarcane crusher) leading to injury of scalp, skull and brain (Sekhon 1969, 1975, Mohanty et al 1978).

Craniocerebral erosion (growing skull fracture) continues to be seen by Indian neurosurgeons in fair numbers. Rao and Subrahmanyam (1963)

and Banerji et al (1967) had reported their initial experience with this condition. The rationale of surgery in growing skull fracture was discussed by Ramamurthi and Kalyanaraman (1970). A systematic pathological, clinical and radiological study of 60 cases carried out at the AIIMS, New Delhi, highlighted the incidence, pattern and severity of brain damage associated with this lesion as well as provided evidence for the progressive nature of brain damage. A leptomeningeal cyst was not encountered in any patient. They recommended that the term cranio-cerebral erosion is most appropriate for this condition (Roy et al 1987, Tandon et al 1987).

Since the installation of the CT scan, we have observed tension pneumocephalus in 5 of 63 cases in whom chronic subdural haematoma was evacuated (Sharma et al 1989). A high index of suspicion is essential for the diagnosis of this easily treated complication.

In a preliminary study on rats, Jayakumar et al (1986) reported the beneficial effects of pulsed electromagnetic field in the reduction of traumatic cerebral oedema.

Miscellaneous Disorders

Fluorosis

Endemic fluorosis has been reported from many parts of the world including India, but neurological complications of endemic skeletal fluorosis have been exclusively reported from India (Raja Reddy 1979). Deposition of fluoride in bones and ligaments leads to narrowing of the spinal canal with resultant compression of the spinal cord. This may be complicated by ischaemia of the radicular arteries. Fluorosis is endemic in parts of Andhra Pradesh, Karnataka and Tamil Nadu in the south and Punjab, Haryana, Rajasthan and Uttar Pradesh in the north. CT scan seems to be the ideal investigation for these cases (Naidu et al 1986). Extensive epidemiological and experimental work on fluorosis has been carried out by Raja Reddy et al (1974, 1985) and Jolly et al (1969). Good results following surgical decompression have been reported by Raja Reddy et al (1974), Hussain et al (1986), Naidu et al (1988) and Kak (1988). Preoperative evaluation of pulmonary function tests and perioperative administration of magnesium hydroxide, calcium and corticosteroids has made surgery much safer (Malhotra et al 1986).

Spinal Conditions

Chatterjee had developed his method of treating spinal vascular malformations by ligation of veins with good results and presented his experience in 1968.

Spinal arachnoiditis is a peculiar lesion occurring in the tropical countries and is different from tubercular arachnoiditis. Ramamurthi (1970) reported 67 cases out of 361 cases of spinal compression. He did not advise surgery except in cases with well defined localised compression. Mani et al (1973)

an earlier report, Siddiqui (1968) had presented his experience of 23 cases of spinal arachnoiditis, of which 20 underwent surgery. He found surgery to be of value in cases of short duration with localised lesions. Kalyanaraman and Kanaka (1963) studied ABO blood groups in 2100 cases and found a greater incidence of blood group O in arachnoiditis (93 cases). Twenty five patients with arachnoiditis underwent surgery in the author's department. These included 6 of tubercular origin. Fourteen patients improved following surgery and the results were similar in both tubercular and non-tubercular groups (Murthy et al 1988).Cases of papilloedema and intracranial pressure associated with spinal tumours have been reported by Mehta et al (1982) and Rath et al (1983), Khosla et al (1985) and Acharya et al (1987) have reported cases of spinal cord compression by haemopoetic tissue in thalassaemia. Two cases of chronic spinal subdural haematomas were reported by Khosla et al (1985).

Neural Transplantation: This will be discussed in a following contribution.

Research Activities

The major preoccupations of the pioneers of neurosurgery in the country were the problems of establishing safe patient care services against several odds. Even so, they were equally concerned with laying down traditions for intellectual pursuits, academic aptitudes and scientific investigations. Sustained research activity demands well equipped and adequately staffed departments, workers with a team spirit and loyal cooperation (Ginde 1970). Neurophysiology and experimental neurosurgery received a boost in the fifties due to Baldev Singh, who was able to devote a substantial part of his time developing these facilities, first at Vellore and later at AIIMS, New Delhi.

Although most of the earlier publications were based on clinical aspects, experimental studies did not lag behind as is evident from the works of Roy and Chandy (1957), Sehgal (1966), Pathak and Prasad (1966), Ramamurthi (1967), Vasan et al (1969), Sil (1969), Tandon et al (1970) and Singh et al (1972). Several research publications, both clinical or experimental, have already been referred to earlier in this text.

Clinical studies of true epidemiological nature are very few, as most surveys are hospital-based. There is an urgent need for initiating population based investigations in different parts of the country. Georgraphical variations exist in the incidence of craniovertebral anomalies, intracranial tuberculomas, anterior encephaloceles, fluorosis, cysticercosis and ecchinococcosis.

Trauma, infective disorders and tumours are common interests at almost all the centres. The early development of basic neuroscience departments at Vellore resulted in research publications on lysosomal enzymes of the

CSF (Bachhawat 1974), cerebral ischaemia and methods of revascularisation (Abraham 1985), brain tumour metabolism (Aruna and Basu 1974) and experimental, clinical and surgical aspects of the managtement of epilepsy (Mathai 1986). Research at Madras has been more oriented towards neurophysiology and includes extensive work during stereotactic surgery, from which the concept of the 'behavioural brain' emerged (Balasubramaniam and Kanaka 1979). Other areas include neural trauma, biogenic amines, epilepsy and biofeedback. Extensive epidemiological and experimental studies have been carried out on fluorosis in Andhra Pradesh (Raja Reddy 1979) and Punjab (Jolly et al 1969).

Research interests at AIIMS, New Delhi, include clinical studies on delineation patterns of neurological disorders, tuberculosis of the nervous system, neural trauma, intracranial tumours, epilepsy and SAH. A number of studies are being carried out on brain tumours utilising modern techniques in molecular biology (Tandon 1987). A microsurgical training laboratorymhas been opened for conducting training courses for faculty members and trainees from all over the country. A national neural transplant facility has also been started and is making good progress.

The major research activities in Bombay have evolved around CNS tuberculosis, craniovertebral anomalies, interventional neuroradiology and physiology of choroid plexus at the K.E.M. Hospital; tubercular meningitis and hydrocephalus, syringomyelia, craniopharyngioma and chemotherapy and immunotherapy of gliomas at the Bombay Hospital and trigeminal neuralgia, head injuries and syringomyelia at the B.Y.L. Nair Hospital.

Research in neural trauma, pineal tumours, SAH and intracranial aneurysms has been going on at Medical College, Trivandrum. At the neighbouring SCTIMST in the same city, ongoing research activities are in the fields of intracranial aneurysms and vascular malformations, third ventricle tumours, craniovertebral anomalies and syringomyelia. Experimental studies include those on hydrocephalus, SAH and a model of communicating hydromyelia (Rout 1988).

Studies on experimental neuro-oncology and brain oedema have been performed at Varanasi. Cervical spondylotic myelopathy and head injuries are the current interests at Calcutta.

Areas of interest at the PGIMER, Chandigarh, include studies on cerebral metabolism following head injury (Gulati et al 1980, Sood et al 1980), studies on cerebral circulation (Subba Rao et al 1980), neuropsychological sequelae of head injury, pituitary tumours, spinal dysraphism, brain abscess and neurocysticercosis.

The above list is by no means comprehensive, but is complimentary to the preceding section. Tandon (1988), referring to neurobiology in the future,

defined neuroscience research as a continuum of study from the molecular to the behavioural level and suggested some areas of researchin the neurosciences. He also pointed to the need for interdisciplinary comprehensive and coordinated research activity in this field to realise the full available potential.

Conclusion

Neurosurgery has now completed 40 years of its existence in India; a relatively small period in the development of any speciality. It is gratifying to note that from a humble beginning at Vellore, Madras, Bombay and Calcutta between 1949 and 1954, the country now has over a dozen centres of excellence and well over 60 centres rendering neurosurgical services to the community (Fig. 1). Yet, the total number of 325 neurosurgeons for a population of over 800 million, with one neurosurgeon per 2.5 million, is grossly inadequate even to provide uniform minimum basic neurosurgical facilities! In spite of the initial difficulties, the pioneers of neurosurgery in the country did not forget the importance of research. This review of contributions and research activities of Indian neurosurgeons covers the areas this reviewer considered significant in the national context. An attempt has been made to give a balanced presentation from the work of early pioneers to the contemporary neurosurgeons, highlighting the variety of therapeutic challenges and their geographical variations.

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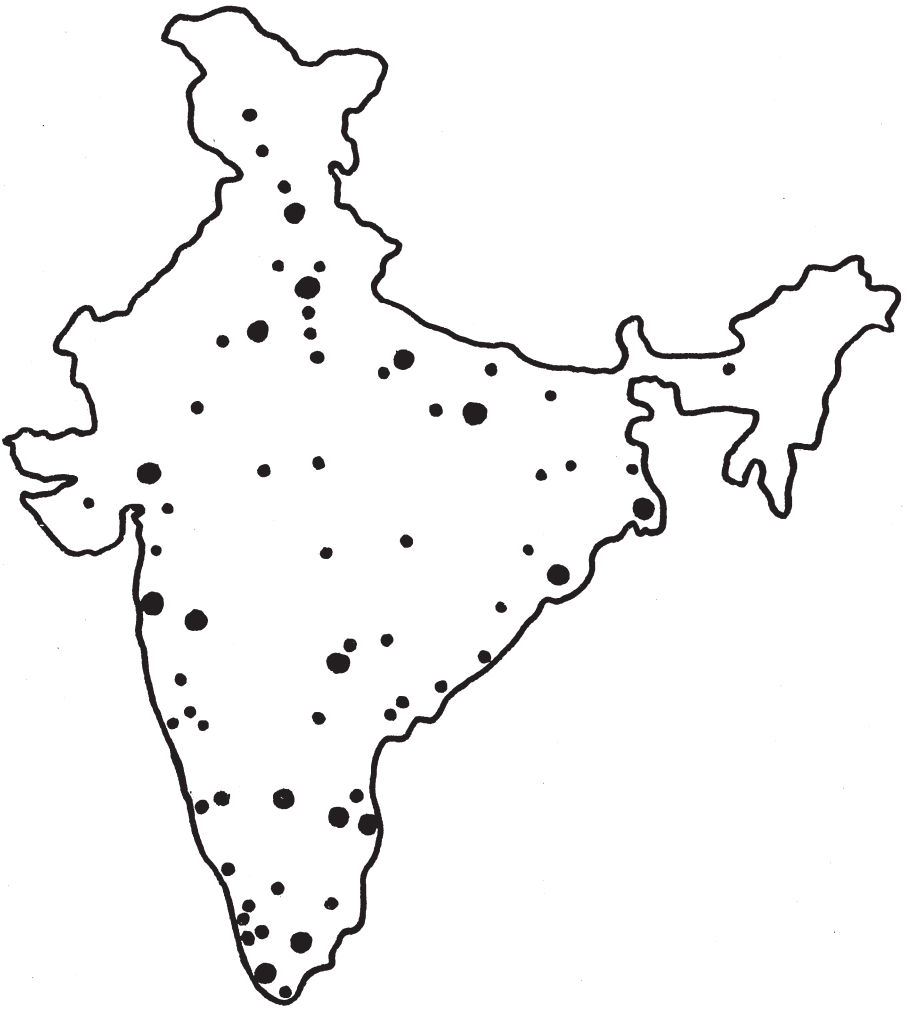

Fig. 1: Neurosurgical facilities in India.

Neuroanaesthesia

A.Rout

Introduction

Review of ancient Indian literature makes one feel proud of our heritage in medicine. Surgical procedures carried out on this subcontinent 5000 years B.C are documented in the Rigveda. However, there are no details of the art and science of anaesthesia employed for such operations and prevention of pain during surgery (Pramanik 1980).

During the Buddhist era (500 B.C.) Sushruta, a descendant of Vishwamitra's family, performed all types of surgery including intracranial and plastic operations and wrote his notable book on surgery- *Sushruta Samhita.* Anaesthesia was then the main handicap. The patient was strapped firmly and deeply narcotised by Indian hemp, opium, wine or some other intoxicants. Wine was frequently used as a remedy for pain.(Consul 1926) Jivaka, the physician to Lord Buddha, is reported to have performed craniotomies and laparotomies successfully. Although there is no mention about anaesthesia, craniotomy was carried out with the patient lying down and firmly tied to the bed. Before making the incision, Jivaka used to tell his patients: "If I give you pain -you must not attribute this as a crime, but give me permission thus to afflict you; physicians afflict their patients for their benefit, that by this means they may free them from disease" (Pramanik 1980).

In *Bhoj Prabandh* one finds evidence of a cranial operation being performed by the Asvinis -brothers and surgeons- upon King Bhoj himself (527 A.D.). They used a drug known as *sanmohini* which made the king unconscious before the operation and administered another drug known as *sanjivani* which restored the royal patient to consciousness after surgery. The precise nature of these drugs remains unclear.

Little information is available on anesthesia in neurosurgery between the 6th and 19th centuries. Painless surgery was carried out by James Esdaile under mesmerism at the Imamwada hospital, Hooghly in 1845 before the advent of ether. The discovery of volatile anaesthetics such as ether (1846) and chloroform (1847) ushered in modern anaesthesia and surgery.

More than a century lapsed before modern neurosurgery made a humble

beginning in India in 1949. Indian anaesthetists always keep in mind what Harvey Cushing, the father of modern neurosurgery, felt and wrote in 1908: "Regardless of the drug to be employed, it is essential that it be administered by an expert preferably by one who makes this his speciality". Long years passed before an anaesthetist pursued neuroanaesthesia as his career on the international scene.

The Early Days

Jacob Chandy, a qualified neurosurgeon, started modern neurosurgery in India at Christian Medical College Hospital, Vellore in 1949 with help from G.M. Lewis, the then chief of anaesthesia. However, he continued to operate under local anaesthesia for years. B.Ramamurthi joined the Government General Hospital, Madras, in October 1950. R.S. Kabir and V.Rajagopalan administered neuro-anaesthesia. Just a little later R.G. Ginde joined as honorary neurosurgeon and lecturer at K.E.M. Hospital and Seth G.S. Medical College and K. E. M. Hospital, Bombay and his surgical performances with G.S. Ambardekar as his anaesthetist soon gained fame. These are the pioneers who lit the light of neuroanaesthesia in the early and difficult days without any previous experience and when induction with ether, blind intubation and maintenance with oxygen, nitrous oxide and ether/chloroform were in vogue.

At the end of the forties, local anaesthesia along with basal narcosis by rectal administration of bromethol was the anaesthesia of choice for neurosurgical operations. Long hours of surgery, difficulty in controlling the airway, bleeding from the wound and the need to keep the patient quiet and motionless forced the anaesthetist to switch to the form of general anaesthesia then in vogue. Morphine and atropine were routinely used as premedicants. The adverse effects of morphine and ether combined with the consequences of the patient coughing and bucking during intubation under light anaesthesia when the intracranial pressure(ICP) was already high made them change to more reliable drugs. In the early-1950s the lytic cocktail was used as premedicant. Intravenous administration of thiopentone sodium put an end to stormy induction and permitted smooth anesthesia. The introduction of short acting neuromuscular blocking agents, suxamethonium, (described by Bovet et al in 1949 and used clinically in 1951 by Scurr) made intubation easier. By 1952 induction with thiopentone and intubation with suxamethonium became the practice for neurosurgical anaesthesia in India.(Ambardekar 1954, Rajagopalan 1954) Although the induction and intubation problems had eased, intraoperative maintenance of anesthesia remained stormy. Gallamine triethiodide (synthesised in 1947 by Bovet), was put into clinical use by Mushin et al in 1949. This ill-understood non-depolarising muscle relaxant was not popular because of the respiratory hazards it produced and was sparingly used with ether in our country. The report on controlled ventilation with curare by Furness of Melbourne in 1957 is a milestone in the advancement

of neuroanaesthesia. Controlled ventilation with the use of the sodalime absorption system was soon employed in India for neurosurgical anaesthesia producing a significant change in the total outcome (Ramamurthi 1959). Although curare was initially used for controlled ventilation, gallamine soon became popular abroad and in India. The use of gallamine (40 mg) in combination with curare (10mg) became popular and remained in vogue for years. Pancuronium was introduced into clinical use by Baird and Reid in 1967. This nondepolarising muscle relaxant proved more promising than curare or the combination of curare and gallamine because of the cardiovascular stability it produced and the fact that it did not raise the ICP. (Verma 1971) Although pancuronium is being widely used as the drug of choice in India, research is in progress to find a more suitable non-depolarising muscle relaxant for quick onset of action like suxamethonium, cardiovascular stability, prolonged duration of action, no histamine release and ability to reduce I.C.P. Vercuronium bromide, a relatively newer muscle relaxant, was tried in neurosurgical patients. Although it offered remarkable cardiovascular stability, there was no distinct advantage in regard to I.C.P. or the duration of action.(Rout 1988)

Inhalational anaesthetic agents

With the advent of controlled ventilation in neuro-surgical anaesthesia and the diathermy during surgery, ether went into oblivion. Halothane came into use in India in the sixties. Although it raises ICP and produces systemic hypotension it is still being used in some centres (along with hyperventilation) as isoflurane or enflurane are not available here. The use of trichloroethylene also gained popularity in 1960s in India, replacing ether, chloroform and cyclopropane for patients undergoing posterior fossa surgery in sitting position. Its adverse reaction with sodalime, resulting in toxic cranial neuropathy, made the drug unsuitable for neurosurgical patients requiring controlled ventilation. However, with the use of Bain circuit for controlled ventilation, trichloroethylene has made a re-entry into neuroanaesthesia (Saini 1986).

Endotracheal anaesthesia, positioning and monitoring

Although endotracheal anaesthesia was introduced as early as 1880 (Macewen), it became popular in 1909 when insufflation anaesthesia was established. In India, the first recorded event is that of MacReddie (1880) introducing an elastic catheter into the trachea of a patient and administered chloroform anaesthesia (Pramanik 1980). Endotracheal injection of local anaesthetics was routinely used prior to intubation in the early fifties to avoid the adverse effects of laryngotracheal reflexes. Since the mid-1960s local spray of 4% lignocaine is being routinely practiced prior to intubation.

Although positioning for anterior supratentorial surgery posed no problem

to the anaesthetist, occipital and posterior fossa lesions presented difficulties both for the anaesthetists and surgeons in the early period. When the sitting position was employed, the patient was anaesthetised as usual on the operating table and then shifted bodily and made to sit on an armless chair facing the back rest. The chair was turned with its back towards the head end of the table. The patient was kept in position by tying a draw sheet round his back and round the chair. The chin of the patient rested on the operating table with the arms outstretched on it to facilitate intravenous infusions. If any problem arose this arrangement was dismantled and the patient put face down on the operating table (Ramamurthi 1983). The invention of flexometallic tubes (1955) eliminated the risk of obstruction of the airway when the neck is flexed acutely or the head placed in an awkward position. Development of different chairs for surgery with the patient sitting, head rests, clamps, controlled ventilation, hydrocephalus shunt systems and steroid therapy resolved most of these problems and contributed remarkably towards a better outcome. Continuous monitoring of arterial pressure, ECG, CVP, core temperature and timely blood gas analysis (along with hyperventilation) became a standard practice for all major neurosurgical procedures from the early 1970s (Bhattacharya 1971, Verma 1977, Kak 1978, Kavadia 1977, Kaushik 1983, Pantvaidya 1982). Availability of the above facilities however, influenced the surgeon's preference to keep the patient in the sitting, prone, lateral and park bench positions for posterior fossa surgery (Lall 1969, Kochar 1980, Gilani 1980, Malathi 1983, Devanandan 1984, Goswami 1986, Panigrahi 1986, Saini 1987, Muralidhar 1988).

The anaesthetic management of patients with fluorosis and consequent myelopathy was described by Malhotra et al in 1986.

The effects of various anaesthetics on ICP were studied from the early 1970s.(Logamuthukrishnan 1978, Bali 1979, Nayak 1980, Rout 1982, 1983, 1984, 1986, Appaswamy 1983, Kaushik 1985, Singhal 1986, Goswami 1987, Grover 1987, 1988, Padmanabhan 19987). In recent years continuous ICP monitoring has been employed for diagnosis and in the management of comatose patients with raised ICP (Logamuthukrishnan 1978). Neuromuscular monitoring using nerve stimulator is practiced at various centres (Jain 1983). Since 1980 capnograms are being routinely used in major centres to measure end-tidal CO_2 and thus detect air embolism, particularly during posterior fossa surgery (Gilani 1980, Malathi 1983, Devanandan 1984, Goswami 1986, Panigrahi 1986, Saini 1987, Muralidhar 1988). Doppler, though not as popular, is being used in certain centres for detection of air embolism. (Gilani 1980, Kochar 1980, Malathi 1989, Devanandan 1984). Although monitoring of right atrial pressure is commonly practiced, pulmonary artery pressure monitoring, is used infrequently during surgery. Pulse oximetry, transcutaneous $0_2/CO_2$ tension monitor, being noninvasive, are gaining popularity in recent years and are used in most centres both during surgery and in intensive care

units. Although intraoperative brainstem evoked potential monitoring has a great potential, due to lack of standardisation of its use for intraoperative procedures, it is rarely employed at present.

Reduction of ICP

Raised ICP in patients with large tumours, presenting late, posed a formidable problem both for the anaesthetist and surgeon. In the 1950s intravenous administration of 50% glucose and rectal administration of magnesium sulphate were the only means for reducing ICP. The thrombosing effect of 50% glucose was the main draw back. Towards the late 1950s urea and mannitol became available. Urea was gradually discarded because of its thrombosing property and rebound phenomena. It was replaced by mannitol which remains the decongestant of choice. In the 1960s diuretics like frusemide, ethacrinic acid, corticosteroids and glycerol came into use. Hyper-ventilation continued to play a significant role along with mannitol in the reduction of ICP. In certain circumstances continuous lumbar drainage was a helpful adjunct but this is being given up. Lignocaine hydrochloride was used to reduce brain bulk and ICP during surgery in a multiphased clinical trial in 1980s and along with a small dose of frusemide proved a potent substitute for mannitol (Rout 1982,1983,1984,1986,1987). This technique is being widely used in India. The role of lignocaine hydrochloride in cerebral protection is still under study.

Hypothermia and hypotension

Hypothermia and hypotensive techniques were employed in India as early as in 1954 to reduce brain temperature, cerebral metabolism and bleeding during surgery (Ambardekar 1954, Rajagopalan 1954). Lytic cocktail was then used for premedication instead of morphine in order to prevent shivering during hypothermia and to produce hypotension. (Singh B. 1954) After lytic cocktail premedication and induction of anaesthesia, temperature was reduced to 30-32°C by surface cooling with icebags. At the end of surgery, warming with hot water bags and woollen blankets was a routine practice. Although the whole procedure was cumbersome and time consuming there was no alternative to it till cardiopulmonary bypass and thermal blanket were invented (Narang 1967). Profound hypothermia under cardiopulmonary bypass was never employed for neurosurgery in India. The use of moderate hypothermia gradually declined and was abolished by mid 1970s with availability of better anaesthetics and adjuvant drugs (Kop 1979). Trimetaphan was used to induce hypotension in neurosurgery in India almost simultaneously with its use in the west in 1953 (Singh B 1954). Anaesthetists soon prefered the lytic cocktail in order to avoid tachyphylaxis encountered with trimetaphan (Ambardekar 1954, Rajagopalan 1954, Singh B 1954). Hypothermia and hypotension with lytic cocktail and trimetaphan were employed in the management

of intracranial vascular lesions under general anaesthesia. (Ramamurthi 1961, Narang 1967, Verma 1987). Despite the advent of hyperventilation in 1961 and sodium nitroprusside (SNP) in 1962 in the west, these were sparingly used in India till 1970 due to inadequate monitoring facilities. Thus largactil and halothane remained in vogue for hypotensive anaesthesia in most of the centres for over a decade. SNP regained its popularity in 1970s when propranolol was used along with premedication to avoid tachycardia and rebound hypertension. It also helped to reduce the required dosage of SNP to achieve desired hypotension (Verma 1971, Pal 1973, 1976, Jha 1975, Prabhakar 1983). SNP and halothane are still in popular use in India for aneurysmal surgery (Yajnik 1977, Kop 1979, Deval 1983 Upadhyae 1984). Sporadic use of other hypotensive agents for vascular surgery in recent years include trinitroglycerine (Saini 1981, Rattan 1985); calcium channel blocker - verapamil (Sahani 1986); chloropromazine (Verma 1987) and labetolol (Wig 1987). The role of long acting beta-1-adrenergic blocker (atenolol) as an hypotensive agent in neuroanaesthesia is under study by the author. Initial results are encouraging. Bilateral maxillary nerve block using lignocaine/bupivocaine along with general anaesthesia is being practiced during trans-sphenoidal surgery to prevent hypertensive episode (Rout 1987, 1988). Labetalol is being used at the PGI, Chandigarh, to blunt the hypertensive responses during trans-sphenoidal surgery.(Personal communication: Wig J.)

Anaesthesia for neuroradiological procedures and other techniques

Although most of the diagnostic but invasive radiological procedures were being carried out under sedation using lytic cocktail, ketamine, diazepam, althesin, propinol and propanidid in the past, neuroleptanalgesia and a combination of diazepam and pentazocine are currently being used for prolonged interventional therapeutic procedures (Badve 1972, Verma 1979, Venkataraman 1982, Bharati 1983, Umamaheswar Rao 1983, Kumar 1984, Rao 1987, 1988). Subarachnoid block and dissociative anaesthesia have been employed for surgical repair of lumbar meningomyeloceles and epidural block for lumbar laminectomies (Vaze 1968, Singh C, 1970, Sriram 1971, Suri 1978, Singh CV 1980, Venkataraman 1982, Sarate 1984, Rajauria 1985, Jagger 1986, Mishra 1987).

Neuroanaesthetists in certain centres conduct pain clinics and provide anaesthesia for electroconvulsive therapy.(Chakraborty 1966, Vaze 1968, Bhala 1977, Singh H 1978, Suri 1978, Gopakumar 1979, Saini 1979, Singh CV 1979, Mulay 1979, Divekar 1980, Verma JS 1980, Samtani 1984, Pereira 1984, Viswanathan 1983, Singh P 1984, Sangawar 1985, Vaidya 1988.)

Cerebral protection and intensive care management

Thiopental anaesthesia, hypothermia, hyperventilation, decongestant therapeutics and steroids have been employed to reduce cerebral metabolism, cerebral metabolic requirement for oxygen ($CMRO_2$), cerebral blood flow and ICP. The concept of cerebral protection by barbiturate came into practice in India in the late 70s.(Bhala 1977, Marykutty 1978, Appaswamy 1983, Vidyasagar 1983, Samtani 1984, Parameswar 1985, Deshpande 1988). Barbiturates were used not only in patients with severe head injuries but also in the management of inflammatory, hypoxic, ischemic, toxic and metabolic encephalopathies to preserve brain cell function (Prakash 1972, Padmanabhan 1983, Vidyasagar 1983, Parameswar 1984, Verma 1984, Joshi 1988). The use of barbiturates in incremental anaesthetic dosage later became popular in India for cerebral protection during cardiopulmonary bypass. For the first time lignocaine hydrochloride in large dosage, (up to 20 mg/kg) was used in India in a major series in lieu of mannitol as it satisfactorily reduces ICP, cerebral metabolism, $CMRO_2$ and cerebral blood volume. It also increases cerebral vascular resistance and cerebral perfusion pressure without any cardiopulmonary instability (Rout 1982, 1983, 1984, 1986). It was found to have a special role when used for resection of brain abscesses secondary to cyanotic heart disease (Rout 1984, 1986).

In the late 1950s controlled ventilation was achieved manually. Radcliffe, Blease pulmoflator and Barnet ventilators were available only for ICU use in the 1960s. Volume cycle ventilators with modes like, CPAP, SIMV, IMV, MMV and PEEP with blender to give desired concentration of 02 with nebuliser and facilities to monitor all respiratory parameters are now available in various centres for neuroanaesthesia and intensive care management of patients suffering from spinobulbar palsy, poisoning, tetanus, respiratory distress syndrome and any other conditions requiring respiratory support (Ghosh 1950, Vakil 1969, Prakash 1972, Vidyasagar 1983, Padmanabhan 1983, 1984, Parameswar 1984, Verma 1983, 1984, Rout 1984, Joshi 1988, Vaidya 1988).

Training programmes in anaesthesia

Before independence (1947) there were only 9 teachers in anaesthesia in 11 medical colleges in India. The diploma course in anaesthesia was first started by the Bombay University in 1946 and the postgraduate course (MD/MS) by the Bihar university in 1955. At present there are 121 medical colleges and 4 postgraduate institutes. While the diploma course is taught in 45 universities, postgraduate training leading to MD/MS degree in anaesthesia is currently available in 50 universities and 4 postgraduate institutions. A post doctoral certificate course in neuroanaesthesia is available only at Sree Chitra Tirunal Institute for Medical Sciences and Technology at Trivandrum since 1982.

The Indian Society of Anaesthesia was founded in 1947 by F. Saher and B.N.Sircar and the first national conference of the society was held in December 1949 in Bombay (Pramanik 1980). Although at present the society registers more than 5000 qualified anaesthetists as its members, there are just 30 anaesthetists who pursue neuroanaesthesia as a fulltime career. Symposia and seminars in neuroanaesthesia are being conducted regularly for over a decade. The first National Seminar on Neuroanaesthesia was held at Bangalore in 1983 for future planning and development of the speciality.

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Neurosurgery in the armed forces

Mahendra Singh, Suraj Prakash

Medicine in India goes back to the days when Aryans came from Central Asia some 5000 years B.C. Along the route, they had to fight the local residents. During these wars the surgeons had to attend to the wounded officers and soldiers. Of all the branches of medicine, surgery is the one which has responded best to the challenges of war and since ancient times surgeons have accompanied the armies. Although these ancient surgeons had commented on the management of head wounds and other disorders of brain and nerves, the history of modern military neurosurgery in India dates back to world war II.

The Japanese advance into Burma in 1941-42 brought the war close to India. India was the base for evacuation of all battle casualties from the south east Asia command. The first phase of the campaign in this sector was retreat from Burma in 1942 - also known as 'Dunkirk of the East'. During this period a mobile neurosurgical unit was hurriedly organised and located at Ranchi. However, no head wounds reached this unit.

The second phase of the Burma campaign was a long period of waiting and of training (1942-43). During this phase two mobile neurosurgical units were organised. One was located in the north at Bareilly and the other in the south at Poona. Each consisted of four medical officers (one neurosurgeon, one neurologist, one anaesthetist and one general duty medical officer), two nursing officers and six other ranks. They were equipped with a three ton truck fitted with special operating room equipment (including diathermy and electric generator). Only a few head wounds were treated at these units as the fighting was thousands of miles away.

The third phase of the Burma campaign commenced at the end of 1943 with more frequent attacks on Japanese frontier bunker positions. The mobile neurosurgical units were moved to forward areas in order to receive casualties within 72 hours of head injury. This was not often achieved. The terrain prevented rapid transport. The journey in the majority of cases took five days, partly spent in river sampans, partly in jeep over rough jungle tracks, and a final journey by ambulance car over rough roads. In some 'boxes' evacuation was impossible for two to three weeks.

The fourth phase of the Burma campaign was the siege of Imphal and the first period of really heavy fighting. One mobile neurosurgical unit under the command of Lt.Col. R.T.Johnson (who was also the adviser in neurosurgery to A.L.F.S.E.A.C.) was moved to Comilla in east Bengal as the Japanese had surrounded Imphal and fighting had also flared up in Arakan. Surgeons working with forward field units were given instructions to evacuate cases to a neurosurgical unit without operations provided they could do so within three to four days. Head injuries were placed third in order of priority for evacuation by air. Towards the end of world war II, ninety percent of wounds of the head associated with penetration of dura were treated at one of these neurosurgical units. A large number of patients with such wounds were flown out to Comilla from both the fronts - most of these were treated within 48 hours. Each of these units had the additional burden of urgent general surgery. The war situation, at times, required withdrawal of all nursing officers making the nursing care of these cases a difficult problem over the next few weeks.

A 100 bedded neurosurgical centre was established at the general base hospital in Poona in January 1944. This centre had its own establishment of neurosurgeon as commanding officer, one neurologist, one neuropathologist, one captain IAMC or RAMC, two masseurs, one Corporal WAC(I), and a stenographer. Necessary equipment was provided. This centre was responsible for investigation, management and disposal of all personnel from the armed forces evacuated to the base. The neurosurgical centre thus constituted proved to be of considerable value. The centre organised weekly clinical demonstrations which proved extremely popular with all medical officers in the area.

The administration of the neurosurgical units and the centre came directly under the the consultant neurologists at that time - Brigadier D.McAlpine and Brigadier D. Denny Brown OBE,who worked in close collaboration with the consultant surgeons- the 12th army and ALF SEAC - Brigadier Grant Massey CBE, Brigadier M.F.Nichols and Brigadier John Bruce.

In the early stages of the campaign in Burma, the mortality from head wounds was extremely high, even when the interval between injury and operation was reduced. The high mortality was traced to the frequency of B.Coli encephalitis and meningitis which almost invariably terminated in haemorrhagic ependymitis. Only in the later stages of the war, with the availability of sulphamethazine and penicillin, did the conditions and therefore the statistics improve.

The final phase of the Burma campaign was the triumphant advance to Rangoon in the middle of 1945. By this time the problem of accommodation, staff and equipment had largely been solved. The discipline was excellent. Supplies and prophylaxis against disease greatly improved. Penicillin was freely available.

During the advance of the allied troops into Burma, the two mobile neurosurgical units with the 14th army were attached to various forward medical units (Indian Mobile Surgical Units, Indian Beach Medical Unit, or as an Improvised Surgical Team) in accordance with the tactical and strategic demands. They did much useful work under difficult conditions. Between February 14 and March 6, 1945 these units worked 18 out of 21 nights - the whole night through and on the three remaining nights they worked until past midnight. They worked in collaboration with the ophthalmic units and the mobile surgical units in the field - thus providing a 'specialist trinity' which abundantly proved its worth.

During this period, the hospitals specially staffed and equipped with neurological and allied centres in the India Command were as follows:-

Location	Base Hospital	Beds		Centre for
		British	Indian	
Kirkee (Poona)	6 IBGH	-	1000	Neurosurgery
	7 IBGH	-	1000	Neurology Nerve injury Orthopaedic
Lucknow	129 IBGH	-	1500	Neurosurgery Nerve injury Plastic surgery
Moradabad	131 IBGH	-	1500	Psychiatry
Bangalore	Base Hospital	1200	-	Nerve injury Orthopaedic
Ranchi	133 IBGH	1000	-	Nerve injury Orthopaedic Plastic surgery
	139 IBGH	1200	-	Neurology Neurosurgery Psychiatry
Secund-erabad	127 IBGH	1200	-	Neurosurgery Psychiatry.

(IBGH: Indian Base General Hospital)

At the end of the war most of these centres were disbanded. Of the two British mobile neurosurgical units one was repatriated to the United Kingdom and the other was attached to 127 Indian Base General Hospital for British Troops at Secunderabad. During the war neurosurgical cases

of the Indian armed forces were treated by British and allied neurosurgeons. Till the end of world war II we had no Indian neurosurgeons. Colonel Collins, who at that time was the surgical consultant in India, realised this deficiency and was responsible for initiating the training of young Indian surgeons not only in neurosurgery but also in such other specialities as thoracic and plastic surgery early in 1947.

Capt. John M. Potter was the last British neurosurgeon left in India at that time. He was the one who initiated Capt. A.C.Ray in neurosurgical training in February 1947. Capt. Potter left India in October 1947 and was later to become consultant neurosurgeon to the Manchester Royal Infirmary, Manchester Regional Hospital Board, clinical lecturer in neurosurgery at the University of Manchester, consultant neurosurgeon to the United Oxford Hospitals and examiner in physiology for the Primary FRCS.

In June 1947 the neurosurgical unit (along with Captains Potter and Ray) was moved to Poona and attached to the Indian Military Hospital there. After repatriation of Capt. Potter, Capt. A.C.Ray continued to be in charge of this unit. The outburst of hostilities necessitated his move to Jammu and Kashmir in December 1947. The number of neurosurgical cases among the casualties evacuated to the military hospital, Delhi warranted the opening of a neurosurgical centre at a base hospital to which these casualties could be flown. In view of the logistic and strategic considerations the neurosurgical centre was located at Poona in April 1948. For the next few years the neurosurgical centre meant the neurosurgeon and his set of instruments. In October 1953 the centre was shifted to the Military Hospital at Delhi Cantonment. By now the neurosurgeon also had the assistance of a neurologist.

When the eastern theatre attained importance due to the problems in the North East Frontier Agency and Nagaland, the centre was moved to Military Hospital, Lucknow in August 1956. This unit was progressively organised into a full fledged neurosurgical centre with an updated scale of neurosurgical and general instruments, a 16 channel E.E.G. Machine and a Schonander skull x-ray unit along with their ancillaries.

Two neurosurgeons,(Major Mahendra Singh and Major Virendra Mohan), one neurologist trained in the use of the EEG (Lt.Col.B.C. Chatterjee) and a neuroradiologist (Commander Bhalla) were attached to this centre. Lt. Col. AC Ray was appointed the Adviser in Neurosurgery and headed the unit till August 1966.

After the war with China in 1962 further expansion of the armed forces necessitated neurological centres at Poona (Southern Command) under Lt. Col. Virendra Mohan and at Delhi (Western Command) under Lt. Col.

Mahendra Singh. After the 1971 war another centre was set up at Calcutta (Eastern Command) under Lt. Col. Suraj Prakash. Since 1981, a neurological centre has also been functioning in Northern Command at Udhampur headed by Lt.Col. Ved Prakash. By 1988, 16 neurosurgeons, 15 neurologists, 3 neuroradiologists,2 neuroanaesthetists and 1 neuropathologist had joined the neurological centres after prolonged specialised training in reputed institutions in India and abroad.

Though the establishment of modern full fledged neurological centres in the armed forces is relatively recent, it is gratifying to note that excellent progress has been made by them both during war and peace. They provide complete neurological and neurosurgical investigations and treatment for the personnel of the armed forces, their families and dependents. The specialists from these centres are also available for consultation by other service hospitals for all types of neurological or neurosurgical emergencies. All these centres provide postgraduate training facilities to the surgical specialists and medical officers of the armed forces. The centre at Poona has also been recognised for M.Ch. degree in Neurosurgery by the University of Poona. These centres also have effective research capability in order to keep pace with the operational needs of the armed forces whether on land, sea or air.

Trauma to the brain, spine and the nerves forms a fairly large bulk of the neurosurgical problems dealt with at the armed forces centres. During the Indo-Pakistan conflicts of 1965 and 1971 additional centres were set up at the forward hospitals. The policy underlying the establishment of these centres was derived from the necessity of operation on penetrating wounds of head and spine as early as possible by specially trained surgeons adequately equipped with the facilities for proper neurosurgical management. With this policy, the statistics of the management of neurosurgical casualties during the 1971 war compared favourably with those of the most modern and sophisticated centres operating in the Vietnam and Indo-China theatres of war.

During World War II, the care of patients suffering from traumatic paraplegia had given rise to much anxiety. The long and delayed evacuation led to the formation of deep bed sores from which recovery was slow and difficult. The supply of special mattresses, spinal carriages, revolving beds and ancillaries was, however, extremely limited throughout the war. Such patients tolerated heat poorly and for want of airconditioning had to be treated in the centres in the cooler parts of the country like Dehradun and Secunderabad. The situation did not change much till after the war with China in 1962 when it was decided to establish proper paraplegia centres at Poona and Lucknow. These centres were authorised an adequate number of specially trained personnel. Rehabilitation facilities were also provided along with an occupational therapy set up. The centre at Poona has 100 beds and that at Lucknow has 60 beds.

Among the neurological diseases meningitis, epilepsy, peripheral neuritis, neurological complications of malaria, heat stroke, late effects of head injuries and neuropathies observed in prisoners-of-war were of interest.

10 to 15 per cent of all casualties showed psychiatric symptoms. With the posting of divisional psychiatrists in forward areas, about 25 percent of the patients were returned to duty. In the base areas the number of beds reserved for psychiatric patients varied between 3000 and 4000. Centres in Comilla, Calcutta, Ranchi, Moradabad, Poona and Secunderabad were set up. A 1000 bed hospital was established at Jalahali. Psychiatric symptoms commonly followed malaria and typhus. Conversion symptoms were more frequent in Indian troops while anxiety states were more prominent in British troops. Schizoid episodes were also noted. The sickness rate per 1000 for psychiatric patients on the Indo-Burma front was 1.41 in 1942, 3.10 in 1943, 4.28 in 1944 and 5.33 in 1945. The rise in incidence was due to the altered conditions in which the fighting took place, Exhaustion, malaria and dysentery were generally found in association with psychiatric disabilities. It was rare to find a patient with a clear cut clinical picture.

The armed forces in India are unique in having the Armed Forces Medical College for training undergraduates and postgraduates in the medical sciences. It was started in Poona in 1948 for training postgraduates and was attached to the University of Poona. Since 1962 an undergraduate wing has also been started. Post doctoral courses were set up in 1958.

At present the seniormost neurosurgeon in the armed forces, Lt.Gen. Suraj Prakash, is the commandant of the Armed Forces Medical College, Pune. He is also the Professor of Neurosurgery at the University of Pune.

Work of special interest done at the armed forces neurological centres

War injuries: Since independence, India has been involved in wars in 1962, 1965 and 1971. Craniospinal injuries during war were of special interest to the armed forces. The experience in management of cranio spinal injuries was highlighted by Brigadier Mahendra Singh in his Presidential address to the Neurological Society of India (NSI) in 1978.

Cerebrovascular diseases and strokes in the young. Strokes occurring in elderly population (dependents of serving personnel) are as common as in civil practice. However stroke in the young is also seen in the services and has specially been observed in personnel who have served at high altitudes. This problem was studied by Major G.P. Vijayan and Col. M.L.Suri. A follow up AFRMC project to define the vascular abnormalities in cerebral stroke has been conducted by Lt.Col. P.V.S. Rana. A registry for cerebrovascular accidents is being maintained at Army Hospital, Delhi Cantonment.

Intracerebral haemorrhage is being studied by Lt.Col. R.M. Dhamija.

Neurocysticercosis has been a health problem in the armed forces since the British days. Over the last two decades this has been studied by various workers (Major G.P. Vijayan, Col.M.L. Suri and Col. S. Venkataraman VSM). Since 1975, 200 cases have been studied and a Registry of Neurocysticercosis has been started at the centre in Delhi with Col. S. Venkataraman VSM in charge. Evaluation of treatment by praziquantel and albendazole is being done as an AFMRC Project by Lt.Col. P.C. Sancheti.

Neurological complications of malignancies. Malignant Disease Treatment Centre for the armed forces is located at Pune. All patients with malignant tumours are sent there for confirmation of diagnosis and treatment. Col. A. Narayanaswamy, Senior Adviser in Neurology has been working on the neurological complications in malignant diseases in collaboration with Col. S. Biswas, Senior Adviser in Neurosurgery and the neurosurgeon Lt. Col. H.S. Gill.

Neurological problems related to high altitude have been a subject of special interest to neurologists and neurophysiologists. Many projects are being studied by the DIPAS (under the R and D Department of Ministry of Defence).

Yoga and its effect on human body, the effects of bio-feed back, nerve conduction velocities at high altitude are some of the studies in progress at DIPAS.

Neurological sequelae of malaria. Malaria is a health problem to the armed forces since World War II. With the recent upsurge in malaria especially in the eastern sector many transient and permanent neurological sequelae of malaria are being encountered. This has been recently studied at the centres in Calcutta and Lucknow.

Boxing injuries. Organised sports in the armed forces are part of daily activity. Boxing is an amateur sport in the services. Boxing injuries can result in acute and chronic neurological sequelae. This is being studied as an AFMRC project.

Traumatic paraplegia resulting from injury in war and peace time has already been referred to. Lt.Col. V.S. Madan VSM has been working on this subject and has been awarded E.Merck Medal by the NSI for it.

Peripheral nerve injuries: Until 1943, the majority of peripheral nerve injuries were transferred to Mobile Neurosurgical units. Since the units were on the move a peripheral nerve injury centre with 150 beds was planned and located at an orthopaedic hospital. The work at this centre

was supervised by the consultant neurologist and the consultant neurosurgeon.

The work on peripheral nerve injuries followed the established orthopaedic and neurological practices. The chief interest in the clinical material lay in the high proportion of causalgia consequent upon nerve injuries in India, the incidence of which was twice that reported in Britain, South Africa and USA. Causalgia was much less frequent in the cooler stations. The peripheral nerve injury centre was disbanded after the war. At present these cases are dealt with by the respective neurological centres of the various commands.

Special Problems of the Armed Forces

Besides routine neurological and neurosurgical problems as seen in civil life, problems peculiar to the armed forces stem from the effects of climate vary from dehydration in desert areas on one hand and the effects of cold and high altitude on the other. Soldiers employed at the altitude over 12000-20000 feet have offered an opportunity to study the effects of cold and high altitude on the nervous system.

In the field of aviation medicine, the armed forces have the special problems of biodynamics of head and spinal injuries, epilepsy and EEG abnormalities among the aircrew (post-traumatic or idiopathic) and neuropsychiatric aspects of flying and air accidents. These problems are being studied at the School of Aviation Medicine at Bangalore and AF CME at Delhi.

Problems peculiar to navy comprise of barotrauma during deep sea diving and effects of climate on sailors who have to survive at sea for long periods especially in submarine ships. These are being studied at the School of Underwater Medicine at Bombay. Recently the Navy has been working on problems experienced at the Antarctica.

Academic Activities

Besides routine clinical work and teaching involved in the different centres, neuroscientists from the armed forces participate in all the activities of the NSI. Neuroscientists from the services have contributed papers to *Neurology India* and other national and international Journals.

The Annual meeting of the NSI was conducted in the Armed Forces Medical College, Pune, in 1977.

Honours bestowed on the neuroscientists in the armed forces

Brig. Mahendra Singh was elected President of the NSI in 1978. Col. M.L. Suri was a member of the Executive Committee of NSI (1974). Lt.Col.

P.K. Sethi VSM was an elected member of Projects Review Committee of the US funded Projects of ICMR. Lt. General Suraj Prakash has achieved the distinction of being the first neuroscientist to be promoted to the highest rank in the Army Medical Corps and appointed Commandant of the Armed Forces Medical College, Pune. Lt.Col. T.K. Roy, who heads the neurocentre at Calcutta, has been awarded Ati Vishist Seva Medal. Four neurosurgeons and two neurologists had been awarded the Vishist Seva Medal for their meritorious services in the armed forces.

Brief biographical sketch of Colonel A.C. Ray

Anil Chandra Ray, the third of nine children of a middle class family, was born on May 7, 1912 in a village in north Bengal. He had a brilliant record in his school and intermediate grade examinations. He was married in 1933, while still a medical student. After graduating in 1938 he joined the Indian Medical Service in July 1940 and spent the next four years on active service overseas, the first two as regimental medical officer. The hard work put in by him during the subsequent two years of hospital posting was rewarded by training in surgery. Gifted with a good operating hand, he was graded as a surgeon in January 1946.

After the cessation of war on the eastern front most of the specialised centres which had been operating in India Command were disbanded or returned to their parent units in the United Kingdom or other countries. However, one mobile neurosurgical unit remained attached to 127 Indian Base General Hospital for British troops at Secunderabad. Captain A.C.Ray, who happened to be posted to this hospital at that time, was selected for training in neurosurgery under Captain John M. Potter. After Captain Potter was repatriated to U.K. in October 1947, Captain Ray continued to be in charge of the neurosurgical unit. He was responsible for the development of neurosurgery in the armed forces from its humble beginnings (when the centre possessed just a set of instruments and himself as the sole officer) to a proper, well-equipped and staffed neurosurgical centre at Lucknow in August 1956. During this process of development, Colonel Ray had to face many difficulties and obstacles, but with determination, improvisation and persistence he was able to achieve his goal.

During this phase there were hardly any neurosurgical facilities in India in the civil sector or the medical colleges except at Vellore, Madras and Bombay. When Colonel Ray was posted at Delhi in 1955 he was conducting neurosurgical operations at the Tirath Ram Shah Hospital in collaboration with Dr. Baldev Singh. At Lucknow too,he was often called upon to conduct neurosurgical procedures and operations at the Medical College Hospital.

Colonel A.C. Ray continued to be the Adviser in Neurosurgery till August 1966 when he opted out for administrative duties. Since his superannuation

from service in 1947 he and Mrs. Ray are leading a peaceful retired life at Lucknow. They have two sons and a daughter who are well settled in life.

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Neurosurgery in India: a personal impression

Kristian Kristiansen

In his letter of April 28, 1989 Professor P.N. Tandon wishes an objective account on Indian neurosciences from a person outside India. I am afraid this is difficult in spite of a certain knowledge of the subject through several visits to prominent centers and close cooperation with many outstanding representatives of the neurological sciences in India. The following report is based on fleeting memories and on a few publications and should only be regarded as a personal impression, and not as "an objective account".

My first contact with Indian neuroscientists dates back to 1947-1949 when I was working as a fellow of the Montreal Neurological Institute (MNI). There Jacob Chandy and Ram Ginde became good friends. The training program in the MNI included all aspects of the neurological sciences. This integration of anatomy, physiology, chemistry, radiology and pathology with clinical neurology and neurosurgery was regarded as obligatory for any one who wanted to work with patients suffering from diseases of the nervous system. The fellows at the MNI hailed from all over the world and they brought these principles back to their native countries. This pattern of training is adopted by the leading centers in India and also in other countries.

However, the proceedings of the National Workshop on Clinical Neurosciences in April 1986 in Bangalore stressed the insufficient number of specialists in these fields in India and made several recommendations in order to establish neuroscience centers in all medical colleges and to improve training and closer contact with district hospitals. The discussions were continued in New Delhi in December 1986 where Dr. Chandy emphasized the unity of the neurosciences. I and my wife had the good fortune to be present at the meeting listening to the views of representatives from the different sections of the neurosciences, particularly regarding the training systems. Dr. Baldev Singh was there, the nestor of Indian neurology, whose life and work have set the example for education, teaching and research in the field. Since Professor Baldev Singh and 3 colleagues started the Neurological Society of India in Hyderabad in 1949 and the journal *Neurology India* was born 4 years later, his contributions to clinical neurology and the allied sciences have illustrated an incessant activity and interest in the development of new methods and techniques.

For me it has been a particularly rewarding experience to observe the growth of neurosurgery in many cities in India, beginning with the work of Jacob Chandy in Vellore, Ram Ginde in Bombay and B. Ramamurthi in Madras, who besides his training in England also spent some months in 1950 with Dr. Penfield in Montreal. I had the privilege to have Dr. Prakash Tandon as my assistant during the years 1957-1958, and paid my first visit to India in 1964 when Dr. Tandon had been appointed Professor of Neurosurgery at the University of Lucknow and Head of the neurosurgical service at King George Hospital. As the only Department of Neurosurgery in Uttar Pradesh with 70 million inhabitants the patient material was unlimited and offered possibilities for clinical training and research unheard of in the western world. And we availed ourselves of this opportunity! Every morning at 6 o'clock Prakash came into our bedroom with morning tea for my wife and myself and brought a large bundle of patient records and X-ray films, and we started the day's work with discussions of difficult cases. With small changes this routine has been followed during all our later visits to India. Gradually my former pupil took over the role as the teacher. It is my sincere opinion that young neurologists and neurosurgeons from the western countries should go to India for 6-12 months to complete their education because the size and variety of the patient material will give them an experience and knowledge unobtainable at the medical schools in Europe or the United States. So far my propaganda for this reversal of the usual direction of travel for graduate students has been unsuccessful, but I am optimistic for the future.

Neurosurgery in India – a personal impression

Jules Hardy

The choice to visit India

When I was offered the Sims Commonwealth Travelling Professorship, I had the chance to visit any of the 47 countries related to the Commonwealth. Some countries are particularly attractive for sightseeing and, according to the saying: "The further away from home the more attractive and fascinating is the country". For instance, New Zealand and Australia are most appealing to tour, nevertheless, I had received several invitations from colleagues in India requesting a professor who could teach pituitary surgery and perform surgical demonstrations. For that reason, I had elected to visit the major neurosurgical centres in India before going to the U.K.

My interest was raised even more a few weeks before leaving for India, when the Attenborough movie on Gandhi opened in Montreal and I rushed to see it. The film is an impressive historical review of India and the political activities leading to independence. The greatest paradox was the non-violence philosophy of Gandhi that led to the violence beginning on the night of August 14, 1947, when independence was declared by Lord Mountbatten. The judgment of history will tell whether the decision for independence was made at the proper time. Many countries have reached independence only after turmoil of wars. There was a marked contrast when Canada gained independence by peacefully repatriating its constitution, a simple event in the natural history of the British Commonwealth.

The Commonwealth

In the past, I had the impression that the Commonwealth was a political concept with no clear significance. I became aware of my error in India on March 14, which is *Commonwealth Day,* and on which a worldwide community of 47 independent states celebrates membership in this unique voluntary association. The Commonwealth is not defined by any charter, treaty or constitution. It finds its expression in cooperation, consultation and mutual aid. In 1971, a declaration by the heads of governments of member countries described the principles on which the Commonwealth is founded. Among the bylaws, the Commonwealth pledges to use its efforts

"to overcome poverty, ignorance and disease, to raise standards of life, and to achieve a more equitable international society". The declaration also emphasizes a common belief in international peace and order as essential prerequisites for the security and prosperity of mankind.

It is impressive that the people of the Commonwealth, 25 per cent of the world's population - more than 1,000 million people - drawn from every continent, share a bond that transcends geographical boundaries, political frontiers, and the barriers of facism, creed and color. Every geographical feature and extreme is represented. Economically, its members range from some of the richest and most highly industrialized countries through all stages of industrial and economic development to many of the poorest and least well endowed. Almost every shade of the political spectrum is included. Yet the British Minister, Mr. Francis Pym, described the Commonwealth in a keynote speech in July, 1982, as a "strange animal" largely because of its variety. He adds: "It is characterized by a marvelous spirit of friendship and partnership". This is what I found throughout my trip to India, Sri Lanka, Malasia and Singapore, the desire for unity in people from all racial and religious origins.

In India, there are 14 languages and 46 dialects, so that a physician in Bombay may not be able to understand the language of a colleague in Delhi, Calcutta or Madras. The main Hindu language is spoken so differently that the only common language of communication is English. I am not talking about the basic 300-word vocabulary of the American-English language that is a "master key" around the world but about the sophisticated language of the U.K. which is also spoken at all levels in India. You can find it in a taxi-driver, an elevator operator, a tourist guide in a Hindu temple, a Buddhist priest in Nepal or Sri Lanka, a Sherpa in the Himalayan mountains and in the high class (Brahmin) professionals up to the parliament in India where the main legislative debates are carried out in English for the understanding of all the nation. This is the spirit of the Commonwealth of which I suddenly became aware while visiting India and the other Asian countries.

Moreover, many educated physicians and university professors have completed their training in the universities of the United Kingdom, (many acquiring a master's degree of Royal College Fellowship from this country. Australia or Canada), before returning to India to pursue their academic careers. This practice provides a striking example of the application of the concept of the Commonwealth offering mutual aid between partners.

Overpopulation in India:

Overpopulation is a problem of great concern throughout the eastern countries, but is nowhere more cruel and insoluble than in India. I would like to report a personal experience that has opened my eyes to the

individual human aspect of fertility problems, reproduction and contraception.

Many authorities have advocated rigid measures for contraception and birth control in India. For example, a few years ago, a former minister had promulgated a rule that to be eligible for election, each candidate for a parliamentary seat should be able to list 10,000 citizens who had undergone contraceptive operations (for example, vasectomy for men and tubal ligation for women). However, this rule could not be enforced and the project had to be abandoned.

Since overpopulation is a most serious problem in India. I felt embarrassed to lecture on the treatment of pituitary tumors, particularly those on prolactin-secreting adenomas that present mainly with the symptoms of infertility, amenorrhea and galactorrhea. Hyperprolactinemia is known to be a natural biological contraceptive method and therefore, it seems ironical to promote medical or surgical treatment of infertility in a country where sterility should be desirable for both men and women.

After presenting my surgical results in the treatment of prolactin adenomas, which indicate 80 per cent biological cure with restoration of menstruation and fertility in women, I expressed my embarrassment to a professor, an outstanding endocrinologist who had trained in the United States and the United Kingdom and had elected to return to India to practise reproductive endocrinology. She said that the overpopulation problem in India cannot be settled by political, social or medical means. "This is both a religious and personal problem to each individual". She gave me an enlightening lesson in humanity when talking about a patient who had come to consult her for infertility. I asked her: "Don't you think that it is your duty to convince this woman to remain sterile for the sake of the whole country's welfare?" She answered: "I was born, raised and educated in India. I was treated by my parents as an unique individual and not as a social problem. I would like to treat my patients in the same way. I am not a politician or a social worker but a medical doctor dedicated to treat each individual's problem as her major concern. When a patient comes to my office complaining of sterility, it is my duty to help her with her problem. A sterile woman in India is treated without respect. She is rejected by men. For that reason, women want to become pregnant, to have husbands for their security. So I treat the patient with the most recent advances in modern medicine of surgery to help her achieve her desire of pregnancy. I leave the social problem of overpopulation to politicians."

After my encounter with this professor, I felt more comfortable in continuing to lecture on the treatment of prolactin-secreting pituitary adenomas.

Specialty manpower in India

The problem of medical manpower in India is also a complicated one. In a recent survey by an international neurosurgical journal, the figures for 1982 regarding the number of neurological surgeons and the ratio to the population of all countries around the world have shown a striking difference to the point of deprivation in developing countries. For instance, the ideal ratio has been established as one neurosurgeon per 150,000 people. Such a ratio has been met only by a few countries, such as Austria, Canada, Israel and the United States. In the United Kingdom, for a population of 56 million, there are 150 neurosurgeons, a ratio of one per 372,673 people. In Canada, with 24 million people, there are 175 neurosurgeons (one for 136,800 people), and in the United States, with a population of 226 million, there are 3,000 neurosurgeons (one for 75,000). On the other hand, in India, for a population of 700 million, there are fewer than 200 neurosurgeons (one for four million).

One result of a demand for specialized care that cannot be met is the large numbers of people dying of benign disorders that could easily be treated. For instance, patients with pituitary tumors present for consultation when they are totally blind and harboring voluminous intracranial masses, at which stage they can only be offered decompressive measures. While many of the large cities in India - Bombay, Delhi, Calcutta and Madras - do have one or two major hospitals providing neurosurgical care, most people do not have access to these institutions. In the province of Orissa, with 30 million people, there are only three practising neurosurgeons. Most neurosurgeons are fully occupied with problems of head injuries or spine fractures.

Nevertheless, in a few centres, I found that the quality of practice of neurosurgery was of a high standard, similar to that in developed countries like the U.K., Canada and United States. In those few centres, I saw outstanding technical performances with microsurgery and stereotaxic surgery. However, most hospitals do not have adequate facilities to deal even with the ordinary daily problems so that many people are deprived of neurosurgical attention. One department head had requested funds from the ministry of health to develop microsurgery. The ministry replied that this was a luxury, and that the population's needs were food and vitamins. So far, there are no solutions to these problems.

Teaching of modern surgical techniques

The conflicting demands of modern technical developments and basic needs are illustrated in the following anecdote. On my arrival at a provincial hospital, the head of the department invited me to hear a distinguished professor from another country who was going to lecture about recent technical advances in neurosurgery. At four o'clock. I entered a small room,

where there were three nurses, two neurosurgeons, four assistants, one anesthetist and a layman, a total of 12 people including myself. The professor arrived in a limousine with the ambassador from his country and introduced himself as a missionary to promote the most recent technical advances in neurosurgery.

For the next 45 minutes, he expounded the indispensable role and mandatory use of the ceiling mounted zoom microscope with television monitoring, he extolled the three varieties of laser beam apparatus (the argon, the carbon dioxide and neodymium) all mounted together on one machine at a cost of $200,000. Then he showed the cavitron instrument, which is an ultrasonic aspirator for the removal of intracranial tumours. The audience was amazed to hear about these sophisticated instruments and so was I.

After his presentation, the professor offered to show a film on the instruments in use. After a few minutes, the movie projector started to malfunction and then it stopped. The professor was uncomfortable and impatient to continue the projection. After failing to restart the projector, the projectionist said:" Sir,we are sorry, but this is the only machine we have in this hospital and unfortunately we do not have a budget to purchase a new one". And that was it! We always have to ask ourselves: is neurosurgery a luxury? Is all modern technical development a luxury or a priority? Although such a situation is most likely to be found in developing countries, I cannot easily obtain all the equipment that I need in Canada and I hear that the determination of priorities of expenditure "occasionally" creates difficulties even in the U.K.

When I came to present my lecture in that same hospital, I was aware that the valuable technical developments are not those that are so complicated that only a few surgeons can perform the procedure, but are those that are simple so that they may be learned by every surgeon who wishes to do so. I have watched transsphenoidal pituitary surgery progress from being a procedure done only by a few, rather secretive specialists, into a technique that is widely and well practised in all developed countries.

Thanks to the Sims Commonwealth Professorship. I have had the chance to travel in developing countries. I have aimed to spread the knowledge of transsphenoidal pituitary surgery for the benefit of the people of those countries. This has given me a lot of pleasure and satisfaction. Moreover, I deeply appreciate the honor of holding this professorship.

Neurosurgery in India: a personal impression

C. G. Drake

Prakash Tandon has asked me to comment and reminisce about my association with Indian neurosurgery and its scientists.

I have been to India on two occasions, the first time with Ruth for more than a month in April-May 1979, as the Simms Travelling Professor for the Royal College of Surgeons in England. We visited Madras, Vellore, Trivandrum, Bombay and Delhi. It was a remarkable journey in which we were met with so many kindnesses and remarkable hospitality throughout.

On arriving in your country the culture shock must be over-whelming to everyone - the throngs, the traffic and its conveyances, the poverty, the illiteracy (except in Kerala) and the use of the labour force rather than machines. There were the beautiful ancient things - temples, rock sculptures, handicrafts ....

The spectrum of disease is also so very different: tuberculosis, leprosy, parasitic disease, even rabies. I saw much far advanced disease with huge tumors but few gliomas and there was the apparent rarity of vascular disease. Then there were the unique disorders - fluorosis, congenital atlantoaxial dislocation with block vertebrae, pachymeningitis. I saw the large wards everywhere, under staffed and over crowded and there were the long lists of very sick people awaiting treatment. Posterior fossa tumors often had to be shunted just so that they could survive to wait out their turn for craniotomy. The diagnostic facilities were limited but all of us were impressed with the ingenuity of Indian radiologists in their management of limited materials, often using their knowledge of mathematics and physics to do so.

And we saw the utter dedication of Indian families to their sick and injured.

Indian surgeons are not blessed with all the equipment that we see in North America which made even more impressive to me their surgical virtuosity in dealing with those huge and dangerous tumors. In the midst of the incredible burden of clinical material there was still time and effort for research in at least two of the institutions I visited - good fundamental investigation without the modern tools of science.

And then there was the thirst for knowledge that I saw. In several of the centres the young surgeons would not let me stop talking. I remember one where my voice began to give out after four hours although they had replenished my fluids with jug after jug of ice cold lime juice for the temperature was over 100 degrees F. Over the years, not a few of our many visiting surgeons have come from India to see what we are doing and we have heard their presentations to our neuroscience group, many of which have been quite remarkable.

My last visit to India was in December 1983, with a team from our unit to the All India Institute of Medical Sciences. It was a teaching session but again there was that thirst for hearing what was going on outside of your continent. Two highlights occurred during that week - a visit to Bharatpur where in one day I saw nearly 80 new bird species and three pythons! The other, of course was a meeting with Indira Gandhi for coffee, only a few months before the tragedy. She was so charming and so proud of what had been accomplished in her country.

Elilepsy in India — as I saw it 20 years ago

A. Earl Walker

Early in 1970, the Grass Foundation established the Lennox Visiting Professorship to enable an American physician to review the medical and social status of epilepsy in different parts of the world. I was offered this fellowship to visit a number of countries in Africa and Asia. One of the countries visited was India. K. V. Mathai of the Christian Medical College, Vellore, an outstanding medical center, arranged a suitable schedule for a tour of the Indian medical centers. He very kindly outlined a plan to enable me to visit some twenty centers and to give a lecture or two on the diagnosis and treatment of convulsions and to meet with professional and lay people interested in epilepsy. The itinerary was so arranged that I would be able to obtain an unbiased impression of the status and medical interest in epilepsy in all parts of India. Mathai explained that as the general public shunned epilepsy as stigmatized, in medical circles it had a low priority and was usually treated in crowded pediatric or medical clinics.

The observations which I made on this tour may illustrate the medical problems encountered in caring for patients with epilepsy in India twenty years ago.

1. Although the clinical aspects of epilepsy were thoroughly studied and documented by well trained medical personnel of the hospitals, the laboratory investigations and pharmacological therapies, except in major medical centers, were quite limited.

2. Specialized diagnostic facilities for the study of disturbed brain functions were available only in the medical colleges and some private clinics. In 1970, electroencephalographs, so valuable for the diagnosis of seizures, were used in half of the neurological centers visited. Even where such instruments were available and in working order, paper was limited so that the recording had to be curtailed. Radiological film was in equally short supply.

3. Anticonvulsive drugs, even diphenylhydantoin and phenobarbital, were scarce, and accordingly, the prescribed dosage was often suboptimal. The newer drugs - carbamazepine and valproic acid - were not generally

available. Patients, or, in the case of children, parents often did not understand the necessity of continuing the medications, so when the prescribed drug was exhausted and another attack occurred, they were discouraged and refused further medical aid.

4. Except for one or two centers, facilities for the determination of blood levels of drugs were not available. As a result, it was difficult to monitor anticonvulsant therapy.

5. Many people in the general population had misconceptions regarding epilepsy. One quarter considered it contagious and 70% shunned social contact with the epileptic subject. As a result, only half of the population was agreeable to having an epileptic child associate with their normal children in school. These prejudices and financial considerations often deprived the epileptic child of an education. In the employment market, prejudices against the epileptic person also existed. In Vellore, one half of the epileptic workers had trouble keeping a job - to some extent on account of the seizures.

There was limited community interest in the problems of the epileptic person. Lay organizations had been established in some centers e.g. by Drs. Anil Desai and E. P. Bharucha in Bombay and K. S. Mani in Bangalore, to enlighten the public but in many parts of the country no such groups existed. With the exception of a few centers, for example Vellore, literature on epilepsy for the laity, either in English or the native language, was not available.

Some interest in the study of epilepsy had been generated by the P-480 program in which six centers in India were participating. The first project to be funded was an epidemiological study of seizures which was carried out at Vellore under the direction of Mathai. This survey, completed in 1970, indicated an incidence of 15 per 1,000 population of which 6 per 1,000 were febrile seizures. The second project was a collaborative program to study the effect of socio-economic and dietary (vegetarian, meat-eaters etc.) factors on the incidence and treatment of epilepsy. Each of five centers, among the best equipped in India, while evaluating the above factors, had special interests (biochemical at Madras and Calcutta, surgical at Madras and New Delhi, environmental at Bangalore, cultural at Bombay and longterm effects at Calcutta).

The results of this Collaborative Study should be of special interest to developing countries for many medical decisions had to be made on clinical grounds alone. It seemed that approximately half of the patients had their attacks controlled adequately without the benefit of electroencephalograms, scans, determinations of drug levels in blood etc.

This summary of the medical status of the epileptic patient in India 20

years ago may serve as a basis for comparison of the current treatment.

Quite unrelated to epilepsy, I have vivid recollections of other experiences in India at that time - the bell which summoned the people of communities to hear the news, the Krishna dam under construction with its wooden scaffolding swarming with workers like monkeys in a tree, a large dinner at which the places were set with plates but no utensils so my hostess silently with a smile untied her bandanna handkerchief which served as a handbag and handed me a knife, fork and spoon (later, I was told that the food always tasted better if eaten with the fingers), a flat tire on a country road which my physician associates admitted they didn't know how to repair - they had always had a driver to do that - so I had to fix it, the floral garlands of the south, the invigorating climate of Bangalore, the delightful dinners at the homes of colleagues even if you had to step over sleeping servants in the halls as you left, and particularly the warm reception by people you had not met previously. These are memories which make India so intriguing and so inviting.

Neurological Society of India - a brief history

Sunil K. Pandya

Origin

The story of this society begins with the meeting of four individuals at the residence of Dr. S.T.Narasimhan in Madras at 6 p.m. on 8 December 1951: Dr. Jacob Chandy, neurosurgeon, Dr. Baldev Singh, neurologist,(both of the Christian Medical College and Hospital, Vellore); Dr. S T Narasimhan, physician and electrophysiologist and Dr. B Ramamurthi, neurosurgeon,(both of the Madras Medical College and Hospital).

Dr. Baldev Singh proposed Dr. B Ramamurthi as chairman. Dr. Chandy seconded the motion. At Dr. Ramamurthi's request, Dr. Chandy narrated the steps he had taken to form the Neurological Society of India. All four enrolled themselves as members. (We are fortunate to have with us at present three of the four founding members of the society.)

The first meeting of **The Neurological Society of India** (henceforth referred to as **society**) was held in Hyderabad in 1952. Sir Lakshmanaswami Mudaliar,(a leading gynaecologist and Vice-Chancellor of the University of Madras) and Major General Dr. S L Bhatia (of the Indian Medical Service) graced the occasion.

Dr. Chandy's presidential address was entitled 'Neurology comes to life. The precepts and concepts in neurology'. (**NEUROLOGY INDIA, 1953, 1, 6-10.**)

Growth and activities

In 1952, the secretary noted an enthusiastic response to the founding of the society from doctors all over the country. 32 members were on the society's rolls.

It was resolved that each full member must present a paper at the meeting of the society at least once in two years. Full members failing to attend three consecutive meetings without a reason acceptable to the executive committee would forfeit their membership. The continued membership of associate members would depend on the interest shown by them in the proceedings of the society. They were given all the privileges of full

members except the right to vote. Members were encouraged to hold local meetings of the society in different parts of the country.

By 1953, the society had 58 members: 13 full members and 45 associates. The secretary recorded clinical meetings in Madras and Vellore under the auspices of the society. In 1954, the society had Rs. 559-3-0 to its credit. In 1964 the reserve funds had risen to Rs.10,000. In 1981 it was recorded that the society's journal was now out of the red and had Rs.25000 in balance. In 1982, the society had 378 full members, 258 associate members. On 30 September 1988, the total membership was 905: 578 full members and 327 associate members. The total assets of the society stand at Rs. 755584.

In 1956 the society rejected a motion proposing that doctors not practising neurology full time but interested in neurology be permitted full membership. Instead, it resolved that 'medical colleagues attached to teaching institutions as neurologist, neurosurgeon or psychiatrist but not carrying on full time work in the subject be accepted as full members.' The society has rejected suggestions that it be subdivided into groups of neurologists, neurosurgeons and so on, preferring to preserve the interactions between the various disciplines within the neurosciences for mutual benefit.

Dr. Ginde's suggestion in 1956 that the presidency of the society should go, by rotation, to each of the neurological sub-specialities has been generally followed since.

In 1961 the society sent a strongly worded resolution to the Medical Council of India, advising against the introduction of regional languages for medical education. (On 27 May 1961, the Medical Council, in reply, confirmed that English would remain the medium of instruction for medical education throughout the country.)

The earlier annual conferences were held along with those of the Association of Physicians of India, the Cardiological Society of India, the Association of Pediatricians of India and the Indian Association of Chest Diseases. Since 1963 the society has held its meetings independent of the Association of Physicians of India and other organisations.

The society has formulated the specifications for neurosurgical instruments, operation tables and other neurological equipment for the Indian Standards Institution.

In 1968, the president, Dr. Anil Desai, raised the question of acquainting the lay public with information on neurology. It was decided to make a start with epilepsy. An organisation of patients and their families, other interested persons, paramedical and medical persons was proposed. This

body has taken roots and has grown into the fullfledged Indian Epilepsy Association. It now has chapters all over the country with patients and their relatives as active members.

Dr.Gajendra Sinh's suggestion, in 1963, that ways and means be found by the society to make possible visits by members to the various departments of neurology, neurosurgery, neuropathology etc. in the country to further their activities and foster development was unanimously welcomed. The society has, since, established travelling fellowships and scholarships that are made available to all those requesting them. It is a tribute to the efforts of the office bearers - in particular Drs. P N Tandon, A K Banerjee, M Sambasivan and V K Kak - that the funds available outstrip the demands made on them.

As the Society grew in strength it extended its activities and interacted with regional associations. Thus, the **17th annual conference** was held at All India Institute of Medical Sciences, New Delhi in 1967 along with the 8th annual conference of the Middle East Neurosurgical Society.

The **21st annual conference** was merged with the III Asian and Oceanian Congress of Neurology and the II Asian & Australasian Congress of Neurosurgery and held at the Taj Mahal Hotel, Bombay.

This year (1989), the Society plays host to the congresses of the World Federation of Neurosurgical Societies, World Federation of Neurology and the International Epilepsy Association in New Delhi.

In 1978, the secretary, Dr. A K Banerji and Dr. Jacob Abraham organised a conference of nurses involved in the care of patients suffering from neurological disorders. This was held along with the annual conference of the society. The **Association of Neurological Nurses** was founded as a subsection of the Neurological Society of India. The house cheered this development. The nurses conference is, since then, held as part of the annual conference of the society. The first **EEG technicians conference** was held as part of our annual conference in 1985. As with the nurses, this body also meets annually along with the society.

The society awards on alternate years the **Dr. Jacob Chandy Oration** and the **Dr. B. Ramamurthi Oration** to distinguished researchers in the neurological sciences, the orations being delivered at the annual conference of the society. Fittingly, **Dr. Ramamurthi delivered the first Chandy oration** in 1969 and reviewed the development of neurosciences in Madras, with particular reference to work done at the Institute of Neurology at the Madras Medical College and Hospital. The Dr. B. Ramamurthi oration was established in 1974. **Dr. Jacob Chandy was the first Ramamurthi orator.**

In 1975 Dr. Asoke Bagchi instituted the **Professor H. Krause medal** to be presented to the author of the best paper on neuro-oncology at the annual conference. In 1984 he set up a travelling fellowship in memory of the late Dr. Dwija Das Bagchi.

Members of the Society have received and continue to receive national and international recognition and awards. The list is too long to be included here. Mention must, however, be made of the honours bestowed by the President of India. In 1965 the society recorded with pride the award of Padma Bhushan to Dr. Jacob Chandy. Since then, this award has been conferred on three other members: Drs. Baldev Singh, B. Ramamurthi and P. N. Tandon.

Honorary members

The following have been elected honorary members of the society:

Dr. Jacob Chandy
Dr. B Ramamurthi
Dr. Baldev Singh
Dr. T K Ghosh.

Honorary corresponding members

The following have been elected honorary corresponding members of the society:

1953 : Drs. Wilder Penfield, Sir Geoffrey Jefferson and Hans Hoff.
1954 : Drs. Denny Brown and I. S. Wechsler.
1957 : Professor Sophia Ossipova, Docent V. Ossipova and Dr. Hoffman.
1959 : Dr. Ivan Lesny.
1978 : Drs. Charles Drake, Kristian Kristiansen, A. Earl Walker and Pierre Vinken.
1980 : Dr. Hans Werner Pia.
1984 : Drs. John A Simpson, John Walton, Theodore Rasmussen and Lindsay Symon.

Honorary associate members

The following have been elected honorary associate members:

1953 : Drs. K L Wig, R N Cooper and A V Baliga.
1956 : Major General Dr. S L Bhatia, Colonel Dr. Amir Chand, Drs. K A J Lalkaka, A S Erulkar, M B Mody, R V Sathe and W S Tirodkar.

Neurology India

The journal was launched in 1953 with an initial print order for 100 copies. Dr. Chandy offered to bear any extra expenditure involved and paid Rs. 201-13-0 towards the publication of the first issue. The quarterly journal was edited and published by the secretary, Dr. B. Ramamurthi. By 1955 the financial position of the journal was sound.

The next year, Dr. Ginde bemoaned the lack of a sufficient number of papers of high standard for the journal and suggested reducing the frequency of appearance of the journal. Patience was counselled by Dr. Jacob Chandy.

The wisdom behind that counsel is obvious from the fact that the journal is now published every two months. Details on some of the notable papers published in it are available in *Neurological Society of India - a calendar of events published* at the end of this volume.

Training in the neurological sciences

At Dr. N H Wadia's suggestion the training of neurologists and neurosurgeons in India was discussed by the society and the following resolutions passed at its annual conference in 1969:

1. The Neurological Society of India recommends an uniform standard of examination in the neurological sciences throughout the country.
2. The Medical Council of India is requested to withdraw its insistence that candidates desirous of appearing for postgraduate degrees in neurology and neurosurgery possess the M.D. in medicine and M. S. in surgery. The council is also asked to raise the period for training in neurology and neurosurgery from 2 to 3 years.

The subject has, since, featured at several meetings of the society. In April 1986, the National Institute of Mental Health and Neurological Sciences (NIMHANS), Bangalore hosted a symposium on it and produced unanimously approved guidelines standardising training and evaluation in the clinical neurosciences. This document, ratified by the society in the meeting held at the All India Institute of Medical Sciences, New Delhi on 11 December 1986, is now being implemented by various universities, the National Board of Examinations in the Medical Sciences and other statutory bodies. (See paper by A.K. Banerji in this volume.)

The plea made for careful consideration before creating additional centres for the training of neurologists and neurosurgeons, made by Dr. R G Ginde in 1970, remains valid. He had pointed out that it was important to ensure that funds were available for staff, equipment, maintenance and development before a new centre was set up. He had pointed out that several existing centres were woefully equipped and staffed and those in

charge faced insurmountable hurdles in rectifying the defects. Before thinking of new centres, it was necessary to ensure that all existing centres were provided their needs and brought to international standards. This remains undone.

Dr. Ginde's review, in that year, of the development of neurosurgery in India and its status then remains an important work of reference. We are happy to be able to publish it in this volume.

In 1972 the society sponsored publication of textbooks in neurosurgery and neurology to be edited by Drs. B. Ramamurthi and K. S. Mani respectively. The **Textbook of Neurosurgery** in two volumes, containing chapters by Indian authors and edited by Drs. B Ramamurthi and P N Tandon was published in 1980.

In 1974 the society decided upon a **Continuing Medical Education Programme** to be held along with the annual conference with the intention of providing updates on selected topics and encouraging interdisciplinary interaction among trainees in the various branches of the neurological sciences. Thanks to the organising skills of Dr. S Kalyanaraman and later those of Dr. K K Sinha this has been an eagerly awaited and well attended feature at subsequent conferences. The proceedings were initially cyclostyled. As the demand for them grew, they were published under the title of the programme. Since 1985 they are published as **Progress in Clinical Neurosciences.**

As a result of the efforts of Professor P. N. Tandon, the Department of Science and Technology, Government of India has agreed to support and fully finance five annual courses on the basic neurosciences. The first two courses held in 1987 and 1988 were organised by Professors P. N. Tandon, V. Bijlani and S. Wadhwa at the All India Institute of Medical Sciences, New Delhi. *Techniques in basic neurosciences* and *Lectures in neurobiology* have been byproducts of these courses. The next course on neurobiology will be held at NIMHANS.

M.Ch. Neurosurgery and D.M. Neurology

The first examination in the country for the M.Ch. in neurosurgery was held at the Madras University in 1961, Dr. K. V. Mathai of the Christian Medical College and Hospital being the successful candidate.

The first examination for the D.M. in neurology was held in 1969 - again by the University of Madras. Dr. G C Mithra of the Christian Medical College and Hospital, Vellore and Dr.K Srinivas of the Madras Medical College and General Hospital were awarded degrees at this examination.

These examinations are now held at several centres throughout the country.

The society has guided the National Board of Examinations in the Medical Sciences on the appointment of examiners for the speciality examination in neurosurgery. The president and secretary of the society, in consultation with selected senior members, make the nominations.

Epilogue

The Neurological Society of India has thus been a pace-setter in diverse activities beyond the ambit of most professional societies. It was the first Society in the country to institute travelling fellowships for its younger members; organise a regular Continuing Medical Education Programme and publish its proceedings, making them available to members at a nominal cost; lay down guidelines for various postgraduate courses after detailed discussions in the Society; assist various national bodies such as the Indian Standards Institute, National Board of Examinations, Medical Council of India and Indian Council of Medical Research in evolving ways to further the cause of neurosciences in the country. Inspite of its growing membership and the emergence of a number of sub-disciplines, the Neurological Society of India remains a strong, unified body representing all the disciplines in the neurosciences. It is the federal agency representing India at the international bodies for neurology, neurosurgery, neuropathology, epilepsy, EEG and clinical neurophysiology and so on.

Development of the Neurological Society of India

Sunil K. Pandya

Introduction

This account is based on the following documents:

a) The minute books of the Neurological Society of India
b) The souvenirs prepared by the organisers of the annual conferences of the society
c) The programme and abstract volumes distributed at the society's annual conference
d) Issues of **NEUROLOGY INDIA.**
e) **Continuing Medical Education Programme** volumes published since 1977. The volumes for 1982 and 1983 feature biographical essays on the presidents of the society 1951-1983.

Significant events during the year are described under the date on which the annual general meeting of the society was held for that year.

8 December 1951

Four individuals met at the residence of Dr. S.T.Narasimhan in Madras at 6 p.m. on this day:

Dr. Jacob Chandy, neurosurgeon, Christian Medical College and Hospital, Vellore.

Dr. Baldev Singh, neurologist, Christian Medical College and Hospital, Vellore.

Dr. S T Narasimhan, physician and electrophysiologist, Madras Medical College and Hospital.
Dr. B Ramamurthi, neurosurgeon, Madras Medical College and Hospital.

Dr. Baldev Singh proposed Dr. B Ramamurthi as chairman. Dr. Chandy seconded the motion. At Dr. Ramamurthi's request, Dr. Chandy narrated the steps he had taken to form the Neurological Society of India. All four enrolled themselves as members and adopted the following **constitution:**

1. The name of the society shall be **The Neurological Society of India.**
2 The aims and objects for which the society is set up are:
a To foster close association and cooperation among those devoting full time to neurology and its associated branches.
b. To maintain the highest ethical standards in the practice of this speciality.
c. To give adequate training to those who are properly qualified and intend to take up this speciality.
d. To promote and encourage original clinical and experimental research in this speciality.
3. There shall be **full members, associate members, corresponding members and honorary members.**
a. Those devoting all their time to the speciality are eligible for full **membership.**
b. Medical practitioners interested in the speciality can enrol as **associate members.**
c. Foreign specialists in neurology and its associated disciplines can be elected corresponding members.
d. Individuals of proven professional and scientific merit may be elected **honorary members.**

4. The annual fees for full members is Rs.20 and for associate members Rs. 10.

5. The officers of the society shall be: President, Vice-president, Secretary and Treasurer. These shall be elected annually by the executive committee.

6. There shall be at least one general meeting of the society each year.

7. The society shall be affiliated to the international neurological societies.

The following were elected office bearers:

President	: Dr. Jacob Chandy (Vellore)
Vice-president	: Dr. N N Das (Calcutta)
Secretary	: Dr. B Ramamurthi (Madras)
Treasurer	: Dr. S T Narasimhan (Madras).

It was decided to request Sir A Lakshmanaswami Mudaliar to inaugurate the first meeting of the society at Hyderabad in March 1952, with Major General Dr. S L Bhatia presiding. It was proposed to hold sessions featuring long (30 minutes) and short (10 minutes) papers.

Dr. Jacob Chandy, President, signed the minutes of this historic assembly on 2 March 1952. Annual general meeting:

3 March 1952

The first meeting of the The Neurological Society of India (henceforth referred to as society) was held in Hyderabad. Sir Lakshmanaswami Mudaliar and Major General Dr. S L Bhatia graced the occasion.

Present at the meeting were:

Dr. Jacob Chandy	– president
Dr. B. Ramamurthi	– secretary
Dr. S T Narasimhan	– treasurer
Dr. T K Ghosh (Calcutta)	
Dr. N S Vahia (Bombay)	
Dr. Baldev Singh (Vellore).	

Dr. Chandy's presidential address was entitlcd 'Neurology comes to life. The precepts and concepts in neurology'.(**NEUROLOGY INDIA 1, 6-10, 1953**)

The secretary noted an enthusiastic response to the founding of the society from doctors all over the country. 32 members were on the society's rolls.

It was decided that each full member must present a paper at the meeting of the society at least once in two years. Full members failing to attend three consecutive meetings, without a reason acceptable to the executive committee, would forfeit their membership.

The continued membership of associate members would depend on the interest shown by them in the proceedings of the society. They were given all the privileges of full members except the right to vote.

Members were encouraged to hold local meetings of the society in different parts of the country.

It was unanimously decided to publish an Indian journal-**NEUROLOGY** - with an initial print order for 100 copies. Dr. Chandy offered to bear any extra expenditure involved. The journal was edited and published by the secretary, Dr. B Ramamurthi.

Office bearers for 1952 - 1953:

President	: Dr. T K Ghosh
Vice-president	: Dr. N S Vahia.
Secretary	: Dr. B Ramamurthi
Treasurer	: Dr. S T Narasimhan.

2nd annual conference was held at the B J Medical College, Poona along with that of the Association of Physicians.

1 March 1953

The society now had 58 members: 13 full members and 45 associates.

Among the members elected were Drs. Lt. Col. Leo Krainer (Armed Forced Medical College, Poona); C G Subramaniam Iyer and Darab K Dastur (ICMR Neuropathology Unit, Tata Memorial Cancer Hospital, Bombay). Among those elected **honorary associate members** were Drs. K L Wig, R N Cooper, A V Baliga.

The following were elected as **honorary members:**
Professor Wilder Penfield
Professor Sir Geoffrey Jefferson
Professor Hans Hoff.

Dr. T. K. Ghosh's presidential address was entitled 'Creative neurology'. (**NEUROLOGY INDIA 2, 1-4, 1954**) The secretary recorded local clinical meetings held in Madras and Vellore under the auspices of the society.The secretary emphasised that the society was a purely scientific body. During discussion on the rules for membership it was decided that the spirit was to prevail over the letters of the rules.

It was decided that the president would deliver an address at the end of his term.

Among the papers presented were the following:

Electrical discharges of the epileptic brain. Dr. Baldev Singh.

Cysticercosis in India. Dr. Menino De Souza.
Association of acute anterior poliomyelitis and tuberculous meningitis. Dr. Leo Krainer.
Macroscopic demonstration of the fiber anatomy of the brain. Dr. Leo Krainer.
Cutaneous sensations with special reference to leprosy. Dr. Darab K Dastur.
Pituitary apoplexy. Dr. B Ramamurthi. (**NEUROLOGY INDIA, 1954, 1, 60-66**)
Stellate ganglion block in cerebral thrombosis. Dr. Siva Saran Misra.

As there was already a journal called NEUROLOGY in existence, it was decided to rename the society's journal **NEUROLOGY INDIA**. Its first editorial board consisted of:
Dr. B. Ramamurthi (Madras) - Editor
Dr. Jacob Chandy (Vellore)
Dr. Baldev Singh (Vellore)
Dr. E P Bharucha (Bombay)

Dr. C G Subramaniam Iyer (Bombay)
Dr. W Grillmayr (Colombo)
Dr. R B Davis (Ranchi)
Dr. N N Das (Calcutta)
Dr. L Krainer (Poona)
Dr. D K Dastur (Bombay).

3rd annual conference was held at the Tropical School of Medicine, Calcutta along with the meetings of the Association of Physicians of India, Association of Pediatricians of India and the Cardiological Society of India. Annual general meeting:

22 February 1954

Theme for conference seminar: epilepsy.

Among the members elected were Drs. Ram G Ginde and E P Bharucha.The following were elected as **honorary members:**

Dr. Denny Brown
Dr. I S Wechsler.
Dr. T K Ghosh's presidential address was entitled 'Neurological landscape'. (**NEUROLOGY INDIA 2, 25-28, 1954**)

At the seminar on epilepsy were discussed:
Fits in children. Dr. Baldev Singh.
Clinical aspects of epilepsy. Dr. T K Ghosh.
E E G in epilepsy. Dr. S T Narasimhan.Medical treatment of tics. Dr. R B Davis.
Surgery of epilepsy by ablation and hemispherectomy. Dr. Jacob Chandy. (**NEUROLOGY INDIA 2, 37-41,1954, 2, 37-41**) Social problems in epilepsy. Dr. B Ramamurthi.

The society had Rs. 559-3-0 to its credit. The members thanked Dr. Jacob Chandy for his donation of Rs. 201-13-0 towards the publication of the first issue of the journal NEUROLOGY.

Among the papers presented at the meeting were the following:

Tubercular granulomas. Dr. Ram G Ginde. (NEUROLOGY INDIA 2, 29-32, 1954) Dr. Ginde reported a patient where he had removed an extradural tuberculoma at D7 with good results.
Incidence of disseminated sclerosis. Dr. B Ramamurthi. Pathology of muscle in muscular dystrophy. Dr.C G S Iyer. Glioma of the hypophysis. Drs. R G Ginde, C G S Iyer. (**NEUROLOGY INDIA 2, 5-8, 1954**)
Cerebral angiography in intracranial lesions. Dr. B Ramamurthi.

Latent syphilitic diseases and their diagnosis. Dr. W Grillmayr. (**NEUROLOGY INDIA 2, 33-36, 1954**)

Dr. T K Ghosh suggested that the society take up the task of formulating teaching programmes in the neurosciences to be conducted by its members at the various universities.

Office bearers for 1954 - 1955:
President : Dr. Ram G Ginde.
Vice-president : Dr. N S Vahia.
Secretary : Dr. B Ramamurthi
Treasurer : Dr. S T Narasimhan.

4th annual conference held at the Nagpur Medical College along with the Association of Physicians of India.

6th February 1955

Theme for conference seminar: paraplegia.

Among the members elected were Drs. Anil D Desai, O V Jooma (Karachi) and K R Masani.
Dr. Ram G Ginde's presidential address was entitled 'Experiences in the management of intracranial tumours. Based on series of 68 consecutive verified cases from 1951 to the end of 1954.' (**NEUROLOGY INDIA 3, 1-9, 1955**)

The financial position of the journal was sound. The need for papers of a high standard was stressed. It was decided to publish four issues each year. Copies were being sent to Excerpta Medica and Index Medicus.

By a special resolution the secretary was empowered to employ a part time stenographer whose monthly remuneration was not to exceed Rs. 15 (fifteen).

Office bearers for 1955:
President : Dr. R G Ginde
Vice-president : Dr. W Grillmayr.
Secretary : Dr. B Ramamurthi
Treasurer : Dr. S T Narasimhan.

5th annual conference of the society was held at the Majestic Hotel, Bombay.

21 January 1956

Theme for conference seminar: cerebral vascular disease.

Among the members elected were Drs. Menino D'Souza and V. N. Bagadia.

The following were elected honorary associate members:
Major General Dr. S L Bhatia
Colonel Dr. Amir Chand
Dr. K A J Lalkaka
Dr. A S Erulkar
Dr. M B Mody
Dr. R V Sathe
Dr. W S Tirodkar.

Dr. Ram G Ginde's presidential address was entitled 'Treatment of trigeminal neuralgia- a historical review.' (**NEUROLOGY INDIA 4, 5-10, 1956**)

The following were among the papers presented:

Physiology of cerebral circulation. Dr. Baldev Singh.Intracranial aneurysms and vascular malformations. Drs. R G Ginde, Jacob Chandy, B Ramamurthi.

The society rejected a motion proposing that doctors not practising neurology full time but interested in neurology be permitted full membership. Instead, it resolved that 'medical colleagues attached to teaching institutions as neurologist, neurosurgeon or psychiatrist but not carrying on full time work in the subject be accepted as full members.'

Dr. Ginde bemoaned the lack of a sufficient number of papers of high standard for the journal and suggested reducing the frequency of appearance of the journal. Patience was counselled by Dr. Jacob Chandy.

Dr. Ginde's suggestion that the presidency of the society should go, by rotation, to each of the neurological sub-specialities was unanimously accepted.

The emblem of the society prepared by Dr. W. Grillmayr was unanimously approved.

Office bearers for 1956-57:
President : Dr. W Grillmayr
Secretary : Dr. Anil D Desai
Treasurer : Dr. C G S Iyer
Editor : Dr. B Ramamurthi.

6th annual conference of the society was held at **S N Medical College, Agra.**

12 February 1957

Amid those present at this meeting was Dr. Wilder Penfield.

Among the members elected were Drs. N H Wadia, Gajendra Sinh, R N Chatterji, R N Roy, Asoke Bagchi, Balaparmeshwar Rao and R S Dharker.

The following were elected honorary members:
Professor Sophia Ossipova
Docent V Ossipova
Dr.Hoffman.

Dr. W Grillmayr's presidential address was entitled 'In the service of mankind.'

Office bearers for 1957-58:

President	: Dr. Menino D'Souza
Vice-president	: Dr. B Ramamurthi
Secretary	: Dr. Anil D Desai
Treasurer	: Dr. E P Bharucha
Editor	: Dr. B Ramamurthi.

7th annual conference of the society was held at the Medical College and Hospital, Trivandrum.

Annual general meeting:

19 January 1958

Among those present at this meeting were Dr.Douglas Miller and his registrar, Dr. Bleasel.

Among the members elected were Drs. B. Dayananda Rao, Arjun Das and J. N. Sidhva.

Dr. T. Menino D'Souza's presidential address was entitled 'The human mind'. (**NEUROLOGY INDIA 6, 1-3, 1958**)

In keeping with international practice, it was decided to have subsections of neurology, neurosurgery, neuropathology and neuroradiology in the society.

The editorial board of **NEUROLOGY INDIA** was reconstituted thus:

Dr. Ram G Ginde	: Editor.
Dr. Baldev Singh	: EEG and Neurophysiology.
Dr. T K Ghosh	: Neurology.
Dr. C G SIyer	: Neuropathology.
Dr. K M Pillai	: Neuroradiology.

Office Bearers for 1958:

President	: Dr. B Ramamurthi.
Vice President & Treasurer	: Dr. E P Bharucha.
Secretary	: Dr. Anil D Desai.
Editor	: Dr. Ram G Ginde.

8th annual conference was held at Jaipur. Annual general meeting:

19 January 1959

Among the members elected were Drs. Homi M Dastur and R M Varma.

Dr. B Ramamurthi's presidential address was entitled 'The need for a brain research unit' and 'Pituitary tumours'. (**NEUROLOGY INDIA 7, 1-12, 1959**)

Office bearers for 1959:-

President & Treasurer	: Dr. E P Bharucha.
Vice-president	: Dr. R N Chatterjee.
Secretary	: Dr. Anil D Desai
Editor	: Dr. R G Ginde.

9th Annual Conference was held at the University of Delhi Campus, New Delhi along with the Association of Physicians of India, The Cardiological Society of India, the Association of Pediatricians of India and the Indian Association of Chest Diseases. The annual general meeting of the society was held at the All India Institute of Medical Sciences, New Delhi.

Annual general meeting:

27 January 1960

The death of Dr. S T Narasimhan, founder member and past treasurer, from coronary thrombosis, was recorded with grief.

Among the members elected were Drs. K V Mathai, Jacob Abraham, V Balasubramaniam, S Janaki, M G Sarin, V G Daftary and D S Dadhich.

Dr. Ivan Lesny was elected **corresponding member.**

Dr. E P Bharucha's presidential address was entitled 'The brain, the mind and behaviour'. (**NEUROLOGY INDIA 8, 19-21, 1960**)

A resolution was passed agreeing to the formation of the Indian Academy of Medical Sciences with the objective of encouraging research and advanced studies in medical sciences. The academy would confer membership and fellowship as an honour in recognition of work done

irrespective of postgraduate degrees possessed by the person being honoured.

The society did not recommend the formation of a central examining body. Instead, it suggested increasing postgraduate facilities and stipends to students. Drs. B. Ramamurthi and Baldev Singh were elected to represent the society at the meeting for the formation of the academy.

It was decided to form a Central Registry of Neuropathology. Material was to be obtained from all the neuroscience centres in the country. Dr. C G S Iyer was requested to start the registry.

It was decided that members and associate members who have not paid their dues were to be sent one final notice and if they remained defaulters, were to be struck off the rolls of the society.

Drs. B Ramamurthi and R G Ginde represented the society at the meeting of the World Federation of Neurosurgical Societies, Dr. Ramamurthi also representing the Middle East Neurosurgical Societies.

Office bearers for 1960-61:

President	: Dr. R N Chatterjee
Vice-president	: Dr. C G S Iyer
Secretary	: Dr. Anil Desai
Treasurer	: Dr. E P Bharucha
Editor	: Dr. R G Ginde.

10th annual conference was held at Madras Medical College and Government General Hospital, Madras.

14 January 1961

Dr. M Natarajan was elected member.

Dr. R N Chatterjee's presidential address dealt with the role of neurologists in India and the need for interaction between them and those in the basic sciences. (**NEUROLOGY INDIA 1961, 9, 58-60**)

The issue of **NEUROLOGY INDIA** dated July-September 1960 (vol. 8, pages 43-80) is unusual in that it contains just one paper: Dr. B Ramamurthi's exhaustive review of his experiences with tumours of the pituitary region. The subsequent issue is also of special interest for in it we find Dr. N H Wadia's report on six cases with 'Chronic progressive myelopathy complicating atlanto-axial dislocation due to congenital abnormality' (**NEUROLOGY INDIA 8, 81-94**)

The society sent a strongly worded resolution to the Medical Council of India, advising against the introduction of regional languages for medical

education. (On 27 May 1961, The Medical Council, in reply, confirmed that the medium of instruction for medical education would remain English throughout the country.)

Office bearers for 1961:

President:	: Dr. C G S Iyer.
Vice-president	: Dr. Baldev Singh.
Secretary	: Dr. Anil D Desai.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. R G Ginde.

11th annual conference was held at Indore along with those of the Association of Physicians of India, the Cardiological Society of India, Association of Pediatricians of India, Association of Chest Physicians of India and Association of Gastro-intestinologists (as they called themselves then).

20 January 1962

Among the members elected were Drs. Prakash N Tandon and Vijay S Dave.

Dr. C G S Iyer's presidential address was entitled 'Lathyrism'.

The constitution of the society was finalised.

Notable among the papers published in the journal during 1961 are that on encephalopathies in pregnancy and the puerperium by Drs. Baldev Singh et al (**NEUROLOGY INDIA, 1961, 9, 1-11**), those on chordomas by Drs. R G Ginde and H M Dastur (**NEUROLOGY INDIA 1961, 9, 61-82, 83-90**), that on spinal arachnoiditis and arachnoid cysts by Dr. S A Cabral (**NEUROLOGY INDIA 1961, 9, 91-96**), that on intramedullary tuberculoma of the spinal cord by Drs. M G Sarin and Jacob Chandy (**NEUROLOGY INDIA 1961, 9, 103-105**) and that on cryptococcal infection of the brain by Dr. S Sriramachari et al (**NEUROLOGY INDIA 1961, 9, 119-127**).

The secretary was asked to approach all organisations that could help in the early release of Dr. N H Wadia from Portugal.

Dr. K. S. Mani reported on the centenary celebrations of the National Hospital for Nervous Diseases, Queen Square, London in **NEUROLOGY INDIA 1961, 9, 40-42.**

The society recorded the demise of Sir Geoffrey Jefferson on 29 January 1961 at the age of 74.

The first examination in the country for the M.Ch. in neurosurgery held at the Madras University, Dr. K V Mathai of the Christian Medical College and Hospital being the successful candidate. (**The first examination for the D.M. in neurology** was held in 1969 - again by the University of Madras. Dr. G C Mithra of the Christian Medical College and Hospital, Vellore and Dr. K Srinivas of the Madras Medical College and General Hospital were awarded degrees at this examination. For lists of candidates obtaining higher speciality degrees in neurology and neurosurgery see the **Continuing Medical Education Programme** volumes starting from 1981. Part 1 of the volume for 1981 lists candidates from 1961- 1981 on pages 134, 157, 191, 192, 193, 211, 227, 228, and 300. By 1982, 144 had obtained the M.Ch. in neurosurgery and 101 the D. M. in neurology from the various universities offering this degree.)

Office bearers for 1962:

President	: Dr. Baldev Singh.
Vice-president	: Dr. N H Wadia.
Secretary	: Dr. Anil D Desai.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. R G Ginde.

12th annual conference was held at Calcutta.

19 January 1963

Among the members elected were Drs. D R Gulati, B S Singhal, P M Dalal, B J Damany and S N Bhagwati.

Drs. S Kalyanaraman, G N Taori and A K Banerjee were elected associate members.

Dr. Baldev Singh delivered the presidential address on electrical activity in the brain. (**NEUROLOGY INDIA 1963, 11, 39-40**)

Dr.Gajendra Sinh suggested that ways and means be found by the society to make possible visits by senior members to the various departments of neurology, neurosurgery, neuropathology etc. in the country to further their activities and foster development. This was unanimously welcomed.

Notable among the papers published in the journal during 1962 are that on cerebrovascular diseases in India by Drs. E P Bharucha and R S Umerji (**NEUROLOGY INDIA 1962, 10, 137-141**), that on surgical treatment of cervical spondylosis by Dr. Ram G Ginde (**NEUROLOGY INDIA 1962, 10, 13-23**) and that on experiences with auditory neurofibroma by Drs. V Balasubramaniam and B Ramamurthi (**NEUROLOGY INDIA 1962, 10, 29-36**).

It was decided that the society hold its meetings independent of the Association of Physicians of India.

Office bearers for 1963:

President	: Dr. N H Wadia.
Vice-president	: Dr. B K Anand.
Secretary	: Dr. Anil D Desai.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. R G Ginde.

13th annual conference was held at Patiala.

19 January 1964

A midterm symposium on seizures was held at the Postgraduate Institute of Medical Education and Research, Chandigarh in August 1963. (See report in **NEUROLOGY INDIA 1963, 11, 140-149.**)

Themes for conference seminar: dementia (**NEUROLOGY INDIA 1964, 12, 73-120**) and peripheral neuropathy (**NEUROLOGY INDIA 1964, 12, 123-131**).

Professor G Schaltenbrand participated in the symposium on peripheral neuropathy.

Dr. N H Wadia's presidential address was entitled 'The toxic effects of heavy metals on the nervous system.' (**NEUROLOGY INDIA 1964, 12, 29-40**)

It was decided to send an invitation to hold the **3rd Asian and Oceanian Congress of Neurology** in Bombay in 1971.

Drs. Denis Williams and W Walshe visited India.

The society had in its reserve funds Rs.10,000/-.It was decided to build this up further. Membership fees were raised by Rs.5/-.

The executive committee prevailed upon Dr. R G Ginde to continue as Editor.

Notable among the papers published in the journal during 1963 are that by Dr.B Ramamurthi asking whether carotid artery occlusion required surgery (**NEUROLOGY INDIA 1963, 11, 1-3**), report on a study of 37 cases of pulmonary encephalopathy by Dr. Vimla Virmani (**NEUROLOGY INDIA 1963, 11, 4-13**), a report on Wilson's disease in four Indian families by Drs. N H Wadia and Darab K Dastur (**NEUROLOGY INDIA 1963, 11, 41-58**), that on the radiology of spinal arachnoiditis by Dr. J N Sidhva

(**NEUROLOGY INDIA 1963, 11, 59-62**) and that on neurological complications occurring during pregnancy and puerperium by Drs. S Janaki and Lily Thomas (**NEUROLOGY INDIA 1963, 11, 128-135**).

It was decided that members defaulting in payment of their membership fees for 2 years be struck off the rolls without further notice.

Office bearers for 1964:

President	: Dr. B K Anand
Vice-president	: Dr. N S Vahia
Secretary	: Dr. Anil D Desai
Treasurer	: Dr. E P Bharucha
Editor	: Dr. R G Ginde.

14th annual conference was held at the Birla Matushree Sabhagraha, Bombay.

9 January 1965:

Themes for conference seminars: subarachnoid haemorrhage (NEUROLOGY INDIA 1965, 13, 40-61), coma (**NEUROLOGY INDIA 1965, 13, 141-175**)

The society recorded with pride the award of Padma Bhushan to Dr. Jacob Chandy.

Among the members elected were Drs. S Kalyanaraman, S Jagannathan, K K Sinha, A G Krishna, J C Jacob, R D Variava, Freny M Kohiyar, A D Sehgal, T S Kanaka, A C Jain, Goodwin Newton, S S Jolly, P R Thakore, K C Mukherji and P Narendran.

Dr. B K Anand's presidential address was entitled 'Neurophysiological aids to neurology'. (**NEUROLOGY INDIA 1965, 13, 1-6**)

Dr. R G Ginde's resignation from the post of editor was accepted with regret.

Notable among the papers published in the journal during 1964 are that on cerebellar syndromes by Drs. S Janaki and J Chandy (**NEUROLOGY INDIA 1964, 12, 1-6**), that on toxic effects of heavy metals on the nervous system by Dr. N H Wadia (**NEUROLOGY INDIA 1964, 12, 29-41**) and that on percutaneous chemothalamectomy for Parkinsonism by Dr. R M Verma (**NEUROLOGY INDIA 1964, 12, 54-60**).

Drs. E P Bharucha and N H Wadia represented the neurologists and Drs. Jacob Chandy and B Ramamurthi the neurosurgeons at the symposium

on postgraduate medical education organised by the Medical Council of India.

Office bearers for 1965:

President	: Dr. N S Vahia
Vice-president	: Dr. D K Dastur.
Secretary	: Dr. Gajendra Sinh.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. Anil D Desai.

15th annual conference was held at Christian Medical College and Hospital, Vellore.

20 December 1965:

Themes for conference seminars: stereotaxic surgery and neuromuscular disorders (**NEUROLOGY INDIA 1966, 14, 167-196**).

Among the members elected were Drs. Ilona Bubelis, K V Chalapathi Rao, Sanathan Rath, Joy David, Aneel N Patel, D H Deshpande, and U S Vengsarkar. Among those elected associate members were Drs. M Sambasivan, K Vasudeva Devadiga, Ramesh Chandra and K Srinivasan.

Dr. N S Vahia's presidential address was entitled 'Therapeutic values of some neurophysiological concepts. Impressions of a pilot study.' (**NEUROLOGY INDIA 1966, 14, 68-74**)

Notable among the papers published in the journal during 1965 are that on intracranial tumours of infancy and childhood by Dr. Asoke Bagchi (**NEUROLOGY INDIA 1965, 13, 7-12**),that on incidence of cerebral vascular lesions at the Nair Hospital, Bombay by Dr. P M Dalal (**NEUROLOGY INDIA 1965, 13, 37-39**) and that on stereotaxic surgery by Drs. V Balasubramaniam and B Ramamurthi (**NEUROLOGY INDIA 1965, 13, 93-96**).

It was decided that papers read at the annual conference of the society should be submitted to the editor, NEUROLOGY INDIA. The editor was authorised to reject those deemed unsatisfactory for publication by the editorial board. Under exceptional circumstances, the author/s could be permitted to submit the paper read at the conference elsewhere for publication.

Dr. Vimla Virmani's request for the creation of a Delhi branch of the society was considered. It was felt that all meetings should be held only under the aegis of the undivided society.

Office bearers for 1966:
President : Dr. D K Dastur.

Vice-president	: Dr. Anil D Desai.
Secretary	: Dr. Gajendra Sinh.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. Anil D Desai.

16th annual conference was held at All India Institute of Mental Health, Bangalore.

19 December 1966

Themes for conference seminars: epilepsy and increased intracranial tension.

Among the members elected were Drs. Sneha Bhargava, M Sambasivan, G N N Reddy, T Desiraju, A K Banerji, Veera Raghava Reddy, K S Srinivas, V Srinivasan, H S Subrahmanyam, B S Sridhara Rama Rao, Lt. Col. Mahendra Singh and Virendra Mohan.

Dr. Darab K Dastur's presidential address was entitled 'The broad field of neuropathology. A. 1000 brain tumours. B. The encephalitides. C. Wilson's disease in India.' (**NEUROLOGY INDIA 1967, 15, 51-69**)

Notable among the papers published in the journal during 1966 are those on cerebral chromoblastomycosis by Drs. H M Dastur et al and Sharat C Desai et al (**NEUROLOGY INDIA 1966, 14, 1-18**), that on south Indian paraplegia by Dr. K S Mani et al (**NEUROLOGY INDIA 1966, 14, 19-25**), that on lumbar subarachnoid puncture in dogs and pantopaque arachnoiditis by Drs. A D Sehgal et al (**NEUROLOGY INDIA 1966, 14, 89-94**), that on venous and arterial thrombosis in 30 young Indian women by Dr. S N Pathak et al (**NEUROLOGY INDIA 1966, 14, 102-106**), that on spino-cerebellar degeneration in Punjab by Drs. S S Jolly et al (**NEUROLOGY INDIA 1966, 14, 120-124**), that on simultaneous bilateral stereotaxic lesions by Drs. S Kalyanaraman and B Ramamurthi (**NEUROLOGY INDIA 1966, 14, 151-153**) and that on meningo-encephalocele by Dr.P N Tandon (**NEUROLOGY INDIA 1966, 14, 161-164**).

A panel of experts was drawn up to help younger members solve academic problems.

The annual membership fee was raised from Rs. 35 to Rs.45.

By unanimous approval membership was now open only to those with medical postgraduate degrees or diplomas (such as MD, DM, MS, MCh, MRCP, FRCS Ph.D. or their equivalent) and who have been trained for a minimum of 2 years in a subspeciality of the neurosciences at a recognised institute.

Office bearers for 1967:

President	: Dr. Anil D Desai.
Vicepresident	: Dr. B Dayananda Rao.
Secretary	: Dr. Gajendra Sinh.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. Anil D Desai.

17th annual conference was held at All India Institute of Medical Sciences, New Delhi along with the 8th annual conference of the Middle East Neurosurgical Society. The souvenir issued on the occasion contains essays by Drs. Baldev Singh and Ajit Banerjee describing briefly the development of the neurosciences in India. Dr. Banerjee referred to the general surgeons who carried out neurosurgical operations. Prominent among them were Drs. Ardeshir P. Bacha of Bombay (who operated for a suspected brain tumour in 1927), Drs. Rustom N Cooper and A V Baliga (Bombay), Lt. Col. F J Anderson and Provat Sanyal (Calcutta), N S Narasimha Iyer, C P V Menon and U Rama Rao (Madras). In 1948 Drs. Cooper and Baliga had presented their experiences on 59 cases with proven brain tumours to the Association of Surgeons of India. The souvenir also describes, in brief, the development of neurosciences in Delhi at the All India Institute of Medical Sciences, Safdarjung Hospital, Tirathram Shah Nursing Home and Charitable Hospital (where Drs. Baldev Singh and Col. V R Mirajkar were the pioneers), Willingdon Hospital and Lady Hardinge Medical College.

18 December 1967

Theme for conference seminar: infections of the nervous system.

Among those from abroad were Drs. Murray Falconer, Fuad Haddad, Bui Quoo Huung, Y Yase, Ayub Omayya, Richard Johnson, El Banhawy Ahmed, H Narabayashi and Yoshyuki Shinjo.

Dr. Anil D Desai's presidential address was entitled 'Psychomotor epilepsy'. **(NEUROLOGY INDIA 1968, 16, 1-8)**

The panel of experts appointed the previous year did not have a single query or request for help sent to it. The society therefore decided to make this panel concern itself with research and help in identifying and setting up projects relevant to India.

The president, Dr. Anil Desai, raised the question of acquainting the lay public with information on neurology. It was decided to make a start with epilepsy. An organisation of patients and their families, other interested persons, paramedical and medical persons was proposed.

At Dr. N H Wadia's instance, the society resolved to approach the

government of India to obtain permission to import vital drugs, instruments and equipment without the delay caused by present cumbersome licensing procedures. Dr. Dayananda Rao informed the house of his discussions with the Director General of Health Services and proposed following them up in his capacity as President of the society.

The journal, NEUROLOGY INDIA, was not being published on time. This was principally due to delay by authors in returning galley proofs to the editor. The journal was also running short of papers of a high standard.

Office bearers for 1968:

President	: Dr. Dayananda Rao.
Vicepresident	: Dr. Sriramachari.
Secretary	: Dr. Gajendra Sinh.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. Anil D Desai.

18th annual conference was held at the S.S.K.M. Medical College, Calcutta.

17 December 1968

Theme for conference seminar: hydrocephalus.

Among the members elected were Drs. T S Kanaka, Ramesh Chandra, Vasudeva Devadiga, Vijay Kak, G M Taori and Sunil K Pandya.

Dr. B Dayananda Rao's presidential address was entitled 'Skeletal defects in the floor of the anterior cranial fossa. (A rationale for their surgical management.)' (**NEUROLOGY INDIA 1969, 17, 1-10**)

In order to help in the publication of the journal, annual membership fees were raised by Rs. 5 per annum, this sum being passed on to the editor.

Notable among the papers published in the journal during 1968 are that on some unique neurological diseases in the Pacific region by Dr. Yoshiro Yase (**NEUROLOGY INDIA 1968, 16, 9-13**), that on the birth of the subclavian steal syndrome by Dr. Aneel N Patel (**NEUROLOGY INDIA 1968, 16, 14-16**), that on the measurement of arterial trunks on cerebral angiograms by Drs. Gourie-Devi et al (**NEUROLOGY INDIA 1968, 16, 27-34**), those of followup studies and retrospective analyses of a large number of patients with epilepsy by Drs. V Balan, P Gopalakrishnan et al (**NEUROLOGY INDIA 1968, 16, 57-65**), those on cryptococcal infection of the brain by Drs. K V Devadiga et al and P V Ramana Rao et al (**NEUROLOGY INDIA 1968, 16, 117-124**) and that on the effect of manitol on EEG rhythms in increased intracranial tension by Drs. B B Sawhney and Baldev Singh (**NEUROLOGY INDIA 1968, 16, 151-154**).

Dr. B. Ramamurthi found the selection of papers for the annual conference unsatisfactory and suggested that a committee should screen those offered for presentation. He also found the time for discussion limited and suggested it be increased. Dr. Baldev Singh requested publication, in NEUROLOGY INDIA, of the summaries of the papers accepted for presentation at the annual conference.

Dr. Kalyanaraman suggested that a lecture of popular interest, aimed at lay persons, be delivered at each annual conference by a senior member of the society.

The first examination for the D.M. in neurology was held in 1969 by the University of Madras. Dr. G C Mithra of the Christian Medical College and Hospital, Vellore and Dr. K Srinivas of the Madras Medical College and General Hospital were awarded degrees at this examination.

Office bearers for 1969:

President	: Dr. Sriramachari.
Vicepresident	: Dr. Asoke Bagchi.
Secretary	: Dr. Gajendra Sinh.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. Anil D Desai.

19th annual conference was held at Osmania Medical College, Hyderabad.

17 December 1969

Theme for conference seminar: neuromuscular disorders.

Dr. S Sriramachari's presidential address was entitled 'My experiences as a neuropathologist'.

Dr. B Ramamurthi proposed a workshop on microneurosurgery. This was warmly welcomed and he was asked to proceed further.

Dr. Baldev Singh was elected president for the III Asian and Oceanian Congress of Neurology to be held in Bombay in 1971. Dr. E P Bharucha was elected vice-president.

Dr. Sriramachari requested interesting neuropathological material for the Registry of Pathology set up by him in Delhi. Members promised cooperation.

At Dr. N H Wadia's suggestion the training of neurologists and neurosurgeons in India was discussed by the house and the following resolutions passed:

1. The Neurological Society of India recommends an uniform standard of examination in the neurological sciences throughout the country.
2. The Medical Council of India is requested to withdraw its insistence that candidates desirous of appearing for postgraduate degrees in neurology and neurosurgery possess the M.D. in medicine and M. S. in surgery. The council is also asked to raise the period for training in neurology and neurosurgery from 2 to 3 years.

As the roll of members of the society was increasing, at Dr. S Kalyanaraman's suggestion, the number of members on the executive committee was raised from 3 to 6.

The **Dr. Jacob Chandy oration** was established. Drs. Baldev Singh, B Ramamurthi, K V Mathai and Jacob Abraham were asked to formulate rules. It was to be delivered every alternate year, the orator being given Rs.1000 and a commemorative medal. Dr. B Ramamurthi was chosen as first Chandy orator.

Notable among the papers published in the journal during 1969 are three essays on Harvey Cushing including Dr. H M Zimmerman's autopsy report on Cushing published for the first time ever (**NEUROLOGY INDIA 1969, 17, 151-178**), those on skeletal defects in the floor of the anterior cranial fossa by Dr. B. Dayananda Rao (**NEUROLOGY INDIA 1969, 17, 1-10**), neurology in Bombay in the 1840s by S K Pandya (**NEUROLOGY INDIA 1969, 17, 40-44**), epilepsy in ayurveda by Drs. B Ramamurthi and S K Gurunathan (**NEUROLOGY INDIA 1969, 17, 91-93**), stereotaxic surgery for intractable pain by Drs. B Ramamurthi and S Kalyanaraman (**NEUROLOGY INDIA 1969, 17, 109-115**), syndromes of callosal infarction by Dr. Aneel N Patel (**NEUROLOGY INDIA 1969, 17, 191-196**) and sarcomas of the brain by Drs. S Sriramachari and Sarala Das (**NEUROLOGY INDIA 1969, 17, 207-214**).

Office bearers for 1970:

President	: Dr. Asoke Bagchi.
Vicepresident	: Dr. K S Mani.
Secretary	: Dr. Gajendra Sinh.
Treasurer	: Dr. E P Bharucha.
Editor	: Dr. Anil D Desai.

20th annual conference was held at Madras Medical College and Hospital, Madras. On this occasion Dr. Ramamurthi released a bibliography of the publications emanating from his department and institute over the 20 years 1950-1970.

16 December 1970

Theme for conference seminar: sellar and parasellar tumours.

Among the members elected were Drs. P F Irani, Chicot J Vas, C Velumurugendran, Lt. Col. M L Suri, and K Kalyanaraman.

Among those from abroad were Drs.Roger Banister, Lauri Laitinen, Dr. B Guidetti, Dr. Gustilo and Dr. Loew. Dr. Asoke K. Bagchi's presidential address was entitled 'Some observations on hypophyseal adenomas.' (**NEUROLOGY INDIA 1971, 19, 1-3**)

Dr. R G Ginde pleaded for careful consideration before creating additional centres for the training of neurologists and neurosurgeons. He pointed out that it was important to ensure that funds were available for staff, equipment, maintenance and development before a new centre was set up. Several existing centres were woefully equipped and staffed and those in charge faced insurmountable hurdles in rectifying the defects. Before thinking of new centres, it was necessary to ensure that all existing centres were provided their needs and brought to international standards.Dr. Ginde's review of the development of neurosurgery in India and its current status remains an important work of reference.

In order to help in the publication of the journal, it was decided to raised the annual membership fees to Rs. 65, Rs. 20 of which were to be sent to the editor.

Dr. Ramamurthi delivered the first Chandy oration and reviewed the development of neurosciences in Madras, with particular reference to work done at the Institute of Neurology at the Madras Medical College and Hospital.

Notable among the papers published in the journal during 1970 are those on spontaneous EEG discharges in unconscious and deafferentated cats by Drs. G S Chinna et al (**NEUROLOGY INDIA 1970, 18, 1-7**), classic descriptions of neurological disorders by Dr. Charles Morehead (**NEUROLOGY INDIA 1970, 18, 50-65**), experimental tuberculosis of the central nervous system by Drs. P N Tandon et al (**NEUROLOGY INDIA 1970, 18, 81-85**), the brain and meninges in tuberculous meningitis by Dr. D K Dastur et al (**NEUROLOGY INDIA 1970, 18, 86-100**), slow virus infections of the central nervous system by Drs. Gourie-Devi and P N Tandon (**NEUROLOGY INDIA 1970, 18, 129-135**), John Hilton's contributions on atlantoaxial disease (**NEUROLOGY INDIA 1970, 18, 147-157**), surgical treatment of temporal lobe seizures by Drs. K V Mathai and Jacob Chandy (**NEUROLOGY INDIA 1970, 18, 158-164**), cysticercosis of the brain by Drs. Dinakar et al and by Drs. M Natarajan et al (**NEUROLOGY INDIA 1970, 18, 165 - 175**) and pattern of nutritional deficiency disorders of the nervous system in Bombay by Drs. N H Wadia and R Kumarswami (**NEUROLOGY INDIA 1970, 18, 203-219**). Supplement 1 to volume 18 of the journal contained papers on head injuries and stereotaxic surgery emanating from the Institute of Neurology, Madras

on the occasion of its formal inauguration.

Office bearers for 1971:

President	: Dr. Baldev Singh
Vicepresident	: Dr. K S Mani
Secretary	: Dr. Gajendra Sinh
Treasurer	: Dr. E P Bharucha
Editor	: Dr. Anil D Desai.

A mid-term **First All-India Workshop-Conference On Stroke** was held at the Christian Medical College and Hospital, Vellore on 22-23 November 1971. The Indian Council of Medical Research (ICMR) and Social and Rehabilitation Services, U.S. Department of Health, Education and Welfare were co-sponsors. Papers were grouped under 7 heads: vocational rehabilitation, epidemiology, strokes in the young, pathology and management, physiotherapy and occupational therapy, surgical rehabilitation and electrodiagnosis. (The proceedings of the conference have been published by the Christian Medical College and Hospital, Vellore.)

21st annual conference was merged with the III Asian and Oceanian Congress of Neurology and held at the Taj Mahal Hotel, Bombay.

29 December 1971

Among the members elected were Drs. Subimal Roy, G K Ahuja, S S Seshia, and M D Manikal.

Among those from abroad were Drs. Macdonald Critchley, E Graeme Robertson, John Stirling Meyer, R E Ross Russell, John Walton, D Calne, B Johansson, N Matsumoto, K Sano, M Pollock, A Vejjajiva, Y Fukuyama, G Selby, B A Kakulas, A E H Emery, A Kertesz, R W Hornabrook J G McLeod, H Chianondh, Y Yase, J P Simcock, S Okinaka, H Shiraki, I Sobue, S M Lumbantobing and C S Park.

Dr.Baldev Singh's presidential address was entitled 'Some fantasies and facts in ecological neurology.' (**NEUROLOGY INDIA 1972, 20, proc. suppl. 1, 1-7**)

The proceedings of the III Asian and Oceanian Congress were published as supplements to NEUROLOGY INDIA.

At Dr. K S Mani's suggestion, Dr. T K Ghosh was asked to explore the possibility of forming the EEG subsection of the society.

At Dr. Naunihal Singh's suggestion, Drs. Baldev Singh and E P Bharucha were requested to explore the possibility of forming an Indian chapter of Dyslexia International under the auspices of the society.

Dr. Baldev Singh was elected Chandy Orator for 1972.

Notable among the papers published in the journal during 1971 are those on haemorrhagic adenomas of the pituitary gland by Dr. H M Dastur et al (**NEUROLOGY INDIA 1971, 19, 4-12**), intersegmental anastomoses between adjacent dorsal roots of spinal cord in man by Drs. Jacob and Jacob (**NEUROLOGY INDIA 1971, 19, 51-54**), tube feeding syndrome by Dr. D Raja Reddy et al (**NEUROLOGY INDIA 1971, 19, 102-106**), tuberculous atlanto-axial dislocation by S K Pandya (**NEUROLOGY INDIA 1971, 19, 116-121**) and the aortic arch syndrome by Dr. Praful M Dalal et al (**NEUROLOGY INDIA 1971, 19, 155-171**).

Office bearers for 1972:

President	: Dr. K S Mani
Vicepresident	: Dr. B K Bachhawat
Secretary	: Dr. Gajendra Sinh
Treasurer	: Dr. E P Bharucha
Editor	: Dr. Anil D Desai.

22nd annual conference was held at King George Medical College, Lucknow. The souvenir contains accounts of the foundation and development of King George's Medical College, Lucknow and its department of neurosurgery (founded by Dr. Prakash N. Tandon and developed by Dr. Vijay S Dave and his team).

20 December 1972

Among the members elected were Drs. Mary Jacob, Ranjit D Nagpal, D Rout, Brahm Prakash, B S Das,and V S Madan.

Dr. K S Mani's presidential address was entitled 'Interictal EEG in epilepsy. Possible factors associated with definite seizure discharges.' (**NEUROLOGY INDIA 1973, 21, 51-62**)

Dr. Baldev Singh's Chandy Oration dealt with 'Changing concepts of consciousness from ancient to modern times'.

The society decided to sponsor publication of textbooks in neurosurgery and neurology to be edited by Drs. B Ramamurthi and K S Mani respectively.

Messrs. E Merck Ltd. offered awards for the best papers presented at the annual conference by young members (members of less than 7 years standing in the society). Rules for these awards were finalised. The papers would be judged on the basis of originality, central theme, methodology, results, conclusions and presentation. The society also made provision for travelling fellowships for young members to attend the annual conference

and visit neuroscience centres anywhere in the country for the purpose of training.

The society appointed a subcommittee for the standardisation of postgraduate education in the neurosciences in India:

Dr. P N Tandon : Convenor
Dr. B Ramamurthi
Dr. R N Chatterji
Dr. K S Mani
Dr. N H Wadia.

The proposal for the creation of an Association of Neurosurgeons was discussed. Since the society incorporates the neurosurgical fraternity and in addition to providing ample opportunities for its deliberations enables it to interact with neurologists and other neuroscientists, it was decided that there was no need for another association. All members, including the neurosurgeons, were strongly in favour of retaining the unique blend of the neurosciences provided by the society.

The editor made a strong plea that authors review the Indian literature thoroughly before preparing their papers. it was noted that earlier work on the subject by others in India was being ignored.

Notable among the papers published in the journal during 1972 are those on anatomical study of circle of Willis by Dr. D Raja Reddy et al (**NEUROLOGY INDIA 1972, 20, 8-12**), atlantoaxial dislocations by S K Pandya (**NEUROLOGY INDIA 1972, 20, 13-48**), Congenital indifference to pain by Dr. G M Taori (**NEUROLOGY INDIA 1972, 20, 99-103**), a tuberculoma review by Dr. Homi M Dastur (**NEUROLOGY INDIA 1972, 20, 111-131**), malformations of the brain induced by cyclophosphamide in rats by Dr. Shamer Singh et al (**NEUROLOGY INDIA 1972, 20, 152-157**), sex linked muscular dystrophies by Dr. Anil D Desai et al (**NEUROLOGY INDIA 1972, 20, 163-189**) and blood supply of the spinal cord, spinal cord infarction by Dr. Arvind C Mehta (**NEUROLOGY INDIA 1972, 20, 190-216**).

Office bearers for 1973:

President	: Dr. B K Bacchawat
Vicepresident	: Dr. K S Mani
Secretary	: Dr. P N Tandon
Treasurer	: Dr. A K Banerji
Editor	: Dr. Anil D. Desai.

23rd annual conference was held at V S Medical College, Ahmedabad.

18 December 1973

Drs. Jacob Chandy, Baldev Singh and Ram G. Ginde were elected Honorary Members of the society.

Among the members elected were Drs. Ravi Bhatia, A R Bhattacharya, S Dar, K Satyanarayana, P Sreekumar, J P Vaidya, P Kaul, Devika Nag, Nagbhushan S Rao, Zaheer Ahmed Sayeed, V S Lalitha, R Sarasabharati, and T Surya Rao.

Dr. B K Bacchawat's presidential address was entitled 'Lysozomal acid hydrolases in health and disease.' (**NEUROLOGY INDIA 1974, 22, 169-183**)

Dr. Anil D Desai was nominated Chandy orator for 1974.

Notable among the papers published in the journal during 1973 are those on fat embolism by Dr. V K Kak et al (**NEUROLOGY INDIA 1973, 21, 1-10**), postpartum cerebral venous thrombosis by Drs. A K Banerji et al (**NEUROLOGY INDIA 1973, 21, 19-22**), the brain in heatstroke by Drs. A K Pal and S K Chopra (**NEUROLOGY INDIA 1973, 31, 28-31**), interictal EEG in epilepsy by Dr. K S Mani (**NEUROLOGY INDIA 1973, 221, 51-62**), stereotaxic cingulotomy for drug addiction by Dr. V Balasubramaniam et al (**NEUROLOGY INDIA 1973, 21, 63-66**), whether there was SMON in India (**NEUROLOGY INDIA 1973, 21, 95-103**), mechanism for control of neural activity of the cerebral association cortex by Dr. T Desiraju (**NEUROLOGY INDIA 1973, 21, 145-158**) and social aspects of epilepsy by Ms. J M Samant et al (**NEUROLOGY INDIA 1973, 21, 165-174**).

Office bearers for 1974:

President	: Dr. Balaparmeshwar Rao
Vicepresident	: Dr. Gajendra Sinh
Secretary	: Dr. P N Tandon
Treasurer	: Dr. A K Banerji
Editor	: Dr. Anil D Desai.

24th annual conference was held at Christian Medical College and Hospital, Vellore. The silver jubilee of the department of neurological sciences was also celebrated then. The souvenir contains several papers of interest. A brief history of Vellore is followed by an account of the development of the Christian Medical College and Hospital. 'An alumnus' pays a tribute to Dr. Jacob Chandy that opens thus: 'How and where does one start when writing a few lines about Dr. Jacob Chandy as clinician, teacher, neurosurgeon and doctor?' In the subsequent review of the growth and development of neurological sciences over the preceding quarter century we see the then Union Minister of Health, Rajkumari Amrit Kaur

opening the ward for neurology and neurosurgery on 20 February 1954 and Dr. Wilder Penfield laying the cornerstone of the present neurology block on 23 February 1957.The reader can also make acquaintance with each and every staff member and alumnus of the department from its inception. Additional information on the department of neurological sciences is provided by Dr. K V Mathai in the **Christian Medical College Vellore Alumni Journal,** 1986, vol. 20, pages 3-7.

20 December 1974

The house stood in silence to offer condolence over the demise of Dr. Ram G Ginde.

Among the members elected were Drs. K Rajasekharan Nair, V Satyanarayana, A N Achari, S Natchiar, and Mathew J Chandy.

Dr. S Balaparameshwara Rao's presidential address was entitled 'Spinal neurinoma - a study of 80 operated cases'. (**NEUROLOGY INDIA 1975, 23, 1-12**)

Dr. Anil D Desai's Chandy oration was entitled 'Duchenne dystrophy - some facts and fantasies'. (**NEUROLOGY INDIA 1975, 23, 59-69**)

The Dr. B. Ramamurthi oration was established. Dr. Jacob Chandy was nominated the first Ramamurthi orator.

The Indian Standards Institution asked the society to formulate standards for neurosurgical instruments. Drs. P N Tandon, Gajendra Sinh, R M Verma and Mahendra Singh were asked to do so on behalf of the society.

The society decided upon a Continuing Medical Education Programme to be held along with the annual conference with the intention of providing updates on selected topics and encouraging interdisciplinary interaction among trainees in the various branches of the neurological sciences.

It was decided to conduct one or more midterm meetings around June on specialised topics. This would enable detailed discussion on such topics and stimulate young members.

The editor bemoaned the lack of papers of high standard for publication in NEUROLOGY INDIA. It was particularly disheartening that this should be so when the journal was being indexed abroad.

In contrast the number of papers being sent for presentation at the annual conference was becoming unmanageable. It was decided to enforce high standards and reject all papers not meeting them. It was also decided to take some papers as read by title. The secretary of the society and the

executive committee were to form the selection committee.

The society deplored the non-availability of anticonvulsant drugs in the country. The society authorised the secretary to take this up with the relevant ministry in Delhi and ensure rapid correction of the situation.

The secretary pointed to an unusual situation. Whilst the society had increased the number of travelling fellowships available to our younger members, there were not enough applicants!

Notable among the papers published in the journal during 1974 are those on gold and silver foil as dural substitutes by Drs. D R Gulati et al (**NEUROLOGY INDIA 1974, 22,48-50**), postconjunctival radiculomyelopathy by Drs. E P Bharucha and V P Mondkar (**NEUROLOGY INDIA 1974, 22, 79-82**), paralytic rabies by Drs. A K Banerjee and J S Chopra (**NEUROLOGY INDIA 1974, 22, 83-86**), subacute sclerosing panencephalitis by Drs. B S Singhal et al (**NEUROLOGY INDIA 1974, 22, 87-94**), thalamic abscess by Dr. P N Tandon et al and Dr. V G Panchal et al (**NEUROLOGY INDIA 1974, 22, 103-110**), congenital fourth ventricular outlet blocks by S K Pandya et al (**NEUROLOGY INDIA 1974, 22, 111-121**) and cerebral venous and arterial thrombosis in pregnancy and puerperium by Drs. K Srinivasan and M Natarajan (**NEUROLOGY INDIA 1974, 22, 131-140**).

Office bearers for 1975:

President	: Dr. Gajendra Sinh
Vicepresident	: Dr. G Arjun Das
Secretary	: Dr. P N Tandon
Treasurer	: Dr. A K Banerji
Editor	: Dr. Anil D Desai.

25th annual conference was held at the Postgraduate Institute of Medical Education and Research, Chandigarh.

19 December 1975

Among the members elected were Drs. R P Sengupta, Subash R Dharkar, Sushil Kumar, Anil P Karapurkar, Kripal Singh Mann, Bijoy Bhattacharya, Daya K Manghani, B Subba Rao, S Mohanty, Sarosh M Katrak, Manoj J Virani, Mahendra A Parikh, C Vidyasagar, Narayana K Achari, D Lahiri, and Logamuthukrishnan.

Dr. Gajendra Sinh's presidential address was entitled 'Congenital atlanto-axial dislocations'. (**NEUROLOGY INDIA 1976, 24, 69-76**)

Dr. Jacob Chandy's Ramamurthi oration was entitled 'The relevance of specialities in India today'. (**NEUROLOGY INDIA 1976, 24, 14-19**)

Among those from abroad were Drs. F B Maroun, O N Markand and George P Varkey.

Dr. B Ramamurthi announced the workshop on stereotaxic surgery being held at the Institute of Neurology in Madras in February 1976.

The secretary informed the house of the visit by Professors H W Pia and W Piotrowski early in 1976. Scientific sessions by them were being organised in Madras, Delhi and Bombay.

Dr. N H Wadia was nominated the Chandy orator for 1976.

At a detailed session on postgraduate education in the neurosciences it was unanimously decided to support direct recruitment after the M.B.B.S. degree to courses leading to Doctor in Medicine (Neurology) and Master in Chirurgy (Neurosurgery). These courses were to be conducted over five years each, one year being spent in general medicine or general surgery as the case may be. Lateral entry to existing courses leading to these postgraduate degrees after M.D.(Medicine) and M.S.(Surgery) were to continue, the duration of these courses being 3 years.

Dr. Asoke Bagchi instituted the Professor H Krause medal to be presented to the author of the best paper on neuro-oncology at the annual conference.

The National Board of Examiners requested guidance on the appointment of examiners. The president and secretary of the society, in consultation with Dr. B Ramamurthi (member of the Central Committee of the National Board of Examinations) were asked to make the nominations.

Dr. Piroja F Irani enquired about the subsection on EEG in the society. She was asked to re-activate this proposal and work with Dr. T K Ghosh on it.

Drs. Asoke Bagchi and Sunil K Pandya were appointed **historians of the society.** They were to write the history of the society and keep members informed about historically important events.

Notable among the papers published in the journal during 1975 are those on raised intracranial pressure in tuberculous meningitis by Dr. B S Singhal et al (**NEUROLOGY INDIA 1975, 23, 32-39**), neurological involvement in Kyasanur forest disease by Dr. R S Wadia (**NEUROLOGY INDIA 1975, 23, 115-120**), a study of infantile hemiplegia with reference to shift of cerebral speech centre by Dr. K Srinivasan (**NEUROLOGY INDIA 1975, 23, 140-142**), aspergillosis of the central nervous system by Dr. D H Deshpande et al (**NEUROLOGY INDIA 1975, 23, 167-175**) and EEG changes in renal failure by Dr. B B Sawhney et al (**NEUROLOGY INDIA 1975, 23, 176-181**).

Office bearers for 1976:

President	: Dr. G Arjundas.
Vicepresident	: Dr. K V Mathai.
Secretary	: Dr. P N Tandon.
Treasurer	: Dr. A K Banerji.
Editor	: Dr. Anil D Desai.

26th annual conference was held at Jaipur.

22 December 1976

The house offered condolences over the deaths of Drs. Wilder Penfield and S N Pathak.

Themes for conference seminars: head injury (see **NEUROLOGY INDIA 1977, 25, 51-145**), nutrition and the nervous system.

Among the members elected were Drs. Sarala Das, P S Ramani, Pravina U Shah, K K Jain, Mathew Cherian, B C Katiyar, P V S Rana and T K Roy.

Dr. G. Arjundas' presidential address was entitled 'Experiences with neuromuscular disorders in south India'.(**NEUROLOGY INDIA 1977, 25, 1-18**)

Dr. N H Wadia's Chandy oration was entitled 'Heredofamilial spino-cerebellar degeneration with slow eye movements'. (**NEUROLOGY INDIA 1977, 25, 147 - 160**)

Dr. B K Bacchawat was appointed Ramamurthi Orator for 1977.

At Dr. N H Wadia's instance, the secretary was asked to convey the society's opinion to the Medical Council of India that the degrees of D.M.(Neurology) and M.Ch.(Neurosurgery) should be equated with the newly created qualification of Member of the National Academy of Medical Sciences (MNAMS).

The society took a serious view of the substandard electronic equipment (such as EEG, EMG machines) being offered in India. Steps were suggested at ensuring sale and service of equipment of high quality.

The society was concerned at the erratic supply of the life saving, indigenously devised Upadhyaya CSF shunts. The secretary was asked to move the government of India to ensure uninterrupted supply of the raw materials to the manufacturer.

Dr. S Kalyanaraman's proposal for a two day Continuing Medical Education programme was accepted. He was asked to organise the first

such programme in 1977.

Dr. T K Ghosh, talking on the proposal for an E.E.G. subsection, pointed out that the EEG Society of India founded in 1961 had never attained a sound footing.

The secretary was asked to complete formalities to enable neuroscientists in Pakistan, Bangla Desh, Ceylon and Burma to attend our annual conference.

The editor pointed out that many papers presented at our conference were being published abroad. This was against our rules and deprived NEUROLOGY INDIA of material of high standard. Since the journal was now in all international indices, it was important that it be supplied with papers of the highest standard. Some members excused themselves for publishing in foreign journals by claiming that the institutes in which they worked demanded such publication and considered papers in foreign journals when awarding merit. The executive committee of the society offered Rs.10,000 towards the publication of papers of high standard containing more than the permitted number of illustrations. It was hoped that this would serve as an inducement.

Notable among the papers published in the journal during 1976 are those on the neurological basis of sex by Dr. A. Earl Walker (**NEUROLOGY INDIA 1976, 24, 1-13**), cerebral mucormycosis in renal failure by Drs D H Deshpande and A P Desai (**NEUROLOGY INDIA 1976, 24, 20-23**), a study of risk factors in nonembolic cerebrovascular disease by Dr. J K Agrawal et al (**NEUROLOGY INDIA 1976, 24, 125-133**), epilepsy and solar activity - a hypothesis by Dr. K Venkatraman (**NEUROLOGY INDIA 1976, 24, 148-152**) and EEG study of sleep in organic brain damage by Dr. P N Tandon et al (**NEUROLOGY INDIA 1976, 24, 177-181**).

Office bearers for 1977:

President	: Dr. K V Mathai.
Vicepresident	: Dr. Vimla Virmani.
Secretary	: Dr. P N Tandon.
Treasurer	: Dr. A K Banerji.
Editor	: Dr. Anil D Desai.

27th annual conference was held at the Armed Forces Medical College, Poona.

16 December 1977

Theme for conference seminar: tuberculosis of the nervous system.

Among the members elected were Drs. Anand P Desai, Anil V Purohit,

S Venkatraman, H S Srinivas, G Ram Mohan, Shankar D Gokhale, H S Chopra, George J Mathews and B R Kumar.

Dr. K V Mathai's presidential address was entitled 'Intracranial space occupying lesions. Review of 2332 cases.' (**NEUROLOGY INDIA 1978, 26, 157-170**)

Dr. B K Bacchawat delivered the Ramamurthi oration.

It was decided to form working groups within the society to deal with the following:a) medical education and training b) research priorities c) manpower requirements and development of services, community programmes d) instrumentation.

Professor A S Paintal was nominated Chandy Orator for 1978.

The excellent organisation of the Continuing Medical Education programme by Dr.S Kalyanaraman and the encouraging response from all members - young and old alike - made the society, like Oliver, ask for more.

Notable among the papers published in the journal during 1977 are those on 132 patients with neurosyphilis by Drs. K Srinivasan and P Ranganathan (**NEUROLOGY INDIA 1977, 25, 19-25**), a clinicopathological study of 36 cases of tuberculous meningitis by Dr. M D Thomas et al (**NEUROLOGY INDIA 1977, 25, 26-34**), cardiovascular monitoring during intracranial operations by Dr. S S Saini et al (**NEUROLOGY INDIA 1977, 25, 161-165**), tumours of the third ventricle by Dr. Brahm Prakash et al (**NEUROLOGY INDIA, 1977, 25, 166-169**) and the effect of yoga on neuromuscular excitability by Drs. O P Bhatnagar and V Anantharaman (**NEUROLOGY INDIA 1977, 25, 230-232**).

Office bearers for 1978:

President	: Dr. Vimla Virmani.
Vicepresident	: Brigadier Dr. Mahendra Singh.
Secretary	: Dr. A K Banerji.
Treasurer	: Dr. S N Bhagwati.
Editor	: Dr. Anil D Desai
CME Programme Director	: Dr. S Kalyanaraman.

28th annual conference was held at Medical College and Hospital, Trivandrum. The souvenir published on the occasion tells the story of the development of medical education in Kerala over the preceding quarter century. It also describes, briefly, the development of the departments of neurosurgery and neurology at the medical college and hospital. Dr. Sambasivan notes that the McKissock neurosurgical chair and a full set

of craniotomy instruments were in use at the hospital since 1954 but the present department was of neurosurgery was founded in 1966 by Dr. Sambasivan.

23 December 1978

Theme for conference seminar: stroke.

Dr. B Ramamurthi was elected honorary member of the society.

Dr. Baldev Singh was presented a gold medal and a silver plaque on his attaining the age of 75 years.

Among the members elected were Drs. Kalyan Kumar Chatterjee, N V Murthy, K Mahadevan Pillai, N Y Joshi, Ranjit V Acharya, P C Mohanty, S Athiappan, Vrushali V Nadkarni, M C Maheshwari, S Prabhakar, Anil Manchanda, Ranjit K Laha and Uma Kalyanaraman.

The following were elected **honorary corresponding members:**
Professor Charles Drake
Professor Kristian Kristiansen
Professor A Earl Walker
Professor Pierre Vinken.

Dr. Vimla Virmani's presidential address was entitled 'Perspectives in neurology - brain, mind and consciousness'. (**NEUROLOGY INDIA 1979, 27, 53-62**)

Dr. A S Paintal delivered the Chandy oration.

The secretary was asked to prepare a list of essential equipment, instruments and drugs to be included in the list of items that can be imported duty-free.

Professor R Narasimhan was nominated Ramamurthi orator for the year 1979.

The decision of the government of India downgrading the payscales of 3rd year residents in neurology and neurosurgery was deemed unfair to the students. The secretary to take up this matter with the government and convey to it the recommendation of the society that the status quo ante be restored.

The establishment of a library references service was considered and Drs. D Raja Reddy and K V Mathai were asked to put up details.

In order to help junior members, organisers of annual conferences were

asked to provide generous subsidies to them.

Dr. S Kalyanaraman's organisation of the Continuing Medical Education programme commanded universal praise. His suggestion that the texts of the papers presented at this programme be supplied to all those desiring them was accepted. To reduce costs, it was decided to cyclostyle them for distribution.

Dr. Anil D Desai's resignation from the post of editor of NEUROLOGY INDIA was accepted with regret. His single-minded devotion, sincere and painstaking efforts had resulted in the journal gaining acceptance by Index Medicus and other indices abroad and were lauded by one and all. It was hoped that he would continue to associate himself with the running of the journal and help the next editor.

The first volume of the Indian Textbook of Neurosurgery edited by Drs. B Ramamurthi and P N Tandon was released.

Professors Hans W Pia and Ernst Grote had kindly agreed to conduct courses in microneurosurgery in February, March 1979 at Calcutta, Delhi and Bombay.

Notable among the papers published in the journal during 1978 are those on congenital stenosis of the spinal canal by Dr. S R Dharker et al (**NEUROLOGY INDIA 1978, 26, 1-6**), cephalic tetanus by Drs. G K Ahuja and G Kamala (**NEUROLOGY INDIA 1978, 26, 10-13**), primary lymphomas of the brain by Dr. S K Shankar et al (**NEUROLOGY INDIA 1978, 26, 47-54**), HLA antigens in neuro-lathyrism by Dr. Dan F Cohn et al (**NEUROLOGY INDIA 1978, 26, 55-57**), studies in blood coagulation and fibrinolysis in young hemiplegics by Dr. S K Prabhakar et al (**NEUROLOGY INDIA 1978, 26, 63-67**), accumulation of serotonin in human cerebral contusion by Dr. S Mohanty et al (**NEUROLOGY INDIA 1978, 26, 68-70**), head injury by cane-crushing machine by Dr. S Mohanty et al (**NEUROLOGY INDIA 1978, 26, 71-73**) and on the uses of the cowhage plant-mucuna pruriens bak- in the treatment of Parkinson's disease and hyperprolactinemia by Dr. A B Vaidya et al and Dr. Rama A Vaidya et al (**NEUROLOGY INDIA 1978, 26, 171-182**).

Office bearers for 1979:

President	: Brig. Dr. Mahendra Singh
Vicepresident	: Dr. K Jagannathan
Secretary	: Dr. A K Banerji
Treasurer	: Dr. S N Bhagwati
Editor	: Dr. P N Tandon
CME Programme Director	: Dr. S Kalyanaraman.

29th annual, conference was held at National Institute of Mental Health and Neurological Sciences (NIMHANS), Bangalore in association with the 10th All India Convention of Clinical Psychologists, 32nd annual conference of the Indian Psychiatric Society and 5th annual conference of the Indian Society of Psychiatric Social Work. (Details on the foundation of NIMHANS and development of the various departments in the neurosciences can be found in the Silver Jubilee Commemorative Volume published by the institute in 1980.)

9 December 1979

Theme for conference seminar: epilepsy (see **NEUROLOGY INDIA 1980, 28, 118- 196**).

Among the members elected were Drs. A N Subba Rao, B Dibbala Rao, Zenobia Zaiwalla, Dilip Kiyawat, Subhasani Prabhakar, Suresh N Mathuriya, Mohan Sampath Kumar, Kamakshi Shanbhogue, and J Reginald.

Dr. Brigadier Mahendra Singh's presidential address was entitled 'Head injuries.'

The secretary reported success at getting the government to restore the pay scales of 3rd year residents in neurology and neurosurgery.

Professor J A Simpson was nominated Chandy Orator for 1980.

Dr. R Narasimhan's Ramamurthi oration was entitled 'Modelling language behaviour: some neurological implications'.(See **NEUROLOGY INDIA 1980, 28, 1-7**)

The secretary and Dr. Jacob Abraham organised a conference of nurses treating patients with neurological disorders which was held along with the annual conference of the society. **An Association of Neurological Nurses** was founded by the nurses as a subsection of the Neurological Society of India. The house cheered this development and recommended the holding of the nurses conference as part of the annual conference of the society.

The general body welcomed the initiative taken by Dr. Arjun D Sehgal in setting up computerised tomographic scanners in different parts of the country.

Dr. S Kalyanaraman's organisation of the Continuing Medical Education Programme continued to win him high praise. From this year onwards the papers presented at this session are being published as printed volumes instead of the cyclostyled sheets hitherto distributed.

Notable among the papers published in the journal during 1979 are those on the diagnosis of intracranial tuberculoma by Dr. K V Mathai (**NEUROLOGY INDIA 1980, 27, 63-68**), Wilson's disease by Dr. A K Malik et al (**NEUROLOGY INDIA 1980, 27, 73-81**), moyamoya disease presenting as subarachnoid haemorrhage by P V S Rana et al (**NEUROLOGY INDIA 1980, 27, 123-129**), a prospective clinico-radiological study on stroke in the young by Dr. J S Chopra et al (no 27, 160-169) and on rural attitudes to epilepsy by Dr. N Pruthi et al (**NEUROLOGY INDIA 1980, 27, 170-173**).

Office bearers for 1980:

President	: Dr. K Jagannathan
Vicepresident	: Dr. D R Gulati
Secretary	: Dr. A K Banerji
Treasurer	: Dr. S N Bhagwati
Editor	: Dr. P N Tandon
CME Programme director	: Dr. S Kalyanaraman.

30th annual conference held at the Rabindra Sadan and Sisir Mancha, Calcutta. The souvenir published on the occasion bears the unmistakable stamp of Dr. Asoke Bagchi. The cover features the four Nobel Laureates from Calcutta - Rabindranath Tagore, Ronald Ross, C V Raman and Mother Teresa. The development of neurology and neurosurgery in Calcutta have been traced and a special tribute is paid to Dr. Herbert Kraus.

20 December 1980

Theme for conference seminar: pain.

Professor H W Pia was elected **honorary corresponding member.**

Dr. K Jagannathan's presidential address was entitled 'Cerebellar degeneration - an analysis'. (**NEUROLOGY INDIA 1985, 33, 35-47**)

Dr. J A Simpson's Chandy oration was entitled 'Myaesthenia gravis'.(See **NEUROLOGY INDIA 1981, 29, 45-50**)

Among those from abroad were Drs.H W Pia (who delivered a guest lecture on cerebral dysregulation) and Dr. H Fodstad (who talked on antifibrinolytics in subarachnoid hemorrhage).

Dr. J S Chopra highlighted the difficulties faced by him in bringing out the volume on neurology.

The Continuing Medical Education Programme, the initiation of travelling and visiting fellowships, the starting of nurse associate membership and

mini-conferences of nurses in neurological sciences were a few of the important additions to the activities of the society.(Travelling fellowship was increased from Rs. 200 to Rs. 300 and the visiting fellowship from Rs. 500 to Rs. 750.) It was also hoped that the society would gain acceptability with such bodies as the ICMR, CSIR, Ministry of Health. The society impressed upon the Medical Council of India that the minimum period of training in general surgery for candidates doing the 5 year course for the MCh Neurosurgery should be 1 year and not 2 years so that a longer period was made available for training in neurosurgery.

Dr. Sunil Pandya suggested that a special supplement of the journal be brought out featuring the history of our society.

The annual subscription for ordinary members was raised from Rs.50 to Rs. 100. Life membership was raised to Rs. 1500. Members not paying their dues for three years or more would be struck off the rolls. Subscription fees for nurse associate members and neuro-technicians was fixed at Rs. 10 per year. Admission fees for full members was Rs.250, associate members Rs. 150, nurse and neurotechnicians Rs. 25.

It was decided that the vice-president shall be elected from members of at least 10 years standing.

The secrecy of the ballotwas to be ensured by the secretary.

Dr. E P Bharucha was nominated Ramamurthi orator for 1981.

Notable among the papers published in the journal during 1980 are those on neurinomas of the jugular foramen by Dr. Brahm Prakash et al (**NEUROLOGY INDIA 1980, 28, 8-11**), differentiating and de-differentiating potentials in cerebral neuroectodermal tumours by Dr. Subimal Roy at al (**NEUROLOGY INDIA 1980, 28, 17-22**), tuberculosis of the central nervous system by Dr. Darab Dastur et al (**NEUROLOGY INDIA 1980, 28, 197-206**), CT studies in CNS tuberculosis by Drs. Sneha Bhargava and P N Tandon (**NEUROLOGY INDIA 1980, 28, 207-212**) and on anaerobic brain abscess by Dr. A Chandramukhi et al (**NEUROLOGY INDIA 1980, 28, 213-218**).

Office bearers for 1981:

President	: Dr. D R Gulati
Vice-president	: Dr. S Janaki
Secretary	: Dr. S N Bhagwati
Treasurer	: Dr. B S Singhal
Editor	: Dr. P N Tandon
CME programme director	: Dr. S Kalyanaraman.

31st annual conference was held at the Medical College and Hospital, Vishakapatanam. A silver jubilee album featuring the staff members since the inception of the department of neurosurgery was released.

19 December 1981

Theme for conference seminar: Coma and brain death.(**NEUROLOGY INDIA 1982, 30, 203-231**)

Dr. D R Gulati's presidential address was entitled 'The four minutes'. (**NEUROLOGY INDIA 1982, 30, 1-6**)

Dr. Kristian Kristiansen delivered the first Sarveshri oration at the All India Institute of Medical Sciences on 'Subarachnoid haemorrhage and cerebrovascular spasm - a permanent challenge'. (See **NEUROLOGY INDIA 1981, 29, 96-107**)

Dr. E P Bharucha's Ramamurthi oration was entitled Spinal muscular atrophy - the heredofamilial type'.

Among those from abroad were Drs. A Earl Walker, Tadeo Nose, D Bates and Victor McAllister. In addition to participating in the symposium on coma and brain death, Dr. Walker talked on the epidemiology of brain tumours in the U.S.A. Dr. Nose discussed computerised tomography and Dr. McAllister the role of ultrasound in neurological diagnosis.

Various World Federations were invited to hold the congresses in India.

The society's journal was now out of the red and had Rs.25000 in balance.

The archives of the society were located at the Department of Neurosurgery, K E M Hospital in Bombay.

Notable among the papers published in the journal during 1981 are those on evaluation of ventriculo-atrial shunts in posterior fossa tumours by Dr. D C Lodhia et al (**NEUROLOGY INDIA 1981, 29, 1-6**) changes in cyclic nucleotides in infarcted basal ganglia of the primate by Dr. Jacob Abraham et al (**NEUROLOGY INDIA 1981, 29, 7-9**), the treatment of trigeminal neuralgia by injecting anhydrous glycerol by Dr. S S Saini (**NEUROLOGY INDIA 1981, 29,31-34**), tuberculous brain abscess by Dr. B Ramamurthi et al and Dr. A Chandramukhi et al (**NEUROLOGY INDIA 1981, 29, 35-42**), uncommon presentations of neurocysticercosis by Dr. M A Wani et al (**NEUROLOGY INDIA 1981, 29, 58-63**), neurological dysfunction related to open heart surgery by Dr. P P Ashok et al (**NEUROLOGY INDIA 1981, 29, 149- 156**).

Office bearers for 1982:

President	: Dr. S Janaki
Vicepresident	: Dr. Jacob Abraham
Secretary	: Dr. S N Bhagwati
Treasurer	: Dr. B S Singhal
Editor	: Dr. P N Tandon
CME programme director	: Dr. S Kalyanaraman.

32nd annual conference was held at S C B Medical College, Cuttack. In the souvenir released on the occasion, Dr. B N Acharya describes the development of neurosciences in Orissa.

20 December 1982

Mid-term seminar on pediatric neurosurgery was held in August 1982 at NIMHANS,Bangalore. Spinal dysraphism and hydrocephalus were the key subjects discussed. (**NIMHANS Journal, 1984, 2, 49-66**)

A workshop on electrophysiology was organised at the Institute of Neurology, Madras and a seminar on 'Current problems in neurosurgery' held at the Grant Medical College and Sir J J Group of Hospitals in December 1982.

Theme for conference seminar: non-tuberculous infection of the nervous system.(Proceedings published by National Institute of Mental Health and Neurological Sciences, 1982.)

Dr. S Janaki's presidential address was entitled 'A study of cerebrovascular disease with special reference to dysphasics in a multilingual society.'

Among those from abroad were Professor Luc Picard, L Pitts, H Goldsmith and D G T Thomas.

The society now had on its rolls 356 full members, 216 associate members. 169 neurosurgeons, 134 neurologists, 48 other neuroscientists.

Dr. Prakash N Tandon handed over the editorial reins of NEUROLOGY INDIA to Dr. Asoke Bagchi, along with Rs. 10000 as balance in the journal's kitty.

Drs. M C Maheshwari and P N Tandon published, under the aegis of the society, a volume containing the abstracts of all papers published in NEUROLOGY INDIA over the 25 years since its inception (1954-1979). Subject and author indices were also provided. The society expressed its debt to the editors for their painstaking effort and useful product.

Dr. Darab K Dastur was nominated Ramamurthi Orator for 1983.

Notable among the papers published in the journal during 1982 are those on infratentorial midline cystic arachnoiditis by Dr. G N N Reddy et al (**NEUROLOGY INDIA 1982, 30, 23-29**), conservative treatment of intracranial tuberculomas by Sunil K Pandya (**NEUROLOGY INDIA 1982, 30, 30-36**), cholinergic neuropathways of habenular complex in mice by Drs. V V Kakaria and P P Sood (**NEUROLOGY INDIA 1982, 30, 37-38**), antifibrinolytic agents by Dr. H Fodstad (**NEUROLOGY INDIA 1982, 30, 67-82**), dementia by Dr. H V Srinivas et al and Dr. S K Shankar et al (**NEUROLOGY INDIA 1982, 30, 83- 103**), morphology of periaqueductal gray matter in the monkey by Drs. S Wadhwa and G Gopinath (**NEUROLOGY INDIA 1982, 30, 108- 112**) and a prospective study of pulmonary infection among 100 consecutive head injured patients by Dr. V S Mehta et al (**NEUROLOGY INDIA 1982, 30, 131-138**).

Office bearers for 1983:

President	: Dr. Jacob Abraham
Vice-president	: Dr. M Veera Raghava Reddy
Secretary	: Dr. S N Bhagwati
Treasurer	: Dr. B S Singhal
Editor	: Dr. Asoke K Bagchi
CME programme director	: Dr. S Kalyanaraman.

33rd annual conference was held at Madurai. In the souvenir released on the occasion, Dr. S A Kabir describes the foundation and development of the departments of neurology and neurosurgery at the Government Rajaji Hospital and Madurai Medical College.

17 December 1983

The 5th international congress on neurovascular diseases was held in Bombay in January 1983.

An international symposium on technical standards in neurosurgery was held at Maulana Azad Medical College in February 1983.

A national training programme in techniques and application of computer analysis of human EEG and brainstem far-field evoked potentials was held at the National Institute of Mental Health and Neurological Sciences (NIMHANS), Bangalore in July 1983.

A conference on recent advances in epilepsy was held at Medical College and Hospital, Trivandrum in August 1983.

A mid-term seminar on infections of the central nervous system was held

at the Medical Research Centre, Bombay Hospital in September 1983.

A symposium on neurological problems in India (neurology update 1983) was held at Poona Medical Foundation, Poona in September 1983.

A national seminar on recent advances in the neurosciences was held at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum in December 1983.

A symposium on microvascular neurosurgery was held at the All India Institute of Medical Sciences, New Delhi in December 1983.

Just preceding the annual conference was the National Seminar On Recent Advances In Neurosciences at Sree Chitra Tirunal Institute for Medical Sciences of Technology, Trivandrum. Featured in the seminar were symposia on angiomas of the brain, sellar and parasellar lesions, craniovertebral anomalies, chronic meningitis and juvenile motor neurone disease. (The proceedings were published by the institute the same year.)

Theme for conference seminar: disorders of peripheral nerves.

Dr. Abraham's presidential address was entitled ' An understanding of the pathophysiology and management of cerebrovascular disease in man based on experimental data'. (**NEUROLOGY INDIA 1985, 33, 1-24**)

Dr. Darab Dastur's Ramamurthi oration was entitled 'The broad field of neuropathology'.

Among those from abroad were Dr. Theodore Rasmussen (who spoke on brain tumours masquerading as seizure problems), Dr. Peter Rasmussen, Dr. Tetsuo Kanno and Dr. Nobuyuki Suzuki.

Dr. Krishnamoorthy Srinivas stimulated much interest in his presentation of how Babinski failed in the medical examination of 1892 and the events thereafter.

The society now had 378 full members, 258 associate members. "As in the case of any family that gets larger, differences of opinion tend to increase, at times they tend to become unpleasant. However, as differences and disputes are settled by discussion, democratically; harmony and cohesiveness develop."

It was commented that academic research in India in the neurosciences was poor. The Indian Council for Medical Research (ICMR) and Department of Science and Technology (DST) received just 2 new research proposals in the neurosciences during the year.

Notable among the papers published in the journal during 1983 are those on the concept of disorders of muscle in **Caraka Samhita** (**NEUROLOGY INDIA 1983, 31,13-14**), experiences with 70 patients with myasthenia gravis by Dr. G K Ahuja et al (**NEUROLOGY INDIA 1983, 31, 15-24**), the sagittal diameter of normal cervical canal in some south Indians by Dr. R Vedula Rao et al (**NEUROLOGY INDIA 1983, 31, 37-42**), surgery of brainstem tumours by Dr. R D Nagpal (**NEUROLOGY INDIA 1983, 31, 9-16**), myokimia, muscular stiffness and continuous motor unit activity by Dr. Upinder Kaur et al (**NEUROLOGY INDIA 1983, 31, 29-38**), recovery of intellectual function after injury of young brain by Dr. K Srinivasan (**NEUROLOGY INDIA 1983, 31, 47-50**), analysis of variations in the division of the internal carotid artery as studied on 1000 normal angiograms by Dr. P Sanal Kumar et al (**NEUROLOGY INDIA 1983, 31, 55-60**), a followup study of 3216 cases of head injuries by Dr. L R Pathak et al (**NEUROLOGY INDIA 1983, 31, 61-66**), a pathological study of 14 cases of vascular neuropathies by Dr. S Shankar et al (**NEUROLOGY INDIA 1983, 31, 41-50**) and an analysis of craniovertebral anomalies as seen in north-west India by Dr. S Jawalkar et al (**NEUROLOGY INDIA 1983, 31, 15-26**).

Office bearers for 1984:

President	: Dr. M Veera Raghava Reddy.
Vice-president	: Dr. Prakash N Tandon.
Secretary	: Dr. M Sambasivan.
Treasurer	: Dr. Vijay Kak.
Editor	: Dr. Asoke K Bagchi
CME programme director	: Dr. S Kalyanaraman.

34th annual conference was held at Varanasi. In the souvenir released on the occasion Dr. R K Misra describes the evolution of the Banaras Hindu University. Drs. T K Ghosh and K V Mathai review the developmental landmarks in Indian neurology and neurosurgery. Drs. B C Katiyar and S Mohanty trace the history of the departments of neurology and neurosurgery at the Banaras Hindu University.

20 December 1984

A brain-storming session on neurobiology was held at National Institute of Mental Health and Neurological Sciences, Bangalore in November. The aims were to ascertain the work being done in this field in India, list the facilities available, understand the strengths and weaknesses at the different centres, develop collaboration amongst scientists at the various centres and identify new areas and centres for developing scientific programmes in neurosciences in India. The proceedings resulted in a valuable reference work: **Profiles of Research in Neurosciences in India** published by National Institute of Mental Health and Neurological

Sciences, Bangalore the same year.

An International Seminar on Motor Neurone Disease was held at the National Institute of Mental Health and Neurological Sciences, Bangalore in October. (The proceedings have been published under the title **'Motor neurone disease. Global clinical patterns and international research'** by Oxford University Press. Editor: Dr. M. Gourie-Devi.)

The society expressed grief at the unexpected demise of Mrs. Indira Gandhi and six members of the society including Dr. C G S Iyer and Dr. Ramendra Nath Chatterjee. (See **NEUROLOGY INDIA 1984, 32, 13-14** for Dr. Iyer's obituary and **NEUROLOGY INDIA 1984, 32, 15-16** for Dr. R. N. Chatterjee's obituary.)

Theme for conference seminar: epilepsy, brain edema.

The following were elected **honorary corresponding members:**

Professor John A Simpson
Professor John Walton
Professor Theodore Rasmussen
Professor Lindsay Symon.

Dr. M Veera Raghava Reddy's presidential address was entitled ' Some aspects of nutritional disorders of the nervous system'. **(NEUROLOGY INDIA 1985, 33, 161-179)**

Among those from abroad were Professors Hanna Pappius, G Ojemann, Ross Russell and Lindsay Symon. (For Dr. Symon's paper on surgical understanding of the cerebral circulation see **NEUROLOGY INDIA 1985, 33, 77-96)**

Dr. Krishnamoorthy Srinivas continued to evoke enthusiasm in the history of neurology, and dealt, this year, with Douglas Moray Cooper Argyll Robertson - his life, the pupil he described, his love for India, his friendship with the Thakurs of Gondal and his death in India in 1909.

The society set up an Education and Policy Committee consisting of the President, Vice-president, Secretary, Treasurer, Dr. B Ramamurthi, Dr. K Jagannathan, Dr. G N N. Reddy and Dr. A K Banerjee (Chandigarh).

An increase in annual dues became necessary: full members were now to pay Rs.150, associate members Rs. 100.

Dr. M Natarajan, professor of neurosurgery, and his colleagues at Madurai Medical College set up 2 annual awards: for the best poster presented at the conference and for the top scorer in the multiple choice question test

at the conference.

Dr. K V Mathai was named Ramamurthi orator for 1985.

Dr. Asoke Bagchi set up a travelling fellowship in memory of the late Dr. Dwija Das Bagchi.

Dr. Asoke Bagchi handed over the editorial reins of NEUROLOGY INDIA to Dr. S Kalyanaraman. In turn, Dr. Kalyanaraman handed over charge of the CME programme to Dr. K K Sinha.

Notable among the papers published in the journal during 1984 are those on prolonged ambulatory EEG in children by Dr. S S Seshia et al (**NEUROLOGY INDIA 1984, 32, 19-25**), an analysis of 50 cases of painful ophthalmoplegia by Drs. D Nagaraja and T G Suresh (**NEUROLOGY INDIA 1984, 32, 21-24**), analysis of 100 cases of subarachnoid haemorrhage and experience with intracranial aneurysms by Dr. M Sambasivan et al (**NEUROLOGY INDIA 1984, 32, 17-26**) and on visual evoked potentials in tuberculous meningitis by Drs. R Sridharan and L Krishnamurthy (**NEUROLOGY INDIA 1984, 32, 27- 34**). The letter to the editor from Dr. Donald Christopher Rao of Alabama, USA is thoughtprovoking. (**NEUROLOGY INDIA 1984, 32, 81**)

Office bearers for 1985:

President	: Dr. Prakash N Tandon
Vice-president	: Dr. B S Singhal
Secretary	: Dr. M Sambasivan
Treasurer	: Dr. Vijay Kak
Editor	: Dr. S Kalyanaraman.
CME Programme director	: Dr. K K Sinha.

35th annual conference was held at Patna.

17 December 1985

A mid-term conference - the 3rd Pediatric Neurosurgery Meeting - was held at Nizam's Institute of Medical Sciences, Hyderabad in August. It was organised by Dr. D Raja Reddy. The manuscripts and abstracts of the papers presented have been published by the institute the same year. A select bibliography on brain tumours in childhood, compiled by Drs. K V R Sastry and D Raja Reddy was also published by the institute on the occasion.

Dr. K Rajasekharan Nair organised a seminar on stroke at the Medical College and Hospital, Trivandrum.

The society expressed grief at the demise of Professors K Mahadevan Pillai and S S Jolly.

Theme for conference seminar: pituitary tumours. (**NEUROLOGY INDIA 1986, 34, 95-158,165-216**)

Dr. P N Tandon's presidential address was entitled -'Management of head injuries: fads, fashions and facts'. -(**NEUROLOGY INDIA 1986, 34, 1-30**)

Dr. K V Mathai's Ramamurthi oration was entitled 'Epilepsy - some epidemiological, experimental and surgical aspects.' (**NEUROLOGY INDIA 1986, 34, 299-314**)

Professor Luc Picard conducted workshops on interventional neuroradiology at Seth G S Medical College and K E M Hospital, Bombay; NIMHANS, Bangalore and Sree Chitra Tirunal Institute, Trivandrum in November.

The Education and Policy Committee of the society submitted its report. The proposal submitted by Dr. Sunil K Pandya for having an uniform curriculum for the M. Ch. in neurosurgery throughout the country, was generally agreed upon. Dr. G N N Reddy announced a meeting at NIMHANS on planning for the needs in manpower in the neurosciences in the country.

Facilities for training in microneurosurgery at the All India Institute of Medical Sciences, with funds for travel and stay for the purpose were announced by Dr. P N Tandon.

Drs. D. Raja Reddy and B Ramamurthi proposed the formation of a Brain Tumour Registry in the country. It was decided to approach the ICMR for help.

Dr. M Sambasivan's innovative and informative newsletter, published periodically and sent to all members was greatly appreciated.

Dr. Kak's proposals were approved. Members failing to pay their subscription for a year will lose their subscription to the journal. Non-payment of dues for 2 years would bring about removal of the defaulter's names from the society's rolls.

The papers presented at the Continuing Medical Education Programme and some others collected by Dr. K K Sinha were published in the volume entitled **Progress in Clinical Neurosciences.**

The first EEG technicians conference was held as part of our annual conference. The neuro-nurses meeting continues to be held along with our

conference.

Dr. Obaid Siddiqui was nominated Chandy orator for 1986.

Notable among the papers published in the journal during 1985 are those on experimental focal motor sensory epilepsy by Dr. Rakesh Naithani et al (**NEUROLOGY INDIA 1985, 33, 25-34**), an analysis of 200 cases of cerebellar degeneration (**NEUROLOGY INDIA 1985, 33, 35-49**), neural transmission in the spinal cord after spinal cord injury by Drs. K C Alexander and Normal Allen (**NEUROLOGY INDIA 1985, 33, 49-60**), retromastoid microsurgical decompression of the trigeminal nerve in trigeminal neuralgia by Drs. M J Virani and D A Palande (**NEUROLOGY INDIA 1985, 33, 97- 108**) and correlation of CT findings of acoustic neuroma with histology by Drs. A Marthanda Pillai and M Sambasivan (**NEUROLOGY INDIA 1985, 33, 181- 194**).

Office bearers for 1986:

President	: Dr. B S Singhal
Vice-president	: Dr. S Kalyanaraman
Secretary	: Dr. M Sambasivan
Treasurer	: Dr. Vijay Kak
Editor	: Dr. S Kalyanaraman
CME Programme Director	: Dr. K K Sinha.

36th annual conference was held at the Maulana Azad Medical College and the G B Pant Hospital, New Delhi. The volume entitled **Current Status in Neurosciences** released at the conference contains several papers of interest. Dr. Prakash N Tandon reviews neurosciences in India. Dr. Brahm Prakash describes the development of his department and how it has equipped itself with state of the art equipment and capabilities.

14 December 1986.

A meeting on infections and infestations of the CNS was organised by Dr. N K Sharma at Rohtak in February.

An International Seminar on Cervical Spine was organised at NIMHANS, Bangalore by Dr. B S Das in September. (Proceedings of the seminar have been published in **NIMHANS JOURNAL,** 1988, vol.6, no.2, supplement 2, 1-164.)

A mid-term meeting on controversies in neurosurgery was organised by Dr. Vijay Kak at the Postgraduate Institute for Medical Education and Research in Chandigarh in October.

A one day workshop on training and evaluation in the clinical neurosciences

was held at the All India Institute of Medical Sciences, New Delhi in December.

The society expressed grief at the demise of Professor H W Pia, Dr. G C Mitra and Dr K L Wig.

Themes for conference seminars: Drugs and epilepsy (NEUROLOGY INDIA, 35, 271-310, 1987), cerebrovascular diseases and infections of the nervous system.

Dr. B. S. Singhal's presidential address was entitled 'Multiple sclerosis and related demyelinating disorders in the Indian context'. (**NEUROLOGY INDIA 1987, 35, 1-12**)

Among those from abroad were Drs. K Kristiansen, Kemp Clark, Skip J Peerless, A Hartmann, D G T Thomas, Maynard H Cohen, Frank M Yatsu, D Bates, Alan Crockard, Tetsuo Kanno and Rashid Jooma.

Dr. Kristian Kristiansen's reminiscences made the recent developments in the history of neurosurgery come vividly alive to the audience.

Dr. Krishnamoorthy Srinivas continued his series on the history of neurology, discussing Hughlings Jackson as seen through the eyes of an artist and those of Macdonald Critchley.

The EEG, EMG subsection of the society was renamed 'Clinical neurophysiology subsection'.

Dr. Robin P Sengupta was named Ramamurthi Orator for 1987.

Notable among the papers published in the journal during 1986 are those on alpha coma by Drs. P Satish Chandra and M. Gourie Devi (**NEUROLOGY INDIA 1986, 34, 31-40**), experiences with 84 cases of craniopharyngiomas by Drs. M Sambasivan and A. Marthanda Pillai (**NEUROLOGY INDIA 1986, 34, 41-46**), effect of isonicotinic acid hydrazide on the developing central nervous system of chick embryo by Drs. G C Sensharma and S K Pandey (**NEUROLOGY INDIA 1986, 34, 53- 62**), vistas in stereotaxic surgery by Dr. V Balasubramaniam (**NEUROLOGY INDIA 1986, 34, 225-240**), effect of pulsed electromagnetic field in cerebral edema by Dr. K Jayakumar et al (**NEUROLOGY INDIA 1986, 34, 241-248**) and some reflections on the gamma motoneurone by Dr. M S Devanandan (**NEUROLOGY INDIA 1986, 34, 359- 362**).

Office bearers for 1987:

President	: Dr. S Kalyanaraman.
Vice-president	: Dr. Shyamal K Sen.
Secretary	: Dr. M Sambasivan
Treasurer	: Dr. Vijay Kak
Editor	: Dr. S Kalyanaraman
CME Programme Director	: Dr. K K Sinha.

37th annual confarence was hald at Hyderabad. The soqrenir reheased at tha cknference contains accounts of the development of neurosciences in Andhra Pradesh - at Visakapatanam, Hyderabad, Kurnool, Guntur, Warangal, Kakinada and Tirupathi. Dr. A Ramachari takes us past the milestones in the medical history of Hyderabad, with Dr. G Narsing Rao describing the origin and growth of the Osmania Medical College. Dr. D Raja Reddy provides us a tantalising glimpse of what can be learnt from ancient Indian coins.

19 December 1987

Dr. M Gazi Yasargil conducted seminars on microneuro-surgery in Bombay and Bangalore before attending the annual conference of the society in Hyderabad. He held the audiences spellbound with his description of his personal surgical philosophy, demonstration of operative technique and his results. The video recordings of his operations enabled the audience to grasp the finer points.

A midterm workshop on lasers in neurosurgery was organised by Dr. Brahm Prakash at G B Pant Hospital, New Delhi on 31 October.

A course in neurobiology for postgraduates in chilical neurosciences was held by Professor P N Tandon and his colleagues at the All India Institute of Medical Sciences in October.

Themes for conference seminar: dementias, tumour markers.

Dr. S Kalyanaraman's presidential address was entitled ' Stereotaxic surgery- past, present and future'.

Among those from abroad were Drs. M Gazi Yasargil,Fred Plum, Derek Gordon, J C Jacob, S Rengachary and J R Heron.

The preparation of a volume on the development of the neurological sciences in India was taken up.

Dr. Ramesh Chandra offered to prepare a compendium on referral centres for the treatment of paraplegia, speech disorders etc. in India. This has

been welcomed.

Notable among the papers published in the journal during 1987 are those on the use of lasers in medical and surgical practice by Dr. Phillip Harris (**NEUROLOGY INDIA 1987, 35, 325-332**), 24 cases of subacute sclerosing panencephalitis seen in Pune by Drs. J P Thakare et al (**NEUROLOGY INDIA 1987, 35, 333-340**), adverse reactions seen during treatment of neurocysticercosis by praziquantel by Dr. Ashok Verma et al (**NEUROLOGY INDIA 1987, 35, 349- 352**), and management of fluorotic spinal compression by Drs. D Raja Reddy and D Srikanth Reddy (**NEUROLOGY INDIA 1987, 35, 369-374**).....

Office bearers for 1988:

President	: Dr. Shyamal Sen
Vice-president	: Dr. S N Bhagwati
Secretary	: Dr. M. Sambasivan
Treasurer	: Dr. Vijay Kak
Editor	: Dr. S Kalyanaraman

Dr. Praful M. Dalal was named Chandy orator for 1988.

38th annual conference was held at Postgraduate Institute of Medical Education and Research, Chandigarh. A volume describing the evolution of neurosciences at the Institute over the preceding quarter century was released at the conference.

20 December 1988

Dr. P N Tandon and his colleagues held the second course in neurobiology for postgraduates in clinical neurosciences at the All India Institute of Medical Sciences, New Delhi in November.

Themes for conference seminar: craniovertebral anomalies, frontiers in neuro-imaging.

Dr. Shyamal Sen's presidential address was entitled 'Studies on sleep disorders. The need for a sleep research laboratory in India'.

Among those from abroad were Drs. W Ian McDonald, H Lechner and Huw Griffith. Dr. Ian McDonald spoke on optic neuritis and its clinical significance. Dr. Lechner talked on the value of technical medicine in the prevention of ischemic brain disease . Dr. Huw Griffith described his experiences with the use of the endoscope in neurosurgery, illustrating his talk with a movie.

Notable among the papers published in the journal during 1988 are those on protein calorie malnutrition and the nervous system by Drs. J S Chopra

and Upinder K Dhand (**NEUROLOGY INDIA 1988, 36, 1-8**), subependymal giant cell astrocytoma and tuberous sclerosis by Dr. S A Barodawala et al (**NEUROLOGY INDIA 1987, 36, 9-20**) transplantable murine neurogenic teratocarcinoma by Drs. Aruna V Thakare and V S Lalitha (**NEUROLOGY INDIA 1987, 36, 65-72**), surgical management of multiple intracranial aneurysms associated with arteriovenous malformation by Dr. F B Maroun et al (**NEUROLOGY INDIA 1987, 36, 73-80**), percutaneous transcutaneous embolisation by Dr. V R K Rao et al (**NEUROLOGY INDIA 1987, 36, 81-95**).

Recommendations of Symposium on Training and Evaluation in Clinical Neurosciences held at AIIMS, New Delhi on 11th December, 1986

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AIM OF THE TRAINING:

The end product should have acquired knowledge, skills, and attitudes to be able to function as an independent clinician/consultant, and, a junior teacher acquainted with research methodology.

OBJECTIVES:

1. Should be acquainted with the current literature on relevant aspects of basic, investigative and clinical neurosciences.

2. Should have acquired performance skills and ability to interpret relevant clinical investigations.

3. Should be able to diagnose, plan investigations and treat common conditions in the speciality by relevant current therapeutic methods.

4. Should be acquainted with allied and general clinical disciplines to ensure appropriate and timely referral.

5. Should be acquainted with relevant education delivery system.

6. Should be able to identify, frame, and carry out research proposals in ones speciality.

7. Should be aware of ones own limitations.

TRAINING SYSTEM:

Exclusively on whole time inservice basis, preferably on the residency pattern.

MINIMAL REQUIREMENTS OF TRAINING UNIT FOR DM (NEUROLOGY)

1. Separate 20 bedded department with an OPD attendance of at least 4000/year, attached with/having access to a well equipped library and general hospital with casualty services, and investigative facilities, with well equipped departments, of biochemistry, pathology, microbiology, ophthalmology, otorhinolaryngology, general medicine, pediatrics, behavioral sciences, anasthesiology, radiology, forensic medicine and neurosurgery.

2. The radiology department would provide the required support and should be equipped with skull table, myelography table, image intensifiers and facilities for selective angiography. Facilities for intervention radiology, DSA, C.T. Scan, MRI and Ultrasonography are desirable. The availability of 2 trained neuroradiologists is desirable.

3. The department of pathology would provide the required support including autopsy facilities. The availability of 2 fully trained neuropathologists is desirable.

4. Fully equipped clinical neurophysiology laboratory with EEG, EMG, Nerve conduction and evoked potential facilities is essential.

5. A neurochemistry laboratory is essential preferably having 2 trained neurochemists.

6. There should be a faculty of 3 qualified neurologists, at least one of whom should be a recognised teacher.

7. For every recognised teacher 1 five years and one 3 years candidate may be taken per year for training.

MINIMAL REQUIREMENTS OF TRAINING UNIT FOR M.CH. (NEUROSURGERY)

1. Separate 30 bedded department with an OPD and casualty attendance of at least 1000/year, attached with or having access to a well equipped general hospital with casualty services and investigative facilities, with well equipped departments of biochemistry, pathology, microbiology, ophthalmology, otorhinolaryngology, general medicine, pediatrics, behavioural sciences, forensic medicine and neurology.

2. The radiology department would provide required support and should be equipped with skull table, myelography table, image intensifiers and facilities for selective angiography. Facilities for intervention

radiology, DSA, CT Scan, MRI and Ultrasonography are desirable. The availability of 2 trained neuroradiologists is desirable.

3. The department of anaesthesiology would provide the required support. The availability of 2 trained neuroanaesthesiologists is desirable.

4. There should be access to a separate operation theatre and intensive care area of at least 3 beds. In addition to the usual neurosurgical equipment it should have, operating microscope, bipolar cautery, microsurgery instruments, image intensifier and monitors.

5. The department of pathology would provide the required support including autopsy facilities. The availability of 2 fully trained neuropathologists is desirsable.

6. There should be a faculty of 3 persons, at least one of whom should be a recognised teacher.

7. For every recognised teacher one 'five year' and one 'three year' candidate may be taken for training per year, subject to a maximum of 1 trainee per 4 beds at any given time.

ELIGIBILITY CRITERIA FOR ENTRY AND COURSE DURATION

I.	D.M. (Neurology)	
	i) MBBS	-Course duration 5 years
	ii) M.D. (Medicine)	
	or	
	M.D. (Pediatrics)	-Course duration 3 years
II.	M.Ch. (Neurosurgery)	
	i) MBBS	-Course duration 5 years
	ii) M.S. (General Surgery)	-Course duration 3 years.

MINIMUM ROTATION SCHEDULE OF TRAINEES OUTSIDE PARENT DEPARTMENT

I.	D.M. (Neurology)	
	1. Clinical Neurophysiology	- 12 weeks
	2. Neuropathology	- 4 weeks
	3. Psychiatry	- 8 weeks
	4. Neurosurgery	- 8 weeks
	5. Visit to other Institutions	- 6 weeks
	6. Elective to any area of candidates choice	- 6 weeks
	7. General medicine (For the 5 years course)	- 78 weeks