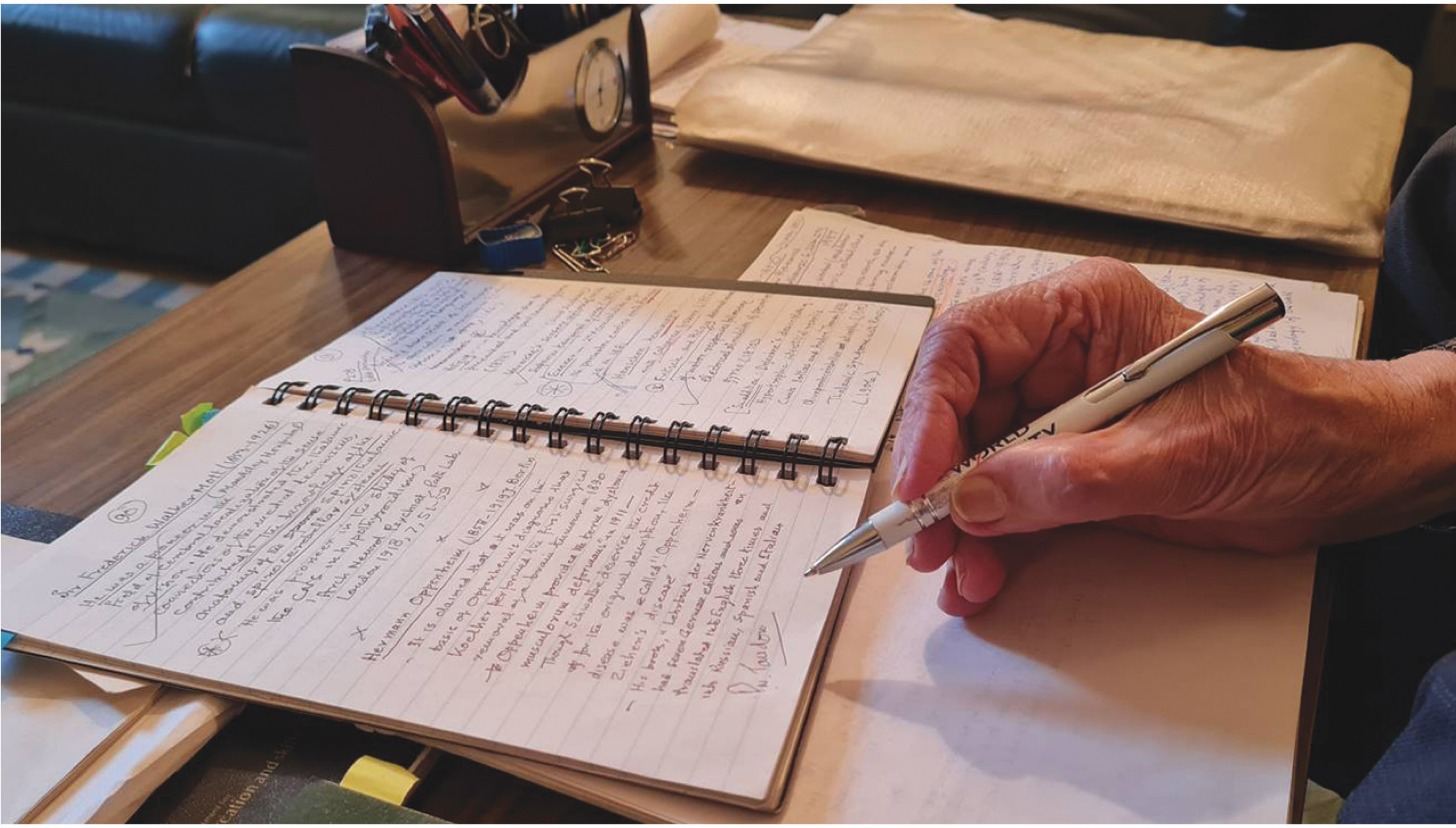
Evolution of Neurosciences

PN Tandon and P Sarat Chandra



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EVOLUTION OF NEUROSCIENCES:

A HISTORICAL REVIEW WITH BRIEF BIOGRAPHIES OF SOME OF ITS SELECTED PIONEERS

"To look into the future, one must first delve into the past"

PREFACE

Newton when asked why he was so great said, "I was not so great, I was standing on the shoulders of giants' '. This deceptively simple reply, reflecting the humility of one of the greatest scientists ever, has many deeper messages like his simple, yet immensely meaningful mathematical equations. It is a reminder to new generations of young scientists the invaluable contributions of their predecessors, often overlooked in the excitement and preoccupation with the "recent advances' '. Acquaintance with the earlier works not only prevents us from repeating it but also shows us the path for future advancement.

Having had the privilege of being mentored by some of greats of the twentieth century and also an opportunity of interacting with many more of them from across the globe – Scandinavia, Canada, USA, UK and most of the European countries aroused my interest in the evolution of neurosciences and biography of pioneer neuroscientists. This interest was vetted further by visits to some of the citadels which gave birth to path breaking discoveries in the field. To name a few I not only worked in some such places e.g. the Ullevål Hospital in Oslo, the Montreal Neurological Institute in Montreal, the Karolinska Institute in Stockholm NIH in Bethesda and several others, I had shorter exposure to the laboratories (and home) of Ivan Pavlov, in St. Petersburg; National Hospital Queen Square, London the Charite in Berlin where greats like Virchow and Koch worked, the Massachusetts General Hospital and Institute & The Peter Bent Brigham Hospital in Boston, several others in Moscow and Kiev and others in France, Germany, Holland, Hungary, Poland, B Wien and Italy. I looked for the traits of the pioneers and their milieu of work to learn some lessons for guiding my future work. Now that I had some time from my formal professional responsibilities I decided to attempt this 'Monograph' which may stimulate the present generation in expanding the horizon of their work in the broad field of neuroscience. The Monograph consists of brief account of the prehistoric era of "Brain Research'' in the UK, Europe and India, The enunciation of the major landmarks – The Neuron Hypothesis:the Synaptic Doctrine:The Ionic Theory of nerve conduction, the attempts at the Functional Localization in the Brain including Gross Anatomy, Histology, Cytoarchitectonics, the Electrical Exploration of the CNS, contributions of Chemical Transmission, the role of Neuronal Circuits. The application of recent advances in Neuroimaging – MRI, fMRI, MRS, Magnetoencephalography in exploring human cognition provide a glimpse of the most recent advances in the field. A brief summary of some of the clinician's contributions to basic neuroscience is included.

This is followed by bibliographic notes on some of the pioneers and path breakers from prehistoric era to recent times. As mentioned elsewhere the Monograph does not reflect a linear temporal account of evolution in various path breaking developments in neurosciences and is not encyclopedic in its exposition. However, it is more detailed and supported by a large number of references and suggested reading material compared to most Biographical memories referred to in the text.

We hope that it would prove to be an interesting 'Source Material' and stimulate further research to answer the many yet unanswered mysteries of what is referred to "as the last frontier of ignorance" – the Brain in particular and Nervous System in general.

P N Tandon

P Sarat Chandra

FOREWORD

While learning the art and science of medicine, we cannot undermine the value of learning history. It is only from history that we can chart our road to the future. Perhaps, no one is more qualified to provide a treatise in this subject in the field of neurosciences other than Prof Prakash Narain Tandon along with Prof P Sarat Chandra.

There is very little that I can speak about Prof. Tandon, the Doyen of Indian Neuroscience, as much is already known about him, and words fail me in this regard. He has received his medical education at K.G. Medical College, Lucknow. He received training in Neurosurgery in Oslo, Norway, and Montreal, Canada. After moving back to India, he started the first academic Neurosurgical Unit in Lucknow. Then he established the first Neurosurgical department at the All India Institute of Medical Sciences (AIIMS), New Delhi. He played a pivotal role in establishing the National Brain Research Centre, in which he served as its Founding President. He is currently one of the most honored neuroscientists in the country. The awards bestowed upon him (including Padam Shree, Padam Bhushan, Padam Vibhushan, and several others) speak less than his contributions to neuroscience and neurosurgery. I had the pleasure and honor of discussing various aspects of neuroscience and interacting with Prof. Tandon on numerous occasions at AIIMS and in multiple meetings and conferences.

I would also like to highlight the contributions of the other author of this book and my colleague Prof. P Sarat Chandra. Prof. Chandra is currently a senior Professor in the Dept of Neurosurgery at the All India Institute of Medical Sciences (AIIMS), New Delhi, for the past 24 years. He was the best outgoing student of his batch in MBBS (MKCG Medical College, Berhampur). Prof Chandra completed his neurosurgical training at the reputed NIMHANS, Bangalore, and then joined AIIMS as a faculty in 1998. In the past 24 years, I note that he has accumulated vast surgical experience (>25,000 cases), published more than 500 papers, and was awarded multiple research grants, awards, and patents. In addition, I note that he is currently the Editor of Neurology under the aegis of which this book is being published. I would like to mention that I enjoy interacting with Prof Chandra whenever possible. He has been a member of several committees at ICMR and has especially helped us create the ICMR-DHR policy on biomedical innovation and entrepreneurship.

This collection describes the seminal contribution of several neural scientists that led to the evolution of neuroscience to its current form as we know it today. The authors have provided the neuroscience right from 570 BC in the introductory chapter. Part A of Chapter 1 describes the work and contribution of ancient Greek philosophers such as Hippocrates, Plato, and Aristotle. Hippocrates is credited with proposing that the brain was an organ of thought and sensation. In the Renaissance era, Da Vinci provided performed anatomical preparation of the nervous system and produced elaborate drawings of the optic nerves. Part B of Chapter 1 describes the contribution of ancient Indian philosophers, physicians, and surgeons to medical science. Charaka described the mind to be a separate entity from the body. The philosophical description of the mind-body relationship is also described in Vedas and Upanishads, the earliest source of this knowledge. The progress made so far and selected biographies of renowned neuroscientists make the content of the other six chapters in this exciting collection.

Chapter 2 describes the works of Robert Remak, Franz Nissl, Ramon y Cajal, and Camillo Golgi in neural science. The neuron Hypothesis by Cajal is considered a pivotal event to set off the era of modern neural science. Chapter 3 describes the works of Charles Sherrington, John Eccles, Bernard Katz, Eric Kandel, and others, which collectively led to the Synapse Hypothesis. Finally, chapter 4 mentions the post-World War-II era of neural science, describing the works of Huxley, Hodgkin, Kenneth Cole, etc. These and the creation of many others established that action potential and nerve propagation had a basis in ion permeability changes.

Part A and B of Chapter 5 sequentially and gradually introduce the works of many neuroscientists, particularly cell biologists, who provided great insights into neural anatomy. Employing histology and electrophysiology, these scientists elucidated the mechanisms of neurotransmission. Carlsson & colleagues were strong proponents of chemical neurotransmission. The chapter further describes how the works of Foerster & Penfield provided valuable information on brain connection between regions and behaviors to establish a Connectome. Further advancements in visualizing techniques led to the development of MRI, fMRI, NMR, and CT for studying the brain.

Chapter 6 is an interesting short chapter describing the Clinician's contributions. It opens with a profound remark made by Gordon Holmes stating that "The search for knowledge of normal function through the study of disorders produced by disease has distinguished neurology during the 60 or 70 years of its existence as a separate specialty…." It then goes to describe a list of pioneers. The authors have noted with a sense of humility that this list is not complete. Those included here would serve as an example of how a very busy clinician with a scientific attitude could contribute some path-breaking knowledge about the structure and function of the nervous system.

Chapter 7A describes the works of several scientists, starting with Thomas Willis, who is credited with laying the foundation of neuroanatomy. Luigo Rolando proposed that the mid-brain was not just a connection between the brain and spinal cord but a vital center regulating the basic function of life. Purkinje first provided an adequate description of myelinated fibers, nerve cells, and nuclei. Virchow provided the first description of perivascular spaces. Brocca was the first to identify the motor speech area. Charcot provided extensive knowledge on cerebral localization and neuropathic joints. Meynert was the first to perceive brain research as an interdisciplinary project and focused on the histology of the cerebrum and brain stem. The work of Jackson covered a diverse field, including epilepsy, speech, and localization of brain functions. The contribution of Hitzig paved the way for the rapid expansion of the field of neurophysiology. In addition to developing staining techniques for nerve cells, Golgi's other contributions include the discovery of Golgi sensory and motor neurons. Though he shared the 1906 Nobel with Cajal, he was a strong opponent of him and rejected Cajal's Neuron Theory. In addition to being a strong proponent of the Neuron Theory, Cajal proposed the unidirectionality of neural signals. Kraepelin's theory formed the basis of the diagnosis of psychiatric disorders.

Along with Cajal, Sherrington introduced the concept of the Synaptic Hypothesis. Nissl uncovered till then, unknown Nissl granules in the nerve cells. Alzheimer's contribution includes clinicopathological approaches to brain diseases such as senile dementia. Among numerous contributions of Cushing, his work had extensive literature such as Tumors of the Nervous Acoustics, Syndrome of the Cerebello, Intracranial Tumors, and Meningiomas. Dale identified acetylcholine and its action as a neurotransmitter. Hortega used silver sodium carbonate staining to describe microglia and oligodendroglia. Adrian demonstrated that all neurons use the exact signaling mechanism, i.e., action potential.

The most prominent work of Penfield included epilepsy, and he identified temporal lobe epilepsy as the most common form of epilepsy. Eccles established the ionic mechanism through which motor neurons generate the inhibitory and excitatory action potentials that permit them to serve as the final common pathway for neuronal integration. Montalcini discovered the first neurotrophin, the nerve growth factor (NGF). Katz found that synaptic receptor for chemical transmitters was ligand-gated and NOT voltage-gated. Along with Huxley and Katz, Hodgkin provided a quantitative account of the ionic currents during the action potential. Huxley's work on giant squid neurons led to the Ionic Theory of nerve conduction. Mountcastle's most path-breaking work was the documentation of the columnar organization of the cortical neurons. Hounsfield's work on automated pattern recognition led to the idea of the development of the EMI and CT scanner. Wiesel worked on the information processing in the visual system and received the 1981 Nobel along with Rogen Sperry. Kandel was awarded a Nobel prize in 2000 for his immense contribution to the field of signal transduction in the nervous system.

Chapter 7B again is a very interesting treatise providing brief biographical notes on William Harvey, Franciscus Sylvius, Jacob Augustus Lockhart Clarke, Silas Weir Mitchell, Wilhelm His, Gustaf Magnus Retzius, Walter Halbrook Gaskell, Constantin Von Monakow, Ludwig Edinger, Alfred Walter Campbell, Prof Oskar Vogt to name a few. Excluding a few, most names are less known, but reading the biography, one immediately comes to know their contribution and is also able to understand the disease or structure named after them. The biography of each is hardly a paragraph, but sums up their contribution in a well readable text.

The annexure at the end provides a text of oration of Prof PN Tandon given at the All India Institute of Medical Sciences. Though the oration was on the topic "Neurons to behaviour", it provides an historical insight of all the people who contributed towards the development of neurosciences. I would also encourage the readers to also look at Table 1, recent advances and future trends, and finally have a look on reproduction of the article on Neurosciences in India: An overview.

I have found the book very different from any other, which provides information on history. It is more like a story book allowing the reader to grasp history as it happened. At the same time, providing extensive information for reference. I daresay that this book will become a classic over a period of time.

In the end, I want to congratulate Prof. Prakash Narain Tandon and Prof. P Sarat Chandra, the authors of this important book demonstrating an exciting historical evolution of the field of neuroscience. The result of their efforts will help neurosurgeons, neurologists, and neuroscientists to understand the history of neuroscience.

I will strongly recommend that this book should become an essential piece of acquisition for every resident and faculty.

In the future, I am sure that we will see a collection of chapters on the evolution of neuroscience in India.

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ACKNOWLEDGEMENT

The material for this monograph has been collected over many years. Biographical information has been culled from books by Webb Haymaker, Earl Walker, S. Finger, MNI (Montreal Neurosciences Institute) foundation day address, Medicine: An Illustrated History, Nobel Prize: Neuroscience (1906–2004), Wikipedia, and so forth. We gratefully acknowledge them. During the past couple of years, a large number of papers on related subjects have been studied. We would also like to thank Prof. Pankaj Seth of the National Brain Research Center (NBRC) and its library for helping us in providing the required reprints and its other published material. We also thank to Kuldeep for converting my handwritten script into computer soft copies. We also acknowledge the support received from AIIMS, New Delhi; the National Academy of Sciences; and the National Brain Research Center (NBRC) for support for academic work post superannuation. Thanks to my wife for providing a supportive environment for pursuing this work.

Special thanks are due to Neurology India and its editor-in-chief, Prof P Sarat Chandra, for converting the draft into a beautiful monograph.

Prof PN Tandon (Author)

It has been my deepest honor and pleasure to work with Prof P.N Tandon in compiling this manuscript. The experience was truly enriching and enlightening.

Irish statesman Edmund Burke is often misquoted as having said, “Those who do not know history are destined to repeat it.” Spanish philosopher George Santayana is credited with the aphorism, “Those who cannot remember the past are condemned to repeat it,” whereas British statesman Winston Churchill wrote, “Those that fail to learn from history are doomed to repeat it.”

Lessons from the past may not always ward off doom, but they can provide insights into the present and even the future.

History has been one of Prof Tandon’s favorite topics, maybe because he has witnessed its development of neurosciences in not only India but also the world over. He was the integral part and leader along with Prof AK Banerji toward the development of the premier neurosurgical department in the country (AIIMS, New Delhi) and then instrumental in developing the research institute par excellence (National Brain Research Center). He has witnessed history-, the development of micro-neurosurgery, the first description of Rasmussenencephalitis at MNI, the first-ever CT scan to mention very few. He saw the landscape of neurosurgery change over years. He has worked closely with some of the greatest ever legends—Wilder Penfield and Hans Pia to name a few.

I enjoyed every minute of my interaction with Prof Tandon, who is a teacher of my own teachers. Going to his home every 2–3 weeks, sitting with his carefully written notes, and discussing with him all the historical anecdotes left me with a sense of awe, amazement, and humility. Not to forget the lunches that I would have with him and madam Tandon completed the fulfilment of this experience of writing this book with him.

There have been several people who have helped despite the busy schedules, and I would particularly like to thank Dr Simranjit Singh, Dr Kota Ravi Chandra, and Dr Nihal Ahemad.

My acknowledgement of gratitude would not be complete if I cannot thank my wife, Dr Manjari Tripathi, who appreciates the importance of my work and pushes me forward; my daughter, Prarthana, who has found love in joining us in this profession; and of course my wonderful parents (Smt Dr. Suvarna Devi and Late Shri Dr. Venugopal Rao), without whom none of this would have been possible.

This book is a must for every neurosurgeon, neurologist, and neuroscientist not only to understand how we reached where we are today but also to appreciate the immense hard work and sacrifices put in by our pioneering fathers (and mothers) to bring us to this day of development. I have often seen the newer batches of residents giving less and less importance to history. I find that even the more senior faculty do not give too much importance to history as they feel that it would do nothing much to contribute toward their professional skill or clinical practice.

However, it is from history that one learns new things for it is here we already find so many roads traveled by seasoned travelers….
It is here where we do not feel alone as we find many Masters traveling with us and showing new roads to explore….
It is here where we find singularity between our profession, our personal lives, and life itself…
I do hope that this book becomes a medium for you to undertake this journey into the future by looking into the past.

P Sarat Chandra, (Author)

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"What is past is prologue" - William Shakespeare

The word "neurologie" first appeared in the translation of the Thomas Willis book "Cerebri Anatome: Cui Accessit Nervorum Descriptio et usus," published in 1664 and translated in English by Samuel Pordage in 1681, reprinted in 1971. The term 'neuron' was coined in 1891 by Waldeyer.

"According to UNESCO, neurosciences is a new discipline that comprises both the biology of the nervous system and the sciences of man and the society, together with the "hard sciences" (mathematics, physics) ranging from the most theoretical and abstract aspects of medical, technological, and industrial approaches". Indeed, there are few areas of knowledge that do not touch upon neuroscience.

The sciences of the nervous system, not to be confused with neuroscience, did not see the light of day until the late 19th century with the combined development of "physiology, histo-anatomy, and clinical anatomical science".[1]

Neuroscience research is a continuum of study from the molecular level to the behavioral level. It encompasses the body of research directed toward understanding the molecular, cellular, and inter-cellular processes mediated through electrochemical signals in the nervous system, integrated to subserve behavior.[2]

Penfield quoted, "I see the field of neuroscience as quite broad, including virtually any activity that contributes to an understanding of the biological basis of mental activity, regardless of species, in health and diseases."

According to Vernon Mountcastle[3], "It is possible to identify at least eighteen disciplines whose concept, methods, and practitioners tend towards union in the current panorama of the brain sciences."

According to the theory of evolution, enunciated by Charles Darwin in 1859, evolution occurs by the process of natural selection of the fittest'. This applies not only to the biological systems but also as a metaphor for the whole knowledge system. Thus, Gerald Edelman coined the word 'neural Darwinism,' implying that the brain grows similar to the Darwinian hypothesis by multiplication and selection. Taking this analogy further, in the context of the subject of the present book, it may be justified to say that neurosciences (like other sciences) evolved gradually, selecting from among multiple different approaches utilized to explore it. Robert Scott Root Bernstein of Michigan State University, Michigan, USA, in his book "Discovering" did precisely this. He made an explicit analogy between evolution and scientific discovery itself; ideas descend, with modification from teacher to apprentice. They proliferate, and a few are selected. New "species" of ideas arise and spread to replace the old ones. Ideas compete for acceptance. Even mass extinctions can sweep through science; not only a new hypothesis but also the development of new tools and techniques of investigation are often responsible for this selection (or advancement) and hence evolution.

Like evolution, the progression of science is not linear. Mutations are random; hence, development is not predictable and not deterministic.

In contrast to the evolution of the biological system being a natural process, development in the knowledge system is human-made. Although serendipity occasionally plays a role in it, more often than not, it is the result of a relentless pursuit of an individual or a group. It requires the awareness of the existing knowledge, a keen desire to advance it, a commitment to pursue this with determination against odds and failures, willingness to seek help, and sharing experience with peers with an open mind.

Having been interested in neuroscience and, to some extent, having witnessed its development (evolution) over more than half a century aroused the senior author's interest to learn more about how it happened and who were responsible for it. Over the years, the author made several attempts to gather this knowledge, record it, and acquire some of the resources for this purpose. The more one learned, the more one got interested. Finding spare time during the "Second Career" (post-superannuation) prompted me to summarize this knowledge so that others who are busy in their professional lives can spare their valuable time to share this excitement. We must acknowledge that this is not an encyclopedic work nor even a comprehensive one. Although we have attempted to include the significant critical milestones, others might have chosen differently.

Similarly, the pioneers, whose biographic information has been provided, are not necessarily the only ones contributing more to this evolution. To some extent, the choice has been subjective and dependent on the availability of information. This has led to the inclusion of relatively brief biographies of an equal number of others, no less important. Intentionally, a list of several publications (books and papers), including some not personally pursued by the author, are included. We also acknowledge that we have accessed all the information through primary and secondary sources. To the extent possible, we have cited them. It may be emphasized that at some places, reliance has been placed on notes of lectures and personal diaries.

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A brief note on "Ancient Neuroscience."

Part A: Greek Period (Pre-Hippocratic Medicine)

Pythagoras (570–495 BC): Pythagoras, the philosopher–scientist/founder of a "school with profound influence on early medicine", was born on the island of Samos, just off the coast of Asia Minor, but migrated to Crotona in southern Italy [**Figure 1A**]. He formed a school of philosophy and a religious cult focussed principally on the soul and the spiritual universe based on the science of numbers.

Around this time, other "Schools" of medicine developed in neighboring regions, Sicily, Rhodes, Cnidos, and Cos. However, Crotona remained the most famous philosophical center. Hippocrates founded the famous medical school on Isle of Cos in the 5th century BC.

Alcmaeeon: A young member of the Crotona school (possibly around the 5th century BC) was **Alcmaeon** [**Figure 1B**]. His book "Concerning Nature" may be the beginning of Greek medical literature. Works by several later writers – especially **Aristotle** – are the principal source of Alcmaeon. He (Alcmaeon) believed that investigation (including dissection), not just philosophy, was needed to understand the body. His combination of direct observation and experimental testing stands out as a unique feature of his time. Although many remarkable facts emerged from his dissections (probably on animals), his most notable contribution was establishing the connection between the sense organs and the brain. Even the optic nerves and their chiasm (crossing) were de-lineated.

Furthermore, he concluded **that the brain was the organ of the mind**, perceiving sensations and responsible for thought and memory. It is remarkable to note that a century later, Aristotle, one of the most outstanding philosopher scientists in history, disagreed entirely with Alcmaeon, believing that the heart was the center of sensation. Several historians have suggested that the breadth of his (Alcmaeon) detailed examinations and rational concepts opened a new view on acquiring medical knowledge**. He can be called virtually the first medical scientist.**

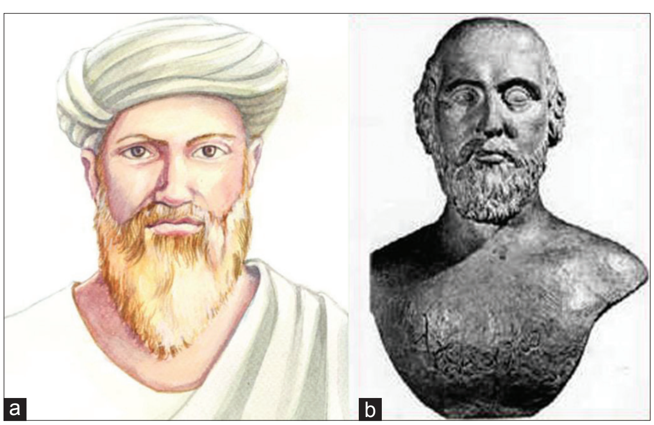

Figure 1: (a) Pythagoras (570-495 BC), (b) Alcmaeon

Five hundred years before Christ, human anatomy as science was begun in southern Italy by Alcmaeon of Crotona, who performed dissections upon animals. Shortly after that, a practical text from the Hippocratic school described the anatomy of the shoulder. Aristotle alluded to anatomical illustrations. In the 3rd century BC, the study of anatomy was advanced considerably in Alexandria, where many discoveries can be attributed to **Herophilus** (325–255 BC) and **Erasistratus (**304–250 BC). They were the **first to perform human dissections** systematically.

Medicine in Hippocratic Times: In attitude toward mental disease, the Greeks, like other people, showed a gradual evolution from belief in the super-natural demoniac cause to a more rational explanation. By the 5th century BC, several philosophers believed that the mind and its derangements were located in the brain. However, even Plato, a contemporary of Hippocrates, classified madness mythologically into four main types: prophetic (mediated by Apollo), ritualistic (as in Dionysian ceremonies), poetic (inspired by muses), and erotic (under the influence of Aphrodite and Eros).

Hippocratic principles of observation, experience, and prognosis: The works of Hippocrates titled "Corpus Hippocraticum" were assembled in the 4th century BC at the great library in Alexandria, Egypt. The total number of works in the collection has been variously estimated. Several historians have claimed that the books number about 72 and the total number of treatises to about 59.

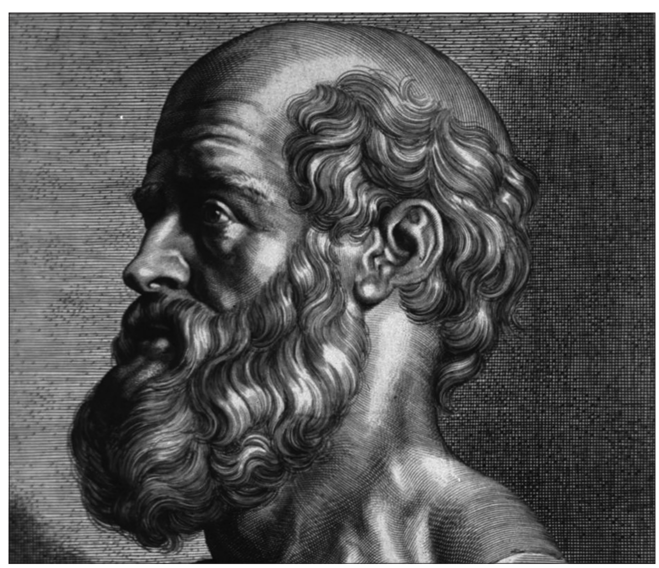

Figure 2: Hippocrates (460–370 BC)

Ptolemy, one of Alexander's generals, established the Alexandria library, and he intended to collect the entire sum of human knowledge in the multi-storied library. The library which got destroyed has recently been developed again and is a source of immense documented history of contributions of Egyptian scholars in all fields of knowledge.

Hippocrates (460–370 BC):

He is credited with being the first to propose that the brain was an organ of thought and sensation. Organic diseases such as epilepsy and delirium tremens and derangements such as depression and anxiety were discussed with perspicacity **[Figure 2]**.

Plato (428–348 BC): He was a contemporary of Hippocrates, a student of Socrates, a teacher of Aristotle. His interests lay mainly in the nature of soul and matter, and his medical speculations – logical but without direct experimentation – led to several faulty conclusions about the human body **[Figure 3A]**.

Aristotle (384–322 BC): The son of a physician and pupil of Plato profoundly influenced medicine, especially among the Arabic authors. In addition, his writings illuminated an extraordinary number of knowledge fields—logic, metaphysics, psychology, politics, zoology, poetry, and drama **[Figure 3B]**.

Aristotle's methods were based on careful investigations of both animals and humans.

Besides embryology, to which he made significant contributions, as far as the nervous system is concerned, his writings on the anatomy of vertebrates and invertebrates were so extensive that they earned him recognition as the **founder of comparative anatomy.**

It is reported that Aristotle had said, "nature does nothing without a purpose." Galen insisted, "he could perceive the purpose".

Galen (129–210 AD): Galen's hometown of Pergamum happened to be the site of a large shrine to the healing God, Asclepius, which Galen's father claimed to have had a dream about, leading Galen to start studying medicine. Galen contributed a substantial amount to the Hippocratic understanding of pathology **[Figure 4]**. Under Hippocrates' bodily humors theory, differences in human moods come as a consequence of imbalances in one of the four bodily fluids: blood, yellow bile, black bile, and phlegm.

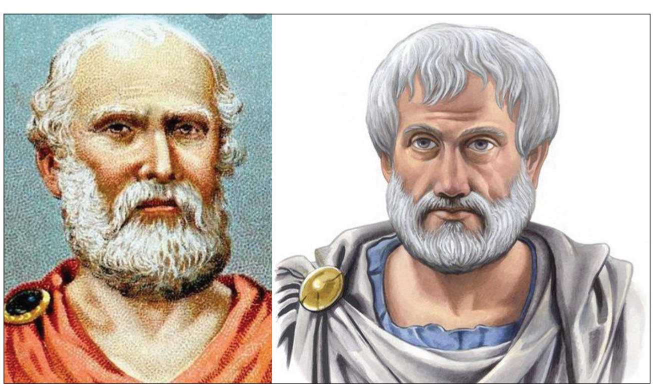

Figure 3: (a) Plato (428–348 BC), (b) Aristotle (384–322 BC)

Galen promoted this theory and the typology of human temperaments. In Galen's view, an imbalance of each humor corresponded with a particular human temperament (blood – sanguine, black bile – melancholic, yellow bile – choleric, and phlegm – phlegmatic). Many theorists, such as Galen, believed that sickness came from within the body and that the best way to treat an imbalance was by bleeding, enemas, and vomiting. However, the practice of bloodletting is no longer used today. Galen's principal interest was in human anatomy, but Roman law had prohibited the dissection of human cadavers since about 150 BC. Because of this restriction, Galen performed anatomical dissections on living (vivisection) and dead animals, mostly focusing on primates. This work was useful because Galen believed that the anatomical structures of these animals closely mirrored those of humans. Galen clarified the anatomy of the trachea and was the first to demonstrate that the larynx generates the voice. In one experiment, Galen used bellows to inflate the lungs of a dead animal. Galen played a major role in the discoveries of the central nervous system. He was also able to describe the nerves that emerge from the spine, which is integral to his research about the nervous system. Galen went on to be the first physician to study what happens when the spinal cord is transected on multiple different levels. He worked with pigs and studied their neuroanatomy by severing different nerves either totally or partially to see how it affected the body. He even dealt with diseases affecting the spinal cord and nerves. Although his work demonstrated inevitable anatomical inaccuracies, his research was integral to the future advances in knowledge about the spinal column, vertebrae, and spinal cord. Galen was a skilled surgeon, operating on human patients. Many of his procedures and techniques would not be used again for centuries, such as the procedures he performed on brains and eyes.

Paracelsus (1493-1541): Paracelsus concluded that the human body was a chemical machine and hence popularized the use of minerals instead of Galen's reliance on plant medicine. It is reported that Paracelsus burned the works of Avicenna and

Figure 4: Galen (129–210 AD)

Figure 5: Leonardo da Vinci (1452–1519)

Figure 6: Rene Descartes (1596–1650):

Figure 7: Franz Joseph Gall (1758–1828)

Galen to symbolize the need to rely on one's own observations rather than authorities.

Michelangelo Buonarroti (1475–1564): Michelangelo, in his Sistine ceiling paintings, revealed his keen interest in anatomy (1511). He spent years in the careful dissection of human bodies. In addition, he devoted at least 12 years in earnest pursuit of anatomical knowledge through personal dissection.

Leonardo da Vinci (1452–1519): Leonardo da Vinci was the first artist to consider anatomy for reasons beyond its practicality in depicting the human form **[Figure 5]**. Leonardo made anatomical preparations from which more than 750 are extant, representing the skeletal, muscular, nervous, and vascular systems. His scientific accuracy was greater than that of Vesalius, and his artistic beauty remains unchallenged.

Most of these illustrate the skeleton and the limb muscles, but one of these in the World Health Organization (WHO), Geneva, shows a sagittal section of the skull, depicting the eye, the optic nerve, and three intra-cranial vesicles.

Andreas Vesalius (1514 – 1564): His illustrated **book on anatomy "De Humanis Corporis Fabrica" (1543)** is considered one of the most outstanding books in the history of man. Born in Brussels and educated in Paris, he completed his medical school in Padua in northern Italy. He wrote of his surprise at finding numerous errors in the works of Galen.

Rene Descartes (1596–1650):

Descartes' "Discourse on Method," published in 1637, supported a generalization of the mathematical method and developed a mechanistic picture of the world [**Figure 6**]. For Descartes, "all natural objects were machines ruled by mechanistic principles". Philosopher–scientist Descartes' most famous drawing (Soul in Pineal) in the Treatise of Man and the Passions of the Soul shows that he was not aware of the crossing over optic nerve fibers to the opposite side of the brain.

Franz Joseph Gall (1758–1828): Franz Joseph Gall was a clinician born in Germany and educated in France and Austria and practiced and lectured in Paris for 20 years. He taught that the shape and irregularities of the skull were projections of the underlying brain and consequently of a person's mental characteristics, a conclusion with no basis. Gall's concept of localizing

cognitive functions was a good idea, but his uncritical exaggeration carried it too far.

However, the very notion that the brain is a composite of discrete but interrelated functions anatomically confined to specific areas, an old but incompletely realized concept, was a principle that was to become the basic tenet of brain physiology and was designated as phrenology.

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Part B: Ancient Indian Contributions

As far as recorded knowledge goes, the earliest instances of rational medical knowledge are to be found in the Rig Vedas and Atharvaveda, both 2nd millennium BC. However, the medical knowledge of pre-Aryan Indians has been mixed, diluted, and absorbed into the Ayurvedic system, which is the oldest well-documented system of health sciences in India and is called Ayurveda. It has been called the "Science of life". The two most well-known proponents of this system are Charaka and Susruta **[Figure 8A and B]**; the former was a physician, and the latter was a surgeon. Their treatises are called 'Samhita', which dates to 2nd century BC.

As far as systematic well-studied and documented knowledge about life science is concerned, it is to be found in many treatises belonging to Ayurveda. The two most erudite proponents of this system are Caraca (also spelt Caraka or Charak), a renowned physician and author of "*Charaka Samhita*," and Susruta, who was the author of "*Susruta Samhita*." Both relied a great deal on empirical observations and analysis. Susruta was probably the first person who resorted to the dissection of the human body, which he considered "the only means of acquiring accurate knowledge of anatomy." This was much before the time of Hippocrates, who did not practice dissection. It was, in fact, Hirophilus, a century after Hippocrates, who resorted to the dissection of the human body and thereby earned undying fame in Europe.[1] Surprisingly, Susruta, who provided detailed information of the rest of the body, did not study the brain. This is attributed to the circumstances in which the bodies for dissection were procured. Caraca regarded the mind (*manas*) as a separate sense (*indriya*) with its object (*artha*) defined as thought. It was, however, considered more than other senses as a conductor of the "Symphony of Senses." In its absence or distraction, pleasure and pain are not felt, nor are different sensory experiences registered. According to him, the mind is a self-complex integrative basis of all sensory experience, motor actions, and life itself. He seems to consider 'Soul 'or 'self' as different from the mind. Not surprisingly, a lot has been written on these subjects in both the Vedic literature and Ayurveda. Another ancient treatise, Bhagavad Gita (Ch. 3.42), states, "Sensory organs are endowed within a body; sensory organs are controlled by the mind; the mind is censored by intellect and intellect by Self (*Atman*)". Brain–mind–consciousness relationship remains an unsolved problem for both for the scientists and the philosophers and even today.

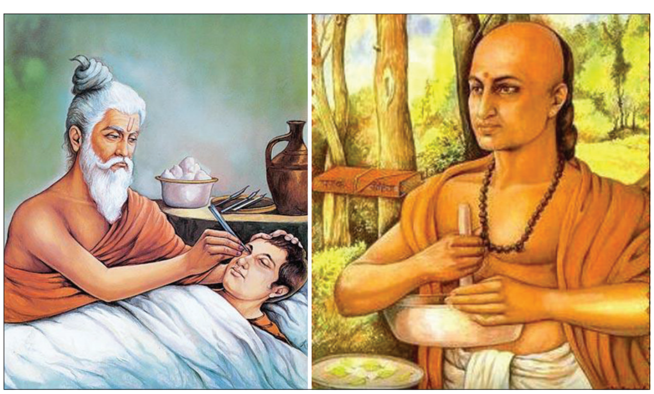

Figure 8: (a) Susruta (800–700 BCE), (b) Charaka (400–200 BCE)

According to Ayurveda, the functions of the brain can be summarized as follows:
Place of soul *(Aatma)*
Center of consciousness *(Chetana)*
The seat of special senses *(Pancha Jnanendriya)*
A storehouse of intellect *(BudhiMedha)*
Seat of sub-conscious mind *(Chitta)*
Storehouse of memory *(Smriti)*
Center of life *(Seevita)*
Regulation of sleep *(Nidra)*
Seat of emotion and passion *(Ragas)*
Center of 'Ego' self-consciousness (Ahankand)[2]

The mind–body relationship has been intensely investigated (philosophically) in Vedas and Upanishads, especially the Kathopanishad (c. 9th century BC). It has been metaphorically described as riding a chariot: known as the soul *(atman self)*. The body is known as the chariot, with the intellect *(buddhi)* as the chariot driver and the mind *(Manas)* as the reins. Katha Upanishad (Katha Upanishad 1.3.3) described the *atman*, that is, self, as the chariot owner and the body as the *buddhi*, the discriminating intellect. The senses are the horses, and the objects are the destination.

The Upanishads maintain that consciousness evolves in each individual from the physical plane to the vital plane and from the vital plane to the mental plane, at which most humanity lives. Some individuals, however, can rise above the mental plane of creative intelligence (*buddhi*) and then that of bliss (*Ananda*).[3]

The Tattriya Upanishad (II 1–5) explores the mind–body relationship using the simile of five sheaths of the mind and the body:
Annamaya Kosha, "food stuff sheath" *(Anna)*
Pranayama Kosha, "energy sheath" *(Prana/apana)*
Manomaya Kosha, "mind-stuff sheath" *(Manas)*
VijnanmayaKosha, "Wisdom" sheath (Vignana)
Ananda maya Kosha, "Bliss" sheath (Anand)

Majumdar[4] in a detailed write-up on Ayurveda, particularly Susruta, proposes, "Thus every living being a complex aggregate in which *Karampura* remains united with a material body, mind, sense organs, and motile organs contributed by the 24 *tattvas **and** Prakrti*." Hence, all living organisms have a soul associated with them, a mind composed of the three real egos (three humors: the counter-parts of the cosmic principles of air, dry heat, and moisture), and a material body composed of five gross elements.

The Susruta Samhita contains six sections, dealing with fundamental postulates, pathology, embryology and anatomy, therapeutics and surgical treatment, toxicology, and a final section on subsequently gained and specialized knowledge of topics dealt with in earlier sections. Susruta describes more than 300 different operations employing 42 different surgical processes and 121 different types of instruments. Among the various operations described here is the mention of serious head injuries with exudation of brain matter (as well as the removal of the fetus by craniotomy).

According to Charaka (400 BCE to 200 CE), the mind is a constituent of the individual. Single and subtle, it serves to connect the self to the sense organs and their objects. Thus, it plays a crucial role in the acquisition of knowledge by individuals.

The mind is the controller of the sense organs and the instrument for reasoning and critical analysis. The mind is active and devoid of consciousness.

It is the self that endows the mind with consciousness. The intellect is at the frontier of the mind. Its operations are tailored to all the sense organs whose data it uses.

Most Western scientists, searching for historical perspectives on scientific research, turn to Greek writings (mentioned above). However, some of the Indian thoughts concerning medical and health sciences antedate these. Although a lot of ancient literature, such as the Greek one, has been lost, a great deal, at least from the Vedic era (approx. 3000 BC), is well preserved. It is hard to say how much of this knowledge was empirical or primarily philosophical. In respect to neuroscience, this was no doubt most early philosophers devoted to subjects such as “Mind,” “Mind–body relationship,” and “Consciousness.” Because these subjects continue to attract the attention of even modern neuroscientists, a brief mention of this is included here.

Upanishads and Vedas are the earliest sources of this knowledge; only a few extracts from these sources are quoted below:

Mandukopanisad describes four states of consciousness: awake *(jagriti)*, dreaming *(swapna)*, deep sleep *(susupti)*, and non-dual or thoughtless *(turiya)*. On the other hand, Taittiriyo Upanishad classifies consciousness differently into the physical *(anna-mayakosa)*, the psychic (*manomaya kosha*), and the “bliss” consciousness (*anand-mayakosa*). In some other treatises, Indian mystics and sages who composed the Veda have referred to the sub-conscious, the transcendental, and the mystic. Rig Veda and Atharvaveda provide similar observations.

Interestingly, several distinguished Western scientists such as Voltaire, Schrodinger, Humboldt, Whitehead, Einstein, Bohr, Capra, and Campbell have frequently referred to writings in Upanishads. A reflection of similar thoughts is found in the writings of Charles Sherrington, Roger Sperry, and Wilder Penfield.[3]

It is well recorded that dissection of the human body for surgical knowledge was first initiated by Susruta, who considered this the most important and the only means of acquiring accurate knowledge of anatomy. As mentioned earlier, it was not practiced even in the school of Hippocrates. As a matter of fact, Herophilus, one century later, restored to the dissection of the human body and thereby earned an undying fame in Europe.

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The Neuron Hypothesis

The first microscopic image of a nerve cell has been attributed to Valentine, one of Johannes Evangelista Purkinje's students. He obtained the image of a nerve cell with its nucleus and nucleolus in 1836.

Two years later, Robert Remak (1815–1865) demonstrated the myelinated and unmyelinated axons. Finally, Franz Nissl (1860–1918) developed the staining technique, which showed the granules in the nerve cells, which are now called Nissl granules. However, the term "neuron" was coined by Wilhelm von Waldeyer Hartz in 1891. During his lecture, Cajal acknowledged Camillo Golgi (1843–1926) developing the silver chromate method of staining nervous tissues in 1873. Initially, between 1870 and 1871, Golgi had studied neuroglia of cerebral gray and white matter [**Figures 9 and 10**]. Cajal, initially working in a small Spanish town virtually isolated from the scientific world, modified Golgi's staining technique. In 1889, he demonstrated his silver impregnated sections before a meeting of the German Anatomical Society at Berlin, presided over by Prof. Rudolf Albert von Kolliker, The Patriarch of German Histology. The latter has been reported to have remarked, "I have discovered you, and I wish to make my discovery known in Germany".[1]

It was only after this that Cajal became known outside Spain. Based on his extensive studies on different regions of the brain of different species at various stages of development, Cajal proposed the "Neuron Doctrine," which contradicted the so-called "Reticular Theory" proposed by Golgi in 1873 and earlier proposed by the German histologist Josef von Gerlach in 1871. Although Golgi believed that the neurons formed a network by anastomosis of axonal fibers, Cajal observed that neurons are discrete cells bounded by membranes and inferred that nerve cells communicate only at specialized opposition points. Charles Sherrington later named these "synapses".[2] Furthermore, Cajal observed that the termination and collateral fibers in the gray matter did not form a diffuse network but remained free, establishing simple contacts with the neuronal cell body and the dendrites of the adjacent nerve cell **[Figure 11]**.

Interestingly, Golgi and Cajal in their Nobel Lectures in 1906 insisted on their contradictory observations, elaborating the "reticular" and "neuronal" doctrines, respectively. In a paper published in 1917, Cajal referred to this discrepancy as "what a cruel irony of fate to pair, like adversaries of such contrasting character.".[1]

Golgi's concept of "convergence" or "anastomosis" of the neuronal processes was already being challenged by His, Kuhna, and Nansen in 1887[3] In a series of papers, Cajal in 1894, 1906,[4] and 1911 highlighted the idea that the neuron was the functional unit of the nervous system. In sharp contrast to Golgi's view, they are discrete cells.[2] Cajal pointed out that the dendrites serve as an input for the neurons, and the axons serve as the output elements. These observations were based on a large number of exquisitely beautiful and faithful drawings of a large number of histological slides from a variety of brains, personally sketched by him (a recent publication, "The Beautiful Brain"). The drawings of Santiago Ramon Y Cajal have made these illustrations more than a century old available to us.[5] One can only admire the clarity and beauty of these figures based on his observations using a relatively poor microscope then available to him. What is even more remarkable is that in these 'static pictures,' based on histological preparations of the fixed nervous tissue, he could visualize dynamic features such as polarization, that is, the unidirectionality of neuronal signals.

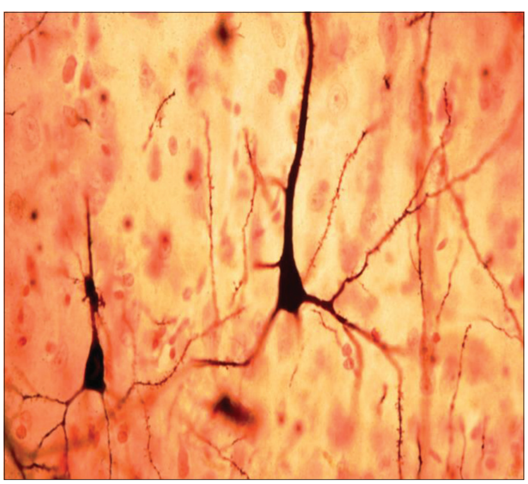

Figure 9: Golgi stained pyramidal cells from layer 3 of the cerebral cortex of a cat. Background neutral red stain. Courtesy: Mitch Glickstein,Golgi and Cajal: The neuron doctrine and the 100th anniversary of the 1906 Nobel Prize,Current Biology,Volume 16, Issue 5,2006)

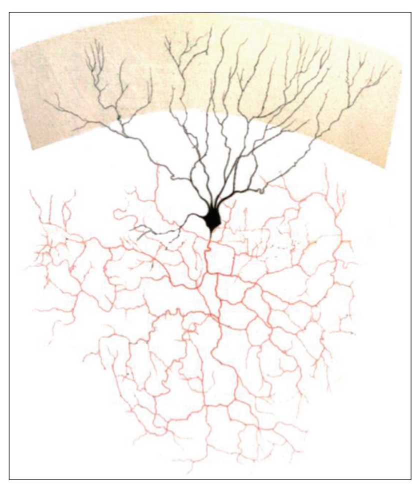

Figure 10: Golgi's drawing of a cerebellar type 2 cell, now called a Golgi cell. The axon remains confined to the vicinity of the cell body. Courtesy: Mitch Glickstein,Golgi and Cajal: The neuron doctrine and the 100th anniversary of the 1906 Nobel Prize,Current Biology,Volume 16, Issue 5,2006)

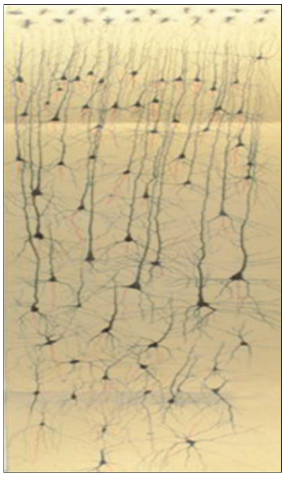

Figure 11: Golgi's drawing of the cell types of the human cerebral cortex. Golgi divided the cortex into three laminae—a superficial layer with small pyramidal cells, a middle layer with large pyramidal cells, and a deep layer with fusiform cells. (**Figure 9, 10, 11 Courtesy:** Mitch Glickstein, Golgi and Cajal: The neuron doctrine and the 100th anniversary of the 1906 Nobel Prize, Current Biology, Volume 16, Issue 5, 2006)

He thus claimed that "neurons generate electrical signals and were responsible for many functions of the brain, receiving sensory inputs, processing this information, storing memories, learning, and controlling out muscles."[5]

It has been reported that it was Sir Charles Sherrington's visit to Cajal which led to a lasting friendship between them and evolution of the "Synaptic Doctrine"[6] (see also Synaptic Doctrine).

According to Albright *et al*.,[2] "Modern neural science, as we know it, began at the turn of the century (20th) when Santiago Ramon y Cajal provided the critical evidence for the neuron doctrine." Sir Charles Sherrington called Cajal "The greatest anatomist of the nervous system ever known."

Lopez–Munoz *et al*.[7] considered "Neuron theory (as) one of the principal scientific conquests of the 20th century, and which has withstood, with scarcely any modifications, the passage of more than 100 years, being re-affirmed by new technologies, as electron microscopy. Today, no neuroscientific discipline could be understood without recourse to the concept of neuronal individuality and nervous transmission at a synaptic level as basic units of the nervous system."

Historical milestones to the development of the Neuron Hypothesis

1836: First microscopic image of a nerve cell (Valentine)
1838: First visualization of axons (Remak)
1855: Consolidation of cell theory (Virchow)
1862: First description of the neuromuscular junction (Kuhne)
1865: Definitive postulate of the reticular hypothesis in the structure of the nervous system (Gerlach)
1871: Introduction of silver-chromate technique as the staining procedure (Golgi)
1886/87: First discrepancies with reticular theory pointed out (His, Nansen, Forel)
1888: Birth of neuron doctrine: the nervous system is made up of independent cells (Cajal)
1889: Dissemination of neuron therapy at the German Anatomical Society Congress (Cajal)
1891: The term "neuron" was coined (Waldeyer), Defence of the physiological significance of the "diffuse network" theory (Golgi)
1892: Laws of dynamic polarization of neurons (Cajal)
1897: Concept of synapse (Sherrington)
1803: Introduction of silver nitrate as the staining technique (Cajal)
1906: Nobel Prizes for Cajal and Golgi.

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The Synaptic Doctrine

Charles Sherrington (1857–1952)[1] used the term “synapse” in 1897. He elaborated it in his famous book, “The Integrative Action of the Nervous System,” published in 1906. It has been stated that the idea probably took its root when he visited Ramon y Cajal in Spain nearly a decade earlier. The latter had enunciated the “Neuron Doctrine” around 1890. Bennett[2] has provided a detailed history of the origin of the synapse concept “from the time of Plato to Sherrington.[1]” In Foster’s Textbook of Physiology, 7th edition (1897), Sherrington stated, “So far as our present knowledge goes, we are led to think that the tip of a twig of the arborescence is not continuous with, but merely in contact with, the substance of the dendrite or cell body on which it impinges. Such a special connection of one nerve cell with another might be called ‘Synapsis.’ On another occasion, he had suggested the term ‘syndesm.’ Interestingly, Foster, the editor of the textbook, consulted his friend Verrall, a classical scholar from the Trinity College who finally suggested the term “synapse,” which was then adopted in the book.[2] According to Sherrington, “synapsis” strictly means a process of contact, that is, a proceeding or act of communication rather than a thing that enables contact.

The important message is that information transfer from a neuron through its axon to a dendrite or a cell body of another neuron occurs at the contact point where a gap exists. This was a confirmation of Cajal’s earlier observation.

Working with Sherrington, John Eccles (1903–1997), using recently developed electrophysiology techniques, studied synaptic transmission in the central nervous system (CNS), sympathetic ganglion, and smooth and cardiac muscles.

Later in New Zealand, in collaboration with Bernard Katz (1911–2003), he developed micro-electrode recording of intra-cellular activity. This enabled them to elaborate on the bio-physical properties of synaptic transmission, resulting in the identification of the excitatory and inhibitory synapses. Sherrington’s other contemporary, John Langley, provided some initial evidence that at most synapses, signaling between neurons in synaptic transmission was chemical in nature. It was mediated through neurotransmitters. Thomas Elliott, a young graduate student of Langley, was responsible for providing the experimental evidence. (For historical details of the work of Elliott, see Rubin[3]). This was further elaborated by Otto Loewi, Henry Dale, William Feldberg, Julius Axelrod, and Von Buler. Katz received the Nobel Prize in 1970 for establishing the release of neurotransmitters from nerve terminals at the synapses. It was thus established that synaptic transmission depends upon the release of a transmitter from the active pre-synaptic nerve terminal into the synaptic cleft. This acts upon the post-synaptic cell membrane. Historically, the discovery of the chemical nature of synaptic transmission begins with the hypothesis of Elliot derived from his studies on the action of adrenaline upon the de-nervated muscle in 1904. This continued with discoveries of acetylcholine and adrenaline at the peripheral autonomic and neuromuscular synapses by Otto Loewi, Henry Dale, and their colleagues during 1914–1936.[4] During the 1960s and 70s, several amino acids, peptides, and other molecules, such as norepinephrine, acetylcholine, serotonin, dopamine, and so forth, were identified as neurotransmitters. With the advent of molecular biology, there has been a further elaboration of the chemical processes at the synapse. In the later part of the 20th century, the diversity of different neurotransmitters became large and complex. As a result, chemical maps of the brain are now available.[5]

On the other hand, working on Aplysia, Eric Kandel[6] observed synaptic changes paralleling the behavioral changes during habituation, sensitization, and classical conditioning. He further elaborated the molecular basis of memory. He found that short-term memory storage required covalent modification of pre-existing synaptic connections. In contrast, long-term memory storage requires gene activation, new protein synthesis, and the growth of new synaptic connections. His book[6] provides a lucid and comprehensive overview of development in neuroscience during the 20th century.

More recently, we have witnessed a whole new concept of synaptic functions, contrary to the well-established paradigm that nervous system functions result from neuronal network activity, that is, the flow of information between pre- and post-synaptic neuronal elements. Numerous studies have established that astrocytes are integral functional elements of the synapses. They exchange information with the neuronal synaptic elements, responding to synaptic activity and, in turn, regulating synaptic transmission. Thus, the term ‘tripartite synapse [**Figure 12**]’ refers to a concept in synaptic physiology based on the demonstration of bi-directional communication between the astrocytes and neurons.[7]

Figure 12: Scheme of the tripartite synapse representing the transfer of information between neuronal elements and

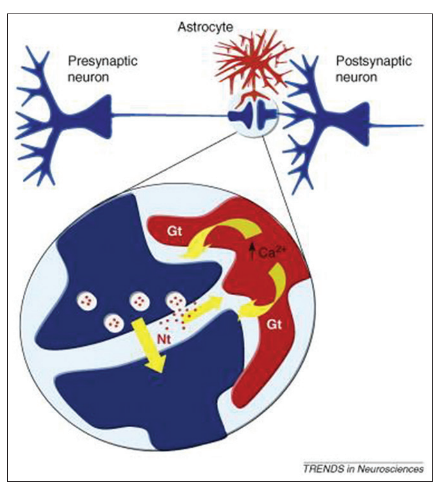

Figure 12: TRIPARTITE SYNAPSE

astrocytes at the tripartite synapse. Astrocytes respond with Ca^{2+} elevations to neurotransmitters (Nt) released during synaptic activity and, in turn, control neuronal excitability and synaptic transmission through the Ca^{2+}-dependent release of gliotransmitters (Gt) [Figure Courtesy[7]].

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Ionic Theory of Nerve Conduction

Soon after the Second World War, from 1946 onward, Andrew Fielding Huxley (1917–2012), Alan Lloyd Hodgkin (1914-1998), and Bernard Katz (1911-2003), working together at Cambridge, UK, explored the physiological basis of nerve conduction including the action potential. They used the squid giant axon for this purpose. They provided a quantitative account of the ionic currents during the action potential. This resulted in the path-breaking ionic basis of action potential proposed by them in 1952. According to Albright *et al*. (2000),[1] the ionic hypothesis proposed by them remains one of the most profound insights in neurosciences. "It accomplished for the cell biology of neurons what the structure of DNA did for the rest of biology." The trio demonstrated that the resting potential and the action potentials depended on the movement of the specific ions Na, K, and Cl through the axonal membrane. Motor neurons generate the inhibitory and excitatory action potentials that permit them to serve as the final common pathway for neuronal integration (Albright *et al*., 2000).[1]

Action Potential: Action potential is the rapidly propagated electrical message that speeds along the axons of the nervous system and over the surface membrane of many muscles and glandular cells. In axons, they are brief, travel at a constant velocity, and maintain a constant amplitude. Similar to all electrical messages of the nervous system, the action potential is a membrane potential change caused by the flow of ions through the ion channels in the membrane.

The membrane potential is defined as the inside potential minus the outside. At rest, the membrane potential is negative. The stimulus initiates an action potential that propagates to the end of the axon. The stimulus must make a supra-threshold membrane de-polarization.

The response is sharp all-or-none (further de-polarization) activity and the stereotyped action potential. Action potentials propagate electrically (and not chemically, as believed earlier). Hodgkin in 1935 argued that de-polarization spreading passively from an exciting region of the membrane to a neighboring unexcited region is the stimulus for propagation.

Cole and Curtis[2] demonstrated that ion permeability of the axon membrane increases during the propagated action potential. Soon after, Hodgkin and Huxley (1939–1945)[3] measured the full action potential with an intra-cellular micro-pipette. It was then established that the membrane becomes selectively permeable to Na^+ ions because of the action potential.

It was thus concluded that there is an exceedingly thin cell membrane, one whose ion permeability is low at rest and much higher during activity. At the exact moment, as the permeability increases, the membrane changes its electromotive force and generates an inward current to de-polarize the cell sodium ions, which are the current carriers. The currents generated by the active membrane are sufficient to excite neighboring patches of the membrane so that propagation, like excitation, is an electrical process.

Thus, based on the work of Alan Hodkings, Andrew Huxley, and Bernard Katz in Britain (and Kenneth Cole and Howard Curtis in USA; 1935–1952), electro-physiologists became convinced that all electrical signals and action potentials, synaptic potentials, and receptor potentials had a basis in ion permeability changes. Thus, during this period, the ionic theory of membrane excitation was transformed from an untested hypothesis to an established fact.

Studies of the action potential establish the critical concept of the ionic hypothesis. These ideas were proven and given a robust quantitative basis using the voltage-clamp technique (introduced by Marmont[4]) by Hodgkin, Huxley, and Katz.[5] They further elaborated these studies using other ions such as K^+, Ca^{2+}, Cl^-.

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Functional Localization in the Brain

A: Gross Anatomical studies

One of the exciting research areas in neuroscience, ever since the recorded history, has been finding specific brain areas involved in special functions. Beginning with the Greek philosopher-scientists Hippocrates (c. 460 BC), Plato (429–347BC), Aristotle (384–322 BC), and Galen (2nd century AD), the initial efforts were to find the seat of "Soul," "Spirit," and "Anima" in the brain. This appears to continue even up to the period of the European Renaissance with contributions from Andreas Vesalius (1514–1564) and Rene Descartes (1596–1650). Andreas Vesalius (1514–1564) published his well-illustrated book on anatomy, "De humanis corporis Fabrica", in 1593. It is considered one of the most outstanding books in the history of man. It may be pointed out that the acknowledged father of modern medicine, Hippocrates, and his school did not practice dissection of human bodies to learn about anatomy. Herophilus and Erasistratus, a century after Hippocrates (c. 3rd century BC), systematically resorted to the dissection of human bodies. Alcmaeon, a member of the Crotona School (Italy), around 5th century BC, is reported to have advocated that investigation (including dissection), not just philosophy, was needed to understand the body. His most important contribution was establishing the connection between the sense organs and the brain.[1]

In contrast to this, Susruta, the founding father of surgery of the Ayurvedic system of medicine, practiced dissection of human cadavers for gaining accurate anatomical knowledge and described in detail the method of preparing a corpse for this purpose.[2] However, the very practice of procuring and preparing the cadaver for dissection failed to provide an opportunity to study the brain.

Thomas Willis (1621–1675) attempted to provide an improved description of the brain's gross anatomy. It would be a unique distinction for any author to achieve what Willis achieved. His most famous book (published in Latin, then the language of anatomy), "Cerebri Anatome: Cui. Accessit Nervorum Descriptio et usus," was published in 1664 and translated in English by Samuel Pordage in 1681 and re-printed in 1971 in 23 editions. He revolutionized the brain's anatomy and not only the Circle of Willis, for which he is known even today. He challenged many of the currently taught anatomical texts written at least 100 years earlier. It is said that "Cerebri Anatome" was in use for 200 years. It contained a description of the brain, the spinal cord, and the peripheral and anatomic nervous systems. Dr. Wilder Penfield wrote the "Foreword" of the tercentenary of this book in 1956.

Willis is credited for coining several neuroanatomical terms, for example, anterior commissure, cerebral peduncles, corpus striatum, medullary pyramid; inferior Olive, Vagus nerve, and nervous ophthalmicus. He recognized that the medulla oblongata regulated the vital functions of the heart, lungs, and intestines. He is reported to be aware of the concept of nerve impulse and reflex action. The seat of higher cognitive functions was ascribed to the cerebral cortex against the prevalent view of Galen, who attributed the animal "Spirit" in the ventricular system to be the source of all intellect.[3] Rene Descartes (1596–1650), another renowned philosopher-scientist of the Renaissance era, dominated the field. He considered the body and the soul as two distinct entities and localized the interaction between the two to the pineal gland. His most famous drawing depicting this concept shows that he was not aware of the crossing over of the optic nerve fibers to the opposite hemisphere.

According to Charles Sherrington,[4] "Thomas Willis practically re-founded the anatomy and physiology of the brain and nerves. He collated bedside observations with anatomical facts. Willis put the brain and the nervous system on their modern footing so far as it could be performed then. It may be mentioned that William Harvey (1578–1657), also from Oxford, had earlier described the continuous circulation of blood within a contained system around 1635 under the title "Exercitatio Anatomical de Motu Cordis et Sanguinis in Animalibus" (On the Movement of Heart and Blood in Animals).

Surprisingly, the authors of the two landmark structures concerning the gross morphology of the brain, that is, the Sylvian Fissure and Rolandic Sulcus, find hardly any mention in the standard books on biographies of neuroscientists. Their brief biography published in the Journal of Neurosurgery has therefore been included in this book (see under Biographies).

Apart from some good gross description of various brain regions several microscopic descriptions surprisingly even as late as the latter half of the 19th century and early years of the 20th century, the search for the site of soul continued [Constantin von Monakow (1853–1930)] to be made throughout Europe. Some of the well-known histologists are Johannes Purkinje (1787-1869), who described the flask-shaped ganglionic cells in the cerebellum later called Purkinje Cell; Camillo Golgi (1843–1926), who published his classical work, "Sulla Fina anatomia degli organi centrali del Sistema Nervosa", in 1885–86; Carl Weigert (1854–1904), who developed the stain for myelin; and Ludwig Edinger (1855–1918), who described the Edinger Westphal nucleus (1885) and the ventral and dorsal spinocerebellar tracts.

Constantin von Monakow (1853–1930), a Russian, who settled in Zurich, studied histology and embryology under Herman Meyer and later worked as an assistant to Hitzig; working with Gudden in Munich, he demonstrated secondary atrophy of the anterior corpora quadrigemina after enucleation of an eye in a cat. He showed that the optic nerve took its root from the ganglion cells in the retina. He studied the nuclei of the thalamus and their projection on the cortex. Among several other anatomical structures he studied was the rubrospinal bundle.

Franz Nissl (1860–1918), in addition to the now well-known Nissl granules in the nerve cells and his work on the pathology of Alzheimer's and other diseases, also worked on the cortico-thalamic projection system in the developing cortex of new-born rabbits. Thus, he contributed to some aspects of cytoarchitectonics. Another outstanding pioneer and visionary of that era was Theodore Meynert (1833–1892), an Austrian neuroscientist considered to be the founder of cytoarchitectonics and cortical localization. According to Seitelberger,[5] all subsequent cytoarchitectural studies rest on Meynert's pioneering observations (see later under cytoarchitectonics). Thus, Meynert has been acclaimed as one of the founding fathers of scientific neurology. However, knowledge of the anatomy of the nervous system was rudimentary in the middle of the 19th century. Nevertheless, Meynert contributed a great deal to it. His first paper, published in 1861, soon after his MD, focused on fibers connecting the frontal cortex with the brain stem. He traced the motor tracts (the pyramidal tract) descending from the cerebral cortex to the spinal cord and the sensory tracts ascending from the spinal cord to the post-central gyrus.

In addition, he is credited to have described major projection fibers, which include dorsal tegmental decussation and nucleus basalis, the habenulo-peduncular tract, the fibers from the superior colliculi to oculomotor nuclei, the dorsal supra-optic commissure, the lamina of pyramidal cells in the cerebral cortex, and the solitary pyramidal cells in the calcarine cortex. Those who worked with him as students, followers, and collaborators include distinguished neuroscientists such as H. Obersteiner, G. Anton, C. Mayer, A. Forel, Von Gudden, H. Waldeyer, L. Edinger, Carl Wernicke, and Paul Flechsig. Even Sigmund Freud is reported to have worked with him for a short time as a trainee. Finally, in 1868, he published a comprehensive work on "The Cerebral Cortex."

August Forel (1848–1931) (Swiss neuroscientist), trained under Meynert in Vienna, worked on the thalamus opticus of mammals for his doctoral thesis. Later working in Munich under Gudden, he published important papers on the tegmental region, describing the tegmental fields, the zona incerta, and various other structures. Oskar Vogt worked in his laboratory on two different occasions.

Magnus Retzius (1842–1919), a Swedish comparative anatomy expert, worked on the membranes and cavities of the nervous system along with Axel Key. Experimentally and by dissection, he established the existence of the foramina of Magendie (discovered in 1825) and the foramina of Luschka (discovered in 1859). He proposed that the cerebrospinal fluid (CSF) escapes from the sub-arachnoid space through the Pacchionian body into the venous system.

Two individuals in this era, both working in the field of nerve supply to the involuntary muscles, heart, viscera, bladder, and bowel, deserve special mention.

John Langley (1852–1925), a student of Sir Michael Foster (and a teacher for Sir Henry Head), beginning his research on the regeneration of nerves, ultimately got interested in the autonomic nervous system, "a term" he introduced in 1898. He had also introduced the terms pre- and post-ganglionic nerves (1893). A few years later, in 1905, he coined the term "parasympathetic system." Remarkably, three of his students, Sherrington, Dale, and Adrian, were awarded the Nobel Prize (but not he!). He single-handedly edited one of the most prestigious journals of neurosciences, the Journal of Physiology, for 30 years. The second one of this duo was Walter Holbrook Gaskell (1847–1914), educated at Trinity College, Cambridge. Later, a faculty member of the University established the histological foundation of the autonomic nervous system upon which Langley expanded. He mapped the nerve supply to visceral organs, including the cardiovascular system. His exhaustive publication on the subject is considered a landmark of the investigation of the sympathetic nervous system, as is his book "The Involuntary Nervous System".[6] Otto Loewi (1873–1961), a German pharmacologist, stimulated by the discovery made by Langley and Gaskell in the UK, discovered the chemical transmission of nerve impulses, that acetylcholine was the substance *(Vagusstoff)* involved with the parasympathetic system, and that a substance closely related to adrenaline played a corresponding role at the sympathetic nerve endings. For these studies, Loewi got the Nobel Prize, along with Henry Dale, in 1936.

Walter Hess (1881–1973), a practicing ophthalmologist who gave up his successful practice, became a Director of the Physiology Institute at Zurich. He worked on the central coordination of vegetative organs. He localized this function to the diencephalon, for which he received the Nobel Prize in 1949 along with Egas Moniz.

Solomon Eberhard Henschen (1847–1930), a Swedish physician, Professor of Internal Medicine at Upsala, carried out fundamental studies on the projection of the retina on the calcarine cortex. He is credited to have proved that hemianopia is because of a lesion involving the region of the calcarine fissure (1892). He also worked on auditory, gustatory, and olfactory pathways and aphasia, amusia, agraphia, and acalculia[7] in addition to his well-known studies on spinal reflex, decerebrate rigidly, and the physiology of "synapse." Sherrington (1857–1952) also studied the optic nerve of the rabbit, the sympathetic nervous system of the monkey, and the nerve supply to the bladder and anus.

Fredrick Walker Mott (1853–1926) from Maudsley Hospital, London, is considered a pioneer in cerebral localization of the sense of vision. He also demonstrated the thalamic connections of the medial lemniscus and contributed to the knowledge of the anatomy of the spinothalamic and spinocerebellar systems.

Ludwig Edinger (1855–1918) described the Edinger-Westphal nucleus in the human fetal brain in 1885. Westphal demonstrated this in adults in 1887. Along with his students and colleagues, he is credited with describing for the first time structures such as the ventral and dorsal spinocerebellar tracts and phylogenetic development of the forebrain, striatum, and diencephalon.

Grafton Elliot Smith (1871–1937) was an English anatomist who worked in Cairo with Egyptian mummies for many years. He is reported to have prepared some 20,000 anatomic reports and published several books. His comparative analysis of the pattern of fissures of the brain formed the basis of understanding the phylogenetic changes in the surface topography of the brain.

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B: Histology

The human anatomy of the brain, briefly referred to in the previous section, had been taught in the medical schools since the time of Vesalius (1514–1564). However, histology of the brain could only be developed following the introduction of the powerful microscope by the German optical industry around 1830.

Although the classic publication of Shelden (1838) and Schwann (1839) had laid the framework of histology and cell theory, it was Virchow (1821–1902), the renowned pathologist from Charite in Berlin, who authoritatively pronounced the cells as the basic building block of all tissues in animals and plants. Purkinje (1787–1869), a Czech, obtained his compound microscope in 1832, which he used in his house to establish "a cradle of histology." In 1837, he presented a brief resume of his microscopic survey of the human brain to the German Men of Science and Medicine in Prague. At this meeting, he demonstrated the layers of cerebellum folia, which included a row of "flask-shaped" ganglionic cells, which later came to be known by his name, the Purkinje cells. In addition, this presentation is reported to have illustrations of other nerve cells with their nuclei and dendrites and myelinated fibers. However, it was Camillo Golgi (1843–1926) from Italy who, in 1872, working in his kitchen with the then rather primitive microscope and a few instruments and using candlelight at night, developed the chromate of the silver method for staining of the nervous tissue. These techniques and their future modifications by Cajal (1852–1934), Hortego (1882–1945), and Penfield (1891–1976) revolutionized the histology of the nervous system. Golgi (1843–1926) is thus credited to be the first person to stain an individual nerve cell in 1873, for which he got the Nobel Prize in 1906 (along with Cajal).

It is a historical fact that notwithstanding his outstanding contributions to neuroanatomy, he misinterpreted his observations and promoted the "Reticular theory" of neuronal organization, earlier proposed by the German histologist Josef Von Gerlach. He insisted on the correctness of his views even after it was unequivocally refuted by Cajal, who proposed the "Neuron Hypothesis" (see Chapter on the Neuron Theory).

Cajal (1852–1934), in 1887, 14 years after Golgi, introduced his staining technique and modified and improved it. In 1890 alone, he published 14 papers on the nervous system. However, most of these papers in Spanish and French, not well-known journals, failed to propagate Cajal's unique contributions. It was because of Cajal's presentation to a meeting of the German Anatomical Society at Berlin in 1889, presided over by Prof. Rudolf Von Koliker, the patriarch of German histology, that Cajal's research started to receive wider recognition.[1] Cajal then proposed the now universally acknowledged "Neuron Theory" in 1894 (see Neuron Theory and Cajal's biography). A recent publication of Cajal's drawings of his microscopic observations on diverse aspects of the nervous system, embryonic, fetal, and adult, of several species reflects his genius as a unique neuroscientist.[2] Besides concentrating mostly on neurons, Cajal made equally essential contributions on glia and synapses. He illustrated the relationship of the glial cells (mostly astrocytes) to the neurons, synapses, and blood vessels.

It is even more remarkable that besides the histological details of the cells of the nervous system, he could provide his insight into the physiological functions of these cells (see Cajal's biography).

Nicolas Achucarro (1880–1918), a pupil of Cajal in Madrid, Pierre Marie in Paris, and Kraepelin in Germany, delineated the various cell types in the human cerebral cortex using the silver tannate method of staining (1910).

Rudolf Albert von Kolliker (1817–1905) of Swiss origin, settled in Germany, was one of the leading biologists in the 19th century. He devoted himself to the study of the finer structures of the nervous system. The second volume of his "Handbuch der Gewebelehre Des Menschen," 6th edition (Leipzig, Engelmann, 1889–96), and his third volume of his "Mikroskopische Anatomie" (Leipzig, Engelmann, 18505–4) included his Golgi preparations, considered to be comparable to Cajal.[3]

Pio Del Hortega (1882–1945), a student of Cajal, later established his own laboratory in Madrid modified Cajal's stain and introduced the silver sodium carbonate method. Along with his student, Collado, he was the first one to describe "microglial cells" in detail.

Wilder Penfield (1891–1976), in quest of unraveling the histogenesis and pathology of the post-traumatic cortical scar responsible for epileptic seizures, went to Hortega's lab in Madrid. It was here that he modified the Hortega stain and produced the first clear and complete picture of oligodendroglial cells. Penfield later wrote chapters on Neuroglia and Microglia in "Special Cytology," edited by E.V Cowdry (New York, Hoeber 1928), and in Mc Lung's Handbook of Microscopical Techniques (New York, Hoeber 1928). He later edited the "Cytology and Cellular Pathology," three volumes (New York, Hoeber 1932).

Robert Remak (1815–1865), a Polish settled in Berlin, worked at Charite on the histology of the nervous system. He is credited to have discovered the non-myelinated fibers later called "Remak's fibers."

He also described the myelin sheath, which soon after in 1838 was elaborated by Schwann (1839). He was a pioneer in the study of the development of the neural tube. His students included William His (1831–1904) and Von Kolliker (1817–1905).

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C: Cytoarchitectonics

The initiation of cytoarchitecture is generally attributed to Theodore Meynert (1833–1892), who was Freud's teacher, himself a psychiatrist. In 1867, he first called attention to the regional differences in the cerebral cortex, surprisingly on the basis of rather poor histologic techniques. He provided details of the visual cortex, hippocampal formation, the olfactory lobe, and the septum pellucidum. This field was then actively pursued by a host of other neuroanatomists such as Campbell, Lewis, Eliot Smith, Kolicker, Von Economo, Cecil, and Oscar Vogt. However, with the comprehensive publication of the cortical cytoarchitectural map, Broadmann came to be known as a pioneer in this field.

The consistency of the cytoarchitectonic maps (of not only humans but also other animals) is evident from the following statement of Vernon Mountcastle: "As a result of these studies, the general position was reached that the transition from one cytoarchitectural field with different ones might be abrupt, that the changes occurred almost simultaneously in all the cellular layers, and that the transition could be marked with a line. It is remarkable that (these two) principles remain virtually intact more than a century after their discovery."[1]

Later investigations further confirmed the significance of these basic studies on cytoarchitecture. Thus Mountcastle added, "The intra-cellular injection of molecular markers has established the specificity of neuronal cell types in the cerebral cortex and other regions of the brain allowing direct correlation of their functional, biochemical, and morphological properties." Gerald Edelman (along with Mountcastle) further explored the problem of integrating multiple cortical areas.[2]

As mentioned earlier, the concept that mental activity arises through the action of the brain has been known from the pre-Christian era. Still, it was nearly a century ago that there was enough evidence that the brain is sub-divided into functional regions, each making a specific contribution to human behavior (see biographies of Broca, Wernicke, Korsakov). However, the available mapping of the entire cortex was catalyzed by Theodore Meynert, Alfred Walter Campbell (1868–1937), and Theodor Kaes (1852–1913) and completed by Korbinian Brodmann, Cecile, and Oskar Vogt in the early years of the 20th century. The following account summarizes the evolution of "Cytoarchitectonics."

As anatomy and histology progressed, the long-standing search for localizing functions to distinct areas of the brain was revived. Initially, Franz Joseph Gall (1758–1828), who was born in Germany and educated in France and Austria and later practiced in Paris, proposed that the shape and irregularities of the skull were projections of the underlying brain and consequently of a person's mental characteristics. Without any scientific basis, this promoted the cult of phrenology.

However, recognizing the variations in the histomorphology of different brain regions, it was expected to be related to functional localization.

Gerald Edelman has recently explained the developmental basis and functional significance of such cytoarchitectonic areas. He proposed that neuronal behavior groups are formed during development consisting of local collectives of strongly inter-connected neurons to share inputs, outputs, and response properties. Each group is connected to specific subsets of other groups and possibly to particular sensory afferents or motor efferents. In a given brain area, a different combination of groups is activated preferentially by specific input signals.

Generally, the ultimate credit for this research is attributed to **Korbinian Brodmann** (1868–1918). In 1901, he went to the Neurobiologische Institute in Berlin to work with Oscar Vogt, where he developed the science of comparative cytoarchitectonics. He provided the commonly used 'cytoarchitectonic' map with 50 distinct cortical zones devoted to specific functions in 1908. This was later elaborated in his book "Vergleichend Localisations Lehre der Grosshirnrinde," published in 1909.

It is interesting to note that Gerhardt von Bonin, a biographer of the Australian neurologist Alfred Walter Campbell (1868–1937), claimed that although some spadework had been performed, it is safe to say that architectonics of the cerebral cortex started with Campbell in England and Brodmann in Germany. His (Campbell) magnum opus, "Histological studies on the localization of cerebral function" (Cambridge University Press, 1905), has become a classic. He further claimed that although Brodmann mainly was a comparative morphologist and evolutionist, Campbell thought fundamentally of the neuronal function. Franz Nissl (1860–1918), working in Kraepelin's institute, "Deutsche Forschungsanstalt für Psychiatrie" at Munich, also initiated the study of cytoarchitectonics of corticothalamic projection.

Finally, Theodore Kaes (1852–1913), a German psychiatrist, published a series of papers between 1891 and 1904 on the myeloarchitecture of the human cerebral cortex based on a study of 45 human brains ranging from 3 months post-natal to 97 years. Although well recognized for their contributions to cytoarchitectonics, Vogt assigned a significant part of this work to Brodmann. At the same time, he studied the myeloarchitecture and published a series of papers on the subject. Others who contributed to this field were Strasburger, Braitenberg, Hopf, and Snides.

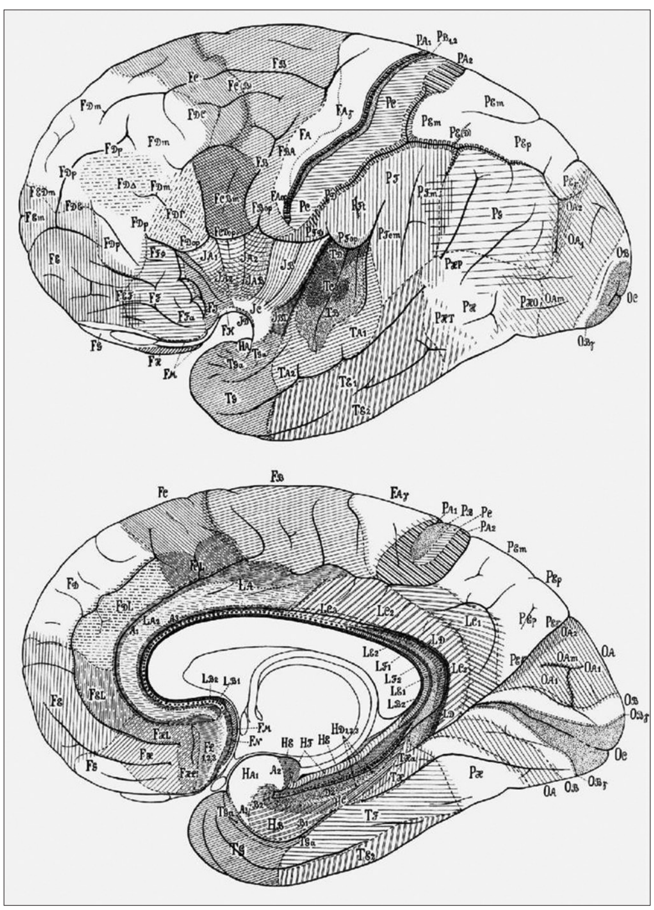

Figure 13: CYTOARCHITECTONIC MAPS

For more information, refer to a detailed review by Rudolf Nieuwenhuys from the Netherland Institute of Neuroscience (see suggested reading).

Paul Emil Flechsig (1847–1929) studied myelogenesis in the developing brain, discovered the auditory radiation, and based on the myeloarchitecture distinguished 36 cortical areas.

Elliot Smith (1871–1937), using Ballinger's stripes as a landmark, was able to distinguish some 40 sharply de-limited cortical areas using a hand lens (not even a microscope)

Constantin von Economo (1876–1931), a brilliant Austrian neurologist, started working on cytoarchitectonics of the adult human cortex in 1912. His comprehensive book on the subject "Die Cytoarchitectonic der Hirnrinde des erwachsene Menschen," Wien, Springer, was published along with Koskinas in 1925 [**Figure 13**].

However, the husband–wife couple Oskar (a German) and Cecile (a French) Vogt deserved much greater credit for developing the field of cytoarchitectonics. Max Bielschowsky, a neurocytologist, worked in their institute, "Kaiser Wilhelm Institute Fur Hirnforschung" in Neustadt in the Black Forest in southern Germany (Oskar was the Director of the Institute). He believed that one could detect a person's personality by anatomically determining the distribution of different types of nerve cells in different areas of the cortex. He attempted to do a comparative study of the brain of intellectuals using the brain of low-grade German criminals as the control. He was invited to Moscow to perform an autopsy and take away Lenin's brain for a detailed study.[3] Otfrid Foerster (1874–1941), a German neurologist who ultimately turned to neurosurgery, to which he contributed a great deal, also contributed to cytoarchitectonics. Although not enough details could be found, his biographer Robert Wartenberg informs us that during the Second International Congress of Neurology in London in 1935, Foerster was invited to deliver a lecture in commemoration of the 100th anniversary of the birth of Hughlings Jackson. His famous cytoarchitectonic map of the human cerebral cortex appeared as an article on the motor cortex in man in the light of Hughlings Jackson's doctrine.[4]

Nearly a century after the initial cytoarchitectural maps were made available and generally accepted, recent studies by Geyer *et al*.[5] and Glasser *et al*.[6] have presented a more detailed map, de-lineating 180 areas per hemisphere (compared to the conventional 50 areas of the Brodmann's map). This has been performed using multi-modal magnetic images of the Human Connectome Project and an objective semi-automated neuroanatomical approach. With the emergence of newer imaging techniques, especially magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and so forth, a large volume of information has accumulated, which has ascribed specific functions to different cortex regions. Cabeza *et al*.[7] have reviewed "Imaging of Cognition" based on 275 studies. (The present author has summarized the subject of "Human Cognition and the Frontal Lobe; Tandon,[8]). Zilles and Ammunks, in their paper, have reported receptor mapping of the MC cerebral cortex.[9]

Figure 13: The cytoarchitectonic map of von Economo and Koskinas, depicting their 107 cortical modification areas on the convex and median hemispheric facies of the human cerebrum. [Courtesy: The 1926 presentation by Georg N. Koskinas (1885–1975) to the Athens Medical Society].

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D: Electrophysiology and Electrical Exploration of the Central Nervous System

The relationship of electricity to study the function of the nervous system is an exciting story of how developments in an unrelated field of science could open unexpected vistas to explore a completely unrelated discipline. Electricity was first discovered as a form of energy in 1792. They initially called it animal electricity when Luigi Galvani in the University of Bologna and Alessandro Volta of Pavio realized that energy was being conducted along the nerve of a frog to its muscles and made this contract. However, nearly 80 years later, two German physiologists, Eduard Hitzig (1838–1907) and Theodore Fritsch (1838–1927), initiated the studies on the electrical excitability of the cerebral cortex of dogs in 1860. It is recorded that the initial studies were carried out on Hitzig's wife's dressing table. This was the beginning of a new era of study of brain physiology. The findings were published in 1870.[1] According to Penfield,[2] Hitzig defined the limits of the motor area in the cerebral cortex of a dog and monkey. Hitzig and Fritch stated that "They have found the place where the spirit enters the body."

It is reported that Robert Bartholow of Cincinnati, USA, was the first to apply electric current to the human brain in 1874. Unfortunately, further details on this are not available. Similarly, reference has been made to Guillaume Duchenne's work, a pupil of Laennec, Magendie, and Cruveilhier, who adopted Faraday's discovery of the induced electric current for the study of electrophysiology, electrodiagnosis, and electrotherapy. Remarkably, Cajal knew that neurons generate electrical signals which are responsible for the main functions of the brain, receiving sensory inputs, processing information, storing memories, learning, and controlling the muscles.[3]

However, this was his conjecture based on histological studies only. This was to be elaborated later by Hodgkin, Huxley, and Katz (see chapter on Ionic Doctrine).

However, Wilder Penfield (1891–1976) recognized the value of Hitzig's experiments in paving the way for the rapid expansion of neurophysiology. He utilized electrical stimulation of the cerebral cortex of conscious, cooperative patients undergoing surgery for epilepsy.[4] He believed that "the electrical stimulation that must be used to guide the surgeon in his removal of the cause of epilepsy would perhaps tell the thoughtful surgeon many secrets about the living functioning brain. This would help the neurosurgeon to understand the interrelationship of mind to localized mechanisms in the brain". He was thus able to localize different somatosensory, motor, psychic, and autonomic phenomena to specific regions of the cerebral cortex. His studies not only revolutionized the surgical treatment of epilepsy but also provided invaluable information on the localization of functions in the cerebral cortex (Penfield and Gage, 1933; Penfield and Boldrey, 1937; Penfield and Erickson, 1941; Penfield and Rasmussen,1950; Penfield and Kristiansen, 1951; Penfield and Jasper, 1954). This was the subject of several books and a large number of papers published by him and his colleagues and students.

This field of neurophysiology got a significant boost from the research studies of Sherrington (1857–1952), Adrian (1889–1977), and Eccles (1903–1997) (see chapter on action potential). Throughout the earlier years of the 20th century, most neurophysiological research was based on electrophysiology, electrically stimulating neuronal structures, and recording (cellular, extra-cellular, and intra-cellular) the response from the respective structures. In this environment, it is not surprising that Johannes Hans Berger (1873–1941), a psychiatrist by training, became interested in studying the physical basis of psychic functions.

He initiated the study of recording the brain's electrical activity through an intact skull, which was published in Archives of Psychiatry in 1929 and gave birth to electroencephalography

(EEG), one of the most useful diagnostic tools for neurological disorder in the 20th century and now forms a routine diagnosis for epilepsy.

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E: Chemical Neurotransmission

Neurotransmitters mediate the transfer of information from one nerve cell to another or from a nerve cell to an effector by the process of synaptic transmission.

The genesis of the concept of chemical synaptic transmission has been attributed to John Newport Langley. Langley, using adrenal medulla extracts (which presumably contained epinephrine and norepinephrine), found responses similar in different tissues to those induced by sympathetic nerve stimulation. Thus, Langley proposed in 1905 that a "receptive substance" was the action of chemical mediators liberated by nerve stimulation.

Around the same time, Paul Ehrlich in Germany was working on the mechanism of action of drugs and toxins. He proposed the concept of bindings of drugs to receptors and called these chemoreceptors.

Thomas Elliott, a student of Langley, expanded Langley's study on the effect of epinephrine and sympathetic nerve stimulation. He postulated that the "effector" stimulated by epinephrine was the "myoneural junction" and not the nerve endings or muscle fiber." This path-breaking work did not receive due recognition and was not pursued initially.

In the 1920s, it was the experiments carried out by Otto Loewi (1873–1961) and Henry Dale (1875–1968) that the debate regarding electrical versus chemical transmission across a synapse was decided in favor of the latter. The dramatic events leading to Otto Loewi's establishment of chemical transmission as a fundamental biological concept beginning on the night before Easter Sunday in 1920 were described in detail by Robin.[1] Loewi provided additional evidence favoring a similar mode of action for "Vagus-stoff", a substance which was later identified as acetylcholine (Ach).

Notwithstanding these elegant studies of Loewi, the controversy regarding chemical transmission continued until early 1930, until Henry Dale's work in London. Dale extended these studies to autonomic and motor nerve fibers and coined the terms adrenergic and cholinergic.

It is reported that the debate between Dale (a proponent of chemical transmission) and Eccles (a proponent of electrical transmission), at times harsh and acrimonious, continued for more than 20 years. At the same time, Dale studied the pharmacology of ACh and found its action similar to that of the alkaloid muscarine. However, it is believed that the physiological relevance of Ach was established by Otto Loewi a few years later. Henry Dale and Otto Loewi received the Nobel Prize in 1936 for their research on the chemical transmission of a nerve impulse. The historical background of "Professional rivalry between Langley, Thomas Elliott, Otto Loewi, and Henry Dale" has been described in some detail by Robin.[1] Julius Axelrod (1912–2004) and Raymond Ahlquist worked several years later to validate the concept of chemical transmission at synapses. Axelrod, along with Ulf von Euler (1905–1983), a Swedish pharmacologist, and Bernard Katz (1911–2003), received the Nobel Prize in 1970 for elaborating the humoral transmitters and their biosynthesis, action, and release inactivation in sympathetic nerves. It is surprising that beginning with the work of Langley and his associate Thomas Elliott in the early 1900s (1904, 1905), with the award of Nobel Prize to Henry Dale and Otto Loewi in 1936, it was only in 1970 that von Euler and Bernard Katz got the prize for work in the field of the chemical transmission of nerve impulses, especially those of the autonomic nervous system.

Obviously, during the interval, improved research methodologies such as intra-cellular recording, micro-iontophoresis on single cells, and fluorometric techniques for measuring the neurotransmitters undoubtedly helped better understanding the mode of action and possible clinical

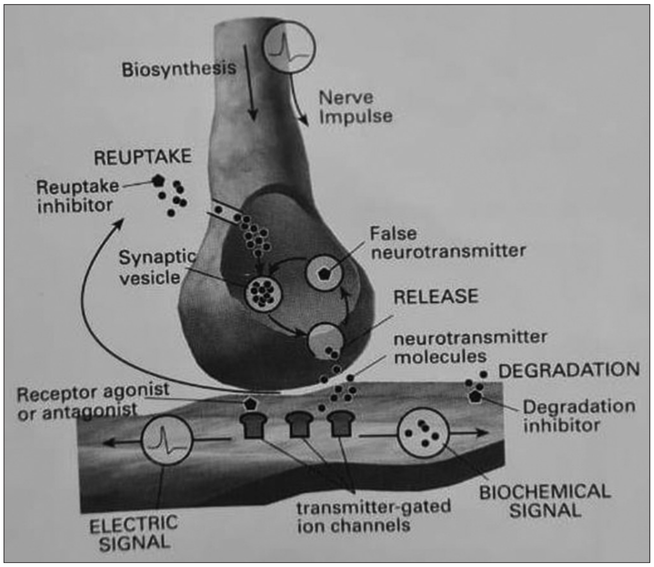

Figure 14: SYNAPTIC NEUROTRANSMITTER RELEASE

application. Needless to say, during these years, many others made valuable contributions in this field. Unlike Langley, Elliott, Loewi, and von Euler, **Arvid Carlsson**, a Swedish pharmacologist, established chemical transmission in the CNS around the 1950s.

Interestingly, Carlsson and his colleagues used reserpine on the rabbit adrenal medulla, heart, and brains and demonstrated the depletion of catecholamines in these tissues. (Reserpine has been known to the Indian System of Medicine to be anti-psychotic and anti-hypertensive). They also showed that administration of dihydroxyphenylalanine (DOPA) to reserpine-treated animals reversed the drug-induced Parkinsonism. (This was the beginning of research on the use of L-DOPA for treatment of Parkinson's disease).[2,3]

Notwithstanding the convincing evidence that this group favored chemical transmission in the CNS, several distinguished pharmacologists, including Dale, had strong reservations. However, after continued efforts, Carlsson, along with a number of his colleagues, established the methodology to localize dopamine, norepinephrine, and serotonin in the CNS and provided irrefutable evidence to overcome the criticism by distinguished colleagues. As a result, Carlsson was awarded the Nobel Prize in 2000, along with Paul Greengard and Eric Kandel for signal transduction in the nervous system.

During the 1960s and 70s, instead of the two classical neurotransmitters – acetylcholine and epinephrine, over 100 different neurotransmitters were identified. These include dopamine, serotonin, gamma aminobutyric acid (GABA), many amino acids, and peptides, each having a specific role and site of action.

More than 50 years after Langley's hypothetical "receptive substance" as the site of action of the chemicals liberated by nerve stimulation, the concept of "receptor" was formulated. This led to identifying a large number and sub-types of receptors that were ultimately utilized for developing specific agonists and antagonists for the therapeutic purpose (examples: B-adrenoceptor blocking agent, H2 receptor antagonist, etc.) [**Figure 14**].

Figure 14-Figure of synapse showing the mechanism of neurotransmitter release and re-uptake at the synaptic junction in response to a nerve impulse.

Courtesy: VB Mountcastle. Brain Science at the Century's Ebb, Daedalus; Spring 1998).

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F: From Neurons to Neural Networks

According to Spitzer,[1] Sigmund Freud was a pioneer in today's field called "neural network". However, it was a theoretical concept not supported by any empirical data. This was undoubtedly influenced by the quest for the links between mental functions and faculties and specific areas of the brain, a significant concern of philosophers since antiquity, which received scientific support by neuroanatomists of the renaissance period. It progressed to the enunciation of the 'neuron hypothesis' by Cajal, elaborated by cytogenetic studies of Brodmann and his contemporaries.

Electrical stimulation of the brain in conscious human beings by Foerster (1873–1941) and Penfield (1891–1976) provided valuable information regarding brain regions involved in behavioral activities. Vernon Mountcastle, David Hubel, and Torsten Wiesel elaborated the modular organization of the cortical neurons and elaborated the circuitry, especially of the somatosensory and visual cortex. However, as we know it

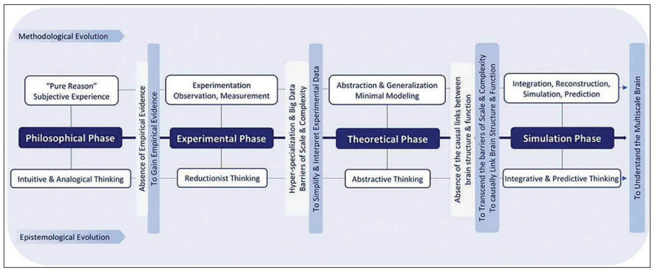

Figure 15: Flowchart depicting the epistemological and methodological evolution of brain research. This consists of four phases, philosophical phase, experimental phase, theoretical phase, and simulation phase.
(**Courtesy:** Fan Xue, Markram Henry. A Brief History of Simulation Neuroscience. Frontiers in Neuroinformatics. 2019; Vol. 3.)

today, the neural network revolution began in 1980, following a paradigm shift in computer science, neuroimaging, and computational neuroscience [**Figure 15**].

A functional area in the brain is defined as a sub-division of the cortex having a unique cytoarchitecture, histochemistry, myeloarchitecture, and connectivity (both afferent and efferent). Recent studies have shown that a given function may not (is generally not) be limited to a single functional area. Every brain mapping technology captures some, not all, aspects of the spatio-temporal pattern of the neural activity associated with a behavior. For example, it is now established that in the case of vision, there are as many as three dozen (or even more) different areas in the monkey's brain, each contributing to a different function, for example, the detection of line orientation, the movement of the object, the color, and so forth. These are widely distributed in the occipital, parietal, and temporal lobes.[2] These functionally different segregated areas are no doubt reciprocally connected. It is now well established that visual information is processed through successive stages in many separate cortex areas. The same is true of other functions as well.[3] How these distributed representations of the visual features have to do with a single object in the world are put together to produce a unified perception is still not fully understood. Thus, brain activation related to voluntary movement has been found in at least 14 areas, including the primary motor cortex.[4,5] No doubt, a vast amount of information has accumulated on neural networks. Studies in a new discipline, "**Connectome**," now combine diverse technologies to provide a more comprehensive map of the connections among all the neurons in a particular behavior—hearing, smell, and vision.[6]

The goals of today's connectome projects range from detailed investigations of synapses where the neurons talk to one another to using big data approaches to produce new insights about how the brain functions.[6] Now, based on these studies, large databases have been established.[7,8] Furthermore, the post-mortem architecture has improved in recent decades by incorporating immunocytochemical and other markers and improved methods of analysis.[9] In addition, there has been the recent emergence of non-invasive procedures for imaging architectonic patterns in humans and non-human primates by generating cortical 'myelin maps'.[7] No doubt, the biggest challenge is to unravel many of the unifying principles at the network level that remain undiscovered. However, attempts are already being made to grow circuits from brain cells and explore methods for studying the integration of neuronal functions in the circuits.[10]

In summary, today, we have a great deal of knowledge about the individual neurons and the way they connect to form functional units. A large number of neurochemicals they use to communicate with each other have been identified. The molecular events associated with neural communication have been unraveled. However, we still do not fully understand how this neural machinery is integrated to subserve higher mental activity [**Figure 15**].

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G: Imaging of the Brain: Exploring Cognitive Operations in the Human Brain

"Man is now able to watch his own brain thinking".
Cognition refers to different processes by which an organism understands and makes sense of the world. Perception, attention, memory, problem solving, and action planning are all parts of cognition. The earliest information on human cognition resulted from psychological and clinico-pathological studies on patients with brain lesions. Thus, brain areas responsible for speech and language, memory, Korsakoff psychosis, and blind sight (mentioned earlier) were identified. Electrical stimulation of the brain of conscious, cooperative patients undergoing surgery for epilepsy, the study of the event-related potentials (ERPs), transcranial magnetic stimulation, SPECT, PET, and fMRI studies provided valuable information on the higher mental functions.[1,2] A brief description of these investigative procedures is as follows:

The ability to image the brain in human beings gave a new direction to neuroscience research. Initially, it helped primarily in clinical diagnosis and, to some extent, in clinical research. Progressively, it has evolved into a very sophisticated discipline to study the higher mental functions – thoughts, emotions, and even conscious awareness – into the realm of "hard" scientific inquiry.[3,4] This was already demonstrated by Raichle and Goldman Rakic[5,6] It is interesting to note that Roger Sperry, only 3 decades earlier, commented, "The inner sensations, feelings, precepts, concepts, mental images, and the like cannot be weighed or measured, photographed, spectrographed, or choreographed or otherwise recorded or dealt with objectively by any known scientific methodology."[7]

In 1918–1919, Dandy introduced the technique of visualizing the ventricular system and sub-arachnoid spaces by injecting air either directly in the lateral ventricle (ventriculography) or through the spinal sub-arachnoid space (pneumoencephalography).[8] Thus, the brain could be visualized for the first time, at least indirectly, which had eluded until then by conventional radiography. It took another decade when Egaz Moniz developed the technique of cerebral angiography in 1927. These, however, provided only an indirect image of the brain. Nevertheless, these, along with electroencephalography and later isotope cephalometry, remained the sheet anchor of diagnostic neuroradiology until the 1960s.[9,10] Although French first described the experimental application of ultrasound for localization of brain tumors, it was Lars Leksell, 1956, who first reported its successful use for evaluation of head-injured patients and coined the term "echoencephalography''.[11,12] However, unlike echocardiography, which is now routinely used, echoencephalography did not become a routine imaging technique for brain disorders.

In 1973, the introduction of computerized axial tomography (CAT or CT) by Hounsfield and Mc Cormack for the first time provided a direct image of the brain itself.[13] Thus, the brain imaging field was revolutionized. One could now see the gray and white matter and the CSF in the ventricles and the cistern delineated. Beginning with axial scanners of the head to obtain cross-sectional two-dimensional (2D) images of the skull and brain, today with spiral (helical) scanners, one can get 3D images and even do CT angiography.

Around the same time, using 133 Xe single-photon techniques, the sensitivity of cerebral blood flow (CBF) to local neuronal activity was demonstrated.[14]

A combination of knowledge thus gained with imaging technology developed for CT scan led to the development of PET scan. The physical principle utilized was described by Phelps *et al*.[15] in their paper "Application of annihilation coincidence detection to transaxial reconstruction tomography." Although PET did not provide image resolution comparable to CT and MRI, it allowed us to study cerebral circulation, metabolism, and even turnover of drugs in the living brain. A PET scan can detect CBF changes of a few percent and localize these changes to the nearest millimeter.[14-18] William Feindel of the Montreal Neurological Institute, Canada, who contributed to the early stages of development of PET, succinctly summarized the status thus, "The Cat Scan gives a picture of the building; the PET gives you a picture of what's going on inside the building, the people, the plumbing, the electricity." **[see Figure 16A,16B]**.

Magnetic Resonance Imaging (MRI)
Although nuclear magnetic resonance (NMR) had been used for chemical analysis for several decades, its translation from spectroscopy to imaging in the intact biological system was performed by Damadian.[19] Edward Purcell and Felix Block had already got the Nobel Prize for discovering the "Phenomenon of NMR". The technique employs radiofrequency radiation in a magnetic field to produce cross-sectional body images, consisting of distribution density maps of mobile protons contained in cellular water and liquids. It provides a much better differentiation between gray and white matter than CT or PET. As a result, structures in the posterior fossa, including the brain stem and the spinal cord, are better visualized than any other imaging technology to date.

Functional Magnetic Resonance Imaging (fMRI)
fMRI demonstrates brain activation to a specific stimulus based on the functional anatomy of the brain. Once the brain is activated using a stimulus, there is a change (increase) in blood flow in the particular region of the brain because of the increased demand for oxygen and glucose. This is termed as a blood oxygen level-dependent (BOLD) contrast image. This has provided new insights into the brain's functioning, especially concerning higher mental functions. Belliveau *et al*.[20] provided an fMRI map of the visual cortex utilizing CBF signals. This was soon followed by Kwong *et al*.,[21] who introduced the BOLD technique for this purpose. With these techniques, one can create spatially, temporally, and behaviorally accurate images of the neural systems associated with diverse functions, including memory, thought, emotion, and cognition [see **Figure 17**].

However, because each imaging technique has its limitations and strengths, attempts are now being made to combine these to get a comprehensive picture of the brain's functional anatomy. Heinze *et al*.[22] and Sharma *et al*.[23] have recently presented a Hadoop-based big data frame integrating non-invasive MRI, MR spectroscopy (MRS), and neuropsychological test outcomes to identify early diagnostic biomarkers of Alzheimer's disease (AD). The brain structure, neurochemical, and behavioral features are extracted from MRI, MR, and neuropsychological scores. A multi-modality-based decision framework (BHARAT)

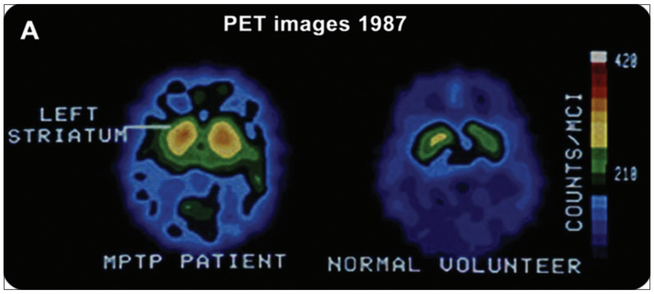

Figure 16A: Earliest PET image using older radio-ligand 18f-Spiperone demonstrating increased uptake in the left striatum of an MPTP-induced Parkinsonism patient in comparison to a normal volunteer taken as the control [Image courtesy LH Portnow et al., History of PET Scanning. Neurology;2013Mar 5 ;80(10):952-56]

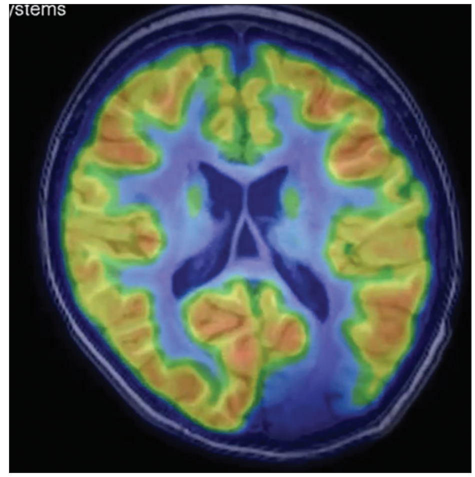

Figure 16B: Latest 18-FDG PET MR fusion images with increased resolution showing a region of hypometabolism correlating with occipital lobe dysplasia on structural MRI in a drug-resistant epilepsy patient. Note the advanced resolution and clarity of images in comparison to Figure A (Courtesy:Nuclear medicine dept, AIIMS, New Delhi)

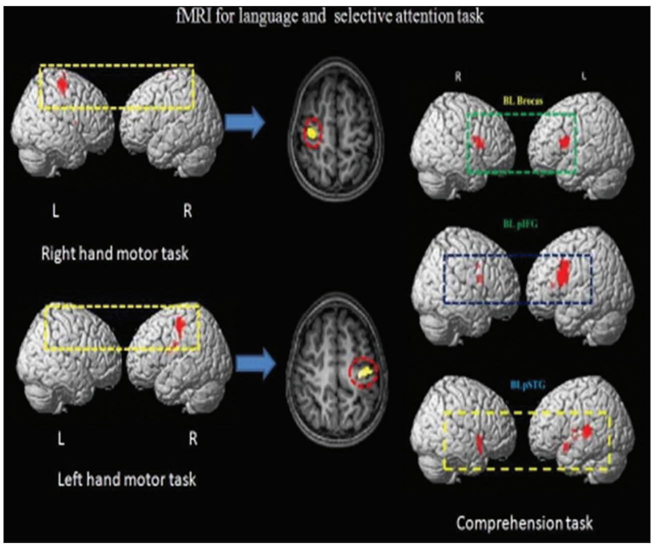

Figure 17: Latest fMRI with motor and language paradigms. Images are acquired using BOLD response as described in the text in response to verbal and visual stimuli. On a motor task, the motor cortex shows activation, which is marked in red on fMRI and yellow on structural MRI. On a language task, Broca's area on inferior frontal gyrus and Wernicke's area in superior temporal gyrus are mapped (red). (Image courtesy-Dept of NMR, AIIMS, NEW DELHI)

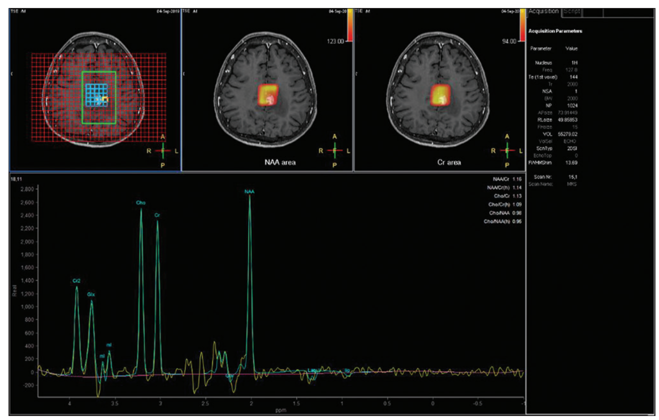

Figure 18: Figure showing MRS of a patient having cingulate gyrus low-grade glioma. The line above shows axial MRI images with voxels of MRS. The line below shows NAA, choline, and creatine peaks, based on the ratios of which tumor characterization is performed. Image courtesy-Department of Neuroradiology, AIIMS, NEW DELHI, 2021)

was developed to help in the classification of early AD. Posner *et al*.[24] summarized the state-of-the art at that time in their book, "Images of the Mind".

Notwithstanding all the advances, we still do not know how the brain creates the mind or does it? The brain remains to be the single-most defiant piece of ignorance. To develop a theory of the mind would complete a scientific hat trick, first the atom, then the gene, and now the mind!

NMR Spectroscopy

NMR spectroscopy has been used to evaluate the biochemistry of normal and pathological brain tissues. Initially, it was used for *in situ* examinations of brain tumors using ^{31}P-NMR signals.[25] This has later been replaced with more sensitive and reliable proton (^{1}H) NMR.[26] With proton spectroscopy, one can detect compounds in millimolar concentration with a spatial resolution of the order of 1 mm. *In vivo* proton NMR spectroscopy has now been refined for routine clinical use, especially for diagnosing brain tumors. Proton NMR spectra can be obtained from single voxels or different voxels simultaneously, the latter providing NMR spectroscopic imaging. Tumor diagnosis utilizes simultaneous consideration of six major chemical resonances observed in the T2-weighted ^{1}H-MR spectroscopy *in vivo*. These include choline (Cho), creatine (Cr), N-acetyl aspartate (NAA), alanine (Ala), lactate (LA), and lipids (Lip).

Preul *et al*.,[27] based on a study on healthy subjects and brain tumor patients, claimed that a pattern recognition analysis of the biochemical information obtained from proton magnetic resonance spectroscopy could enable accurate non-invasive diagnosis of the most prevalent types of supra-tentorial brain tumors. The present classification procedure achieved a success rate of over 99 percent.

Furthermore, the technique permits accurate biochemical characterization and classification of tumors in in-depth or eloquent brain areas non-invasively. [**Figure 18**].

The technique has been further extended to differentiate inflammatory granulomas, for example, tuberculomas from tumors by Gupta *et al*. and early neurodegenerative disorders by Mandal *et al*.[28,29] Mandal *et al*. have utilized MR spectroscopy for evaluation of in vivo biochemical changes in levels of glutathione, GABA, and glutamate in patients with Parkinson's disease and AD. These were correlated to clinical and psychological findings to help in establishing early diagnosis.

NMR spectroscopy of brain tuberculomas differentiated these from brain metastasis. It revealed reduced or absent NAA, without significant elevation of choline, with a markedly elevated lipid peak.[28]

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Clinician's Contributions

Gordon Holmes, one of the founders of British Neurology, while delivering the Foundation Day Lecture at the Montreal Neurological Institute in 1936, pointed out that, "The search for knowledge of normal function through the study of disorders produced by disease has distinguished neurology during the 60 or 70 years of its existence as a separate specialty. In probably no other branch of medicine have physiological questioning played so large a part for the manifestations of disordered activity in the nervous system are frequently so striking as to excite interest, not only in the nature of these disorders but also a prompt enquiry into the significance of the organ with the disease of which they are associated." It is interesting to recall that Otfrid Foerster (1873–1941), a renowned German Neurologist turned neurosurgeon, proposed a resolution, "…………neurology represents an entirely independent specialty in medicine," at the First International Neurological Congress at Bern in 1931, which was unanimously approved.

According to a report in the 1928 edition of Minerva at that time, among circa 86 European Universities, there were 48 Chairs in which psychiatry and neurology were variously combined (psychiatry and neurology 19, neurology and psychiatry 25, psychiatry and neuropathology 6, 40 psychiatry alone, and only 19 of neurology alone).[1]

There is no doubt a long list of these pioneers. Some of them have already been referred to in other chapters. However, the second half of the 19th century and early years of the 20th century provide us a galaxy of names of such scientifically oriented clinicians who laid the foundation of "clinical neuroscience." The list included here is by no means complete or comprehensive. It has been biased by the limitation of personal familiarity with their contributions and availability of their biographical information as collected over the years by the present author, who is deeply conscious of this shortcoming and aware of missing out on many whose contributions to basic knowledge of the functioning of the nervous system are no less critical. Just to name some of them, Pierre Paul Broca (1824–1880), Jean-Martin Charcot (1825–1893), Joseph Jules Dejerine (1849–1917), Pierre Marie (1853–1940), Guillaume Benjamin Duchenne (1806–1875) from France, Wilhelm Erb (1840–1921), Kinnier Wilson (1878–1937), Weir Mitchell (1829–1914), Brown-Sequard (1817–1894), James Putnam (1846–1918), Ramsey Hunt (1872–1937) from USA, James Collier (870–1935), Byrom Bramwell (1847–1931), George Riddoch (1889–1947), Argyll Robertson (1837–1909) from the UK, Moritz Romberg (1795–1873), Heinrich Quinke (1842–1922), and Hans Queckensted (1876–1918) from Germany. Interestingly, most of these names are familiar to present-day neurologists. To this may be added some of the pioneer neurosurgeons, Victor Horsley (1857–1916), Otfrid Foerster (1873–1941), Harvey Cushing (1864–1939), Water Dandy (1886–1946), Clovis Vincent (1879–1947), and Wilder Penfield (1891–1976).

Those included here would serve as an example of how a very busy clinician with a scientific attitude could contribute some path-breaking knowledge about the structure and function of the nervous system. An attempt has been made to provide a brief biography of these selected pioneers. These examples only justify the statement that the history of knowledge tells us that its advance has been mainly the result of individual effort and that much of the most critical work of the past and many of the currently acknowledged concepts and principles provide us with the basis of our current practice. Brief information about these selected pioneers is summarized in **Appendix Table 1** (see appendix Table 1 at the end of text).

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1. Thomas Willis (1621–1675)

Figure 19: Thomas Willis (1621–1675)

Thomas Willis is considered to be one of the greatest neuroanatomists of all times. His work formed the foundation of basic neuroanatomical description and nomenclature and comparative neuroanatomy, even though he was professionally a practising neurologist. Zolton[1] proposes that "For these reasons, Willis' name and achievements should be proclaimed to every new generation of neuroscientists".

Born on January 27, 1621 at Wiltshire, UK, he obtained the Bachelor of Arts degree from Oxford in 1646, and he lived and worked there for most of his life, except for the last 9 years in London.

Time was ripe to challenge the current anatomic texts written at least 100 years earlier by Aristotle, Hippocrates, Galen, Andre Vesalius, and others. William Harvey, who is known for his description of the circulation of blood, was his neighbour at Oxford, while Willis revolutionized the anatomy of the brain and not just the Circle of Willis, for which he is generally known even 400 years later. He studied and compared the nervous system of many different organisms. His most renowned book (published in Latin, then the language of anatomy) "Cerebri Anatome: cui Accessit Nervorum Descriptio et Usus" was published in 1664, translated in English by Samuel Pordatein, 1681, and re-printed in 1971. Writing the foreword to the tenth edition of this book, Penfield (1965) wrote, "The problem of neurology is to understand the man himself." Twenty-three editions of this book were published. The other one was *Pathologie Cerebri et nervosi generis specimen* in 1667. It is said that the former book was in use for 200 years. It contained descriptions of the brain, the spinal cord, and the peripheral and autonomic nervous systems. The word 'neurologie' first appeared in the translation of this book (Oxford English Dictionary).

The vascular supply of the brain and spinal cord, illustrated by the renowned astronomer, artist, and architect – Christopher Wren, was described in detail. Galen's description of cranial nerves was re-classified (although not fully accurate). In his book on the Anatomy of Cranial Nerves published in 1681, the seat of higher cognitive functions was ascribed to the cerebral cortex as against the prevalent view of Galen, who attributed the animal "spirit'' in the ventricular system to be the source of all intellect.

Willis is credited for coining a number of neuroanatomical terms, for example, anterior commissure, cerebral peduncles, corpus striatum, internal capsule, optic thalamus, medullary pyramids, inferior accessory nerve, Olive, Vagus nerve, and nervus ophthalmicus, (Molnar 2004). He recognized that the medulla oblongata regulated the vital functions of the heart, lungs, and intestines. He was aware of the concept of nerve impulse and of reflex action.

According to Charles Sherrington (1951), "Thomas Willis practically refounded the anatomy of the brain and nerves…. He shifted the seat of the animal from the chambers of the brain to the actual substance of the brain……"

Reference

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2. Luigi Rolando (1773–1831)

Figure 20: Luigi Rolando (1773–1831)

Luigi Rolando born in Turin had his medical education, which besides anatomy included drawing and engraving, in Florence. He was appointed the Professor of Practical Medicine at the University of Sassari, Sardinia, in 1804, and 10 years later, he moved to Turin University as the Professor of Anatomy. He was one of the pioneer researchers on localization of functions in the brain. At the time of his anatomical studies (late 18th century and beginning of the 19th century), brain functions had not yet been identified. The brain was considered an amorphous mass, and each function could only be expressed by its entirety. Rolando, however, believed that nervous activities could be differentiated and located in specific areas of the brain.[1] His anatomical research was guided by this belief. This led to his describing the Central Sulcus, later came to be known as the Rolandic Sulcus, which separated the primary motor and sensory cortical areas. This name was given by the French anatomist Francoise Leuret (1795–1851). It is interesting to note that it was nearly 100 years after the description of the Sylvian fissure (see Franciscus Sylvius).

In addition to the Central Sulcus, Rolando described the jelly-like material capping the posterior horn of spinal cord gray matter called "substantia gelatinosa". It is now recognized to be involved in pain perception.

Rolando also described the role of the cerebellum in locomotion based on his experimental animal studies.

It is reported that Rolando, based on his intuition, assumed that the mid-brain was not just a connection between the brain and the spinal cord but a "vital Center" regulating the basic functions of life.

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3. Johannes Evangelista Purkinje (1787–1869)

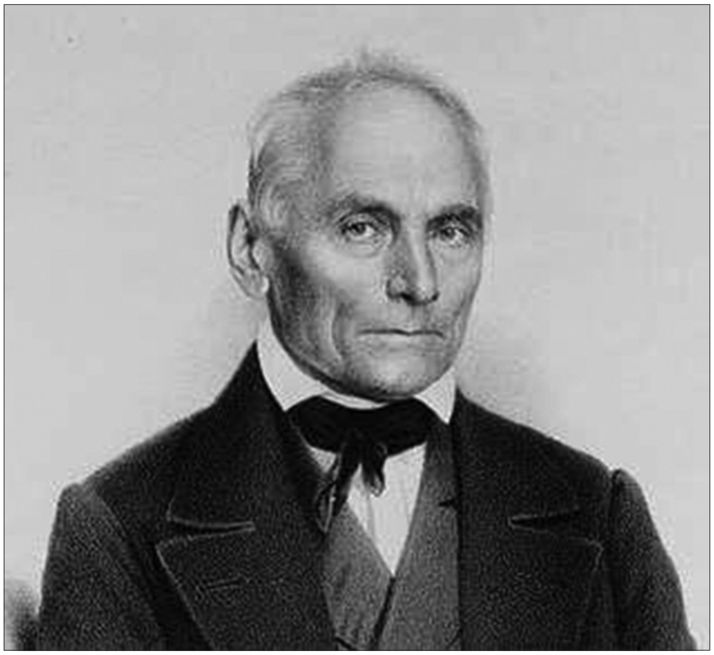

Figure 21: Johannes Evangelista Purkinje (1787–1869)

Johannes Evangelista Purkinje was born at Libochovice in Bohemia, Czech. His father died when he was 10 years old. He was educated by Piarist monks. Just before he was to be ordained in 1808, he went to Prague to study philosophy. In 1810, he became a tutor in the house of Baron Hildprandt, which enabled him to study medicine.

As a medical student, he observed the effects of drugs on himself and described acute poisoning of ipecac, belladonna, and camphor. In 1818, his doctoral dissertation was on the subjective aspect of vision. Later on, he worked on, after images, the different thresholds of various colors. He established the basis for objective optometry and ophthalmoscopy. He reported the earliest data on the individuality of fingerprints.

He was appointed Prof. of Physiology at Breslau. However, the locals opposed the appointment of a Czech. His personal friendship with the famous philosopher Goethe was a great help.

He obtained his compound microscope in 1832, which made his lab "a cradle of histology". The lab later moved to his house. Most of the detailed histological studies by him were published in the name of his students.

In 1837, he presented to the German Men of Science and Medicine in Prague a brief resume of his microscopic survey of the human brain. It included the first adequate description and illustration of myelinated fibers, nerve cells with their nuclei, and dendrites and the layers of a cerebellar folium, including a row of "flask-shaped ganglionic bodies", which later came to be known as Purkinje cells. In 1850, he was invited to the Chair of Physiology at Prague.

He translated Schiller, Shakespeare, and Tasso.

In 1825, he married the daughter of Rudolph, Professor of Anatomy at Berlin. Ten years later, his wife and two children died in an epidemic. He died a much-adored scientist, scholar, and cultural savant in 1869.

4. Claude Bernard (1813–1878)

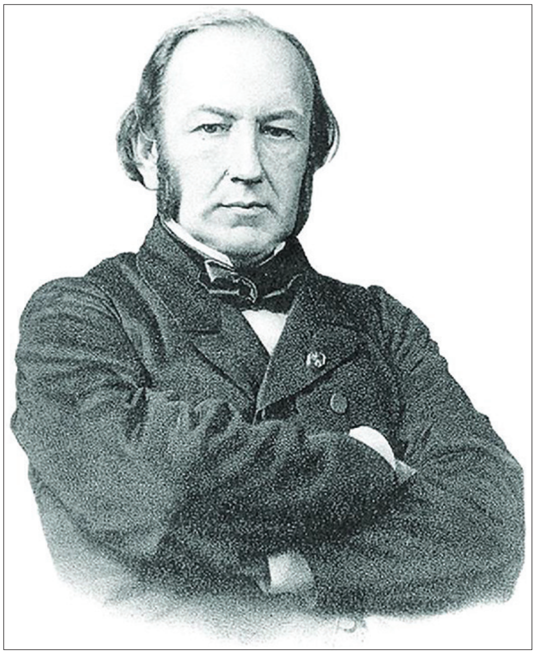

Figure 22: Claude Bernard (1813–1878)

Claude Bernard is known as "the father of experimental medicine". He was born on July 12, 1813, in a small village of St. Julien, France. As a medical student, he interned with Magendie.

His career as a physiologist began in 1841; "at this time, physiology was just beginning to free itself from the scholasticism of the past. The influence of vitalism, which denied the experimental method in the study of the phenomena of living things, was keenly felt."

Besides early work on nutrition, the gastroenteric system, and the glycemic function of the liver, he later worked on the existence of the vasomotor nervous system for both vasodilation and vasoconstrictors.

His numerous publications filled 18 volumes. His concept of *Milieu Interieur*, that is, higher forms of life have within a mechanism for maintaining almost absolute constancy of the body fluids, is a path-breaking event. Of this, he said, "The nervous system is called upon to regulate the harmony between all these conditions."

Fulton commented that "in this forecast lies the greatest problem of physiology and medicine of the immediate future, the regulatory action of the autonomic nervous system."

Bernard, in his first lecture to students, stated, "Scientific medicine, which I am supposed to teach you, does not exist."

In 1865, he published his "Introduction to the Study of Experimental Medicine."

In 1864, Emperor Louis Napoleon, impressed by Bernard, established two laboratories for him, one at Sorbonne and the other at the Museum d' Histoire Naturelle in France.

Bernard died on February 10, 1878 and was given a State Funeral.

Some Quotations attributed to Claude Bernard

The hospital, the library provide the opportunity for making and recording observations, but only the laboratory provides the area where these observations can be tested by carefully designed experiments.

It is the things we do know that are the great hindrance to our learning the things we do not.

Eternal aspiration of human reason towards knowledge of the unknown – the joy of discovery is certainly the liveliest that the mind of man can ever feel.

5. Rudolf Ludwig Carl Virchow (1821–1902)

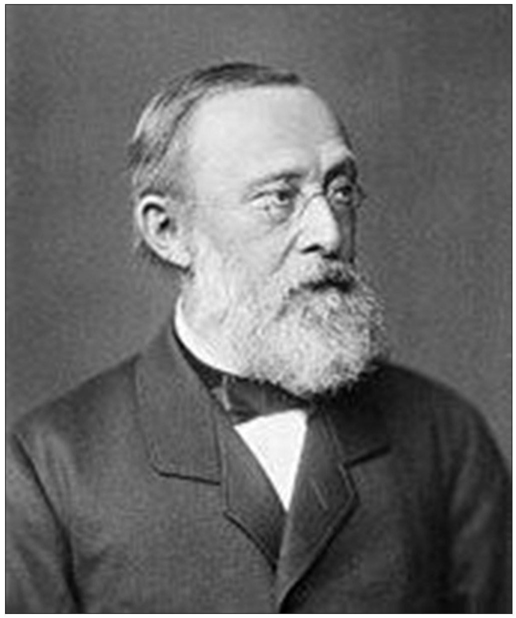

Figure 23: Rudolf Ludwig Carl Virchow (1821–1902)

Born in a small town, Schievelbe, he studied at Berlin University, where Johannes Muller was the Professor of Physiology (along with other students such as Henle, Schwann, and Helmholtz).

After his Doctoral dissertation in 1843, he joined Charite, the renowned medical institute in Berlin.

At 26 years of age, he founded the Archiv fur pathologische Anatomie und Physiologie, in which he published extensively.

In 1848 (27 years old), he was offered a Professorship of Pathology at the University of Wurzburg. Here, he laid the foundation of cellular pathology.

He went back to Berlin (Charite) in 1856 and remained there until the end.

Based on a series of lectures in 1858, he published "Die Cellularpathologie" (translated in English in 1860).

Some years later (1863–1867), he published the well-known survey of neoplasms "Die Krankhafte Geschwulst."

He published on a large number of subjects including Pachymeningitis Haemorrhagica Interna, Cerebral hemorrhage, Tumors of the Nervous system, and Peripheral nerves.

In 1851, Virchow provided the first description of the perivascular spaces – now known as Virchow–Robin space.

In a paper in 1854, he described the cellular nature of the cerebral interstitial substance, which he called neuroglia and 2 years later "DieseBindesubstantanzbildet in dem Rückenmark und den hohlerenSinnesnerven cine Art von Kitt."

In later years of his life, he became increasingly involved in politics, public health, and anthropology.

6. Pierre Paul Broca (1824–1880)

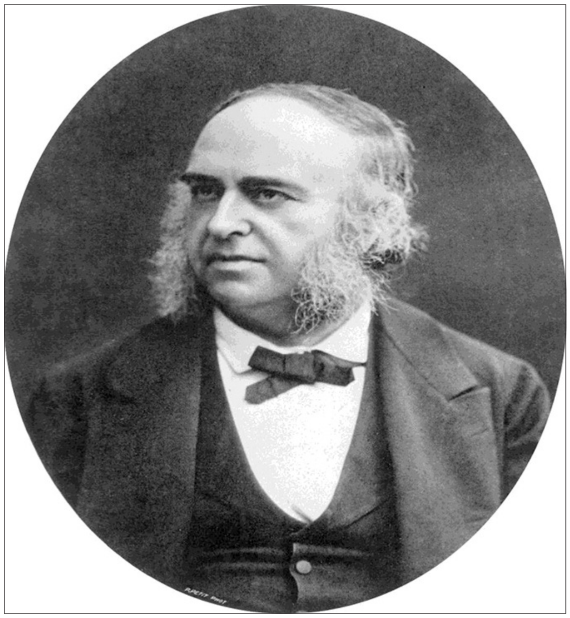

Figure 24: Pierre Paul Broca (1824–1880)

Pierre Paul Broca was born near Bordeaux in France, and he was the son of an army surgeon. He entered the University of Paris at the age of 17 years to study medicine.

For the first 10 years after graduation, he worked mainly on pathology, later shifted to anthropology and ethnography, and became well known for his work on craniometrics and anthropometric studies.

In 1859, he founded the Societe d' Anthropologie.

Under the influence of his friend Gratiolet, he became interested in anatomy and functions of the brain, particularly in problems of localization.

On the basis of a single case, which he had carefully followed clinically, he developed the concept of the relationship of certain symptoms and circumscribed lesions, which was later elaborated by Hitzig, Ferrier, and Charcot. The motor speech area, now called "Broca's area," was assigned to the left inferior frontal gyrus on the basis of an autopsy on two cases of brain tumors. It was in 1861 that he demonstrated before the Societe Anthropologie in Paris this lesion in the left frontal lobe of his patient who suffered from *aphemie* (re-named aphasia by Trousseau in the same year). This area was later called Broca's convolution by Ferrier. His concept was opposed by Trousseau and Hughlings Jackson but later supported by Wernicke, who localized the sensory aphasia in the left parieto – temporal region, in 1874. Pierre Marie (1853–1940) criticized Broca's work in his paper, "The third left frontal convolution has no special role in the function of language."

Just before his death in 1880, Broca was elected a lifetime member of the Senate of the French Republic. He died suddenly in 1880 at the young age of 56. It is reported that a post-mortem study failed to establish the cause of death, which was attributed to "cerebral exhaustion."

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7. Jean Martin Charcot (1825–1893)

Figure 25: Jean Martin Charcot (1825–1893)

Jean Martin Charcot was born in Paris and was the son of a carriage builder. He passed his medical examination with honor and became an intern at the Salpetriere in 1848.

He worked in Clinical Medicine and Pathology and published papers on diseases of the heart, lung, and kidney. It was only at the age of 37 that he was given a formal position there. He became a physician to the Salpetrier in 1860 and shortly afterward built the first great neurological clinic that medicine has known. It was here that neuropathology was developed.

He became a neuropathologist, succeeding Vulpian to the Chair of Pathological Anatomy in 1872. His book "Leçons sur les maladies du système nerveux : faites à la Salpêtrière," published in 1872–1873, is a masterpiece which was translated into English.

He wrote on cerebral localization, disseminated sclerosis (the classical Charcot's triad); neuropathic joints (Charcot's joints); described and gave a name to amyotrophic lateral sclerosis, which one of the neuropathies called Charcot Marie tooth; and contributed to the pathogenesis of poliomyelitis. He laid the foundation of psychopathology, which was elaborated later by his pupil Freud.

Pierre Marie, Babinski, Marinesco, Bekhterev, Gille de la Tourette, and Colin were some of his students.

He was a linguist who spoke English, German, Spanish, and Italian. His interest in art is reflected in two books published in 1887 and 1889.

He died in 1893 of pulmonary edema, while on vacation, probably the result of coronary occlusion. It has been said that he entered neurology in its infancy and left at its coming of age largely nourished by his own contributions.

Advice from Charcot on Medical Research

"Charcot taught that clinical observation must ever remain the supreme court of justification on the Clinic itself," but he added, "without scientific renovation, it soon becomes a belated routine and as it were stereotyped". According to Knur Faber, "It was plain to Charcot that the fundamental sciences were the source from which clinical observation and clinical analysis must always derive their impulse for advance."

8. Theodore Meynert (1833–1892)

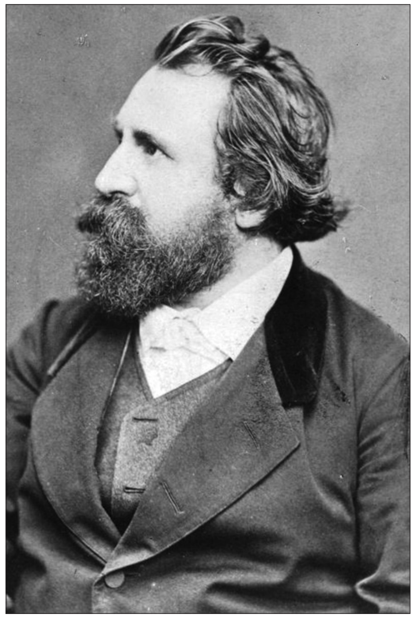

Figure 26: Theodore Meynert (1833–1892)

Theodore Meynert was born on Dresden June 15, 1833, and lived in Vienna; he worked at (and later directed) the First Psychiatric Clinic, established specially for him.

He was the first scientist to perceive **brain research as an inter-disciplinary project** combining neuroanatomy, neurophysiology, neurochemistry, and neuropsychology.

In an international context, he is **one of the founding fathers of scientific neurology**, a relatively young discipline which reached its full concept and methodological development only in the second half of the 20th century.

Knowledge of the anatomy of the nervous system was rudimentary in the middle of the 19th century.

According to the anatomist J Hyrtl (1810–1894), one of Meynert's teachers, the characteristics of the brain were 'obscura texture, obscurior morbi, obscuris image functions.'

Apart from good gross descriptions, several microscopic discoveries were made throughout Europe in the 19th century. Schwann (1810–1882) discovered the cells now known by his name. Others who contributed to the microscopic findings were Charles Bell (1774–1842), F Magendie (1783–1828), B. Stilling (1810–1879), and A. Koelliker (1817–1905), but there was no systematic knowledge of internal structures of the brain, its connections, and functions (Finger 1994). Comparative anatomy was rudimentary. The interest in the brain had been stimulated by pre-scientific 'phrenology' of Gall (1758–1828).

The focal points of Meynert's scientific work were anatomy and histology of the cerebrum and brainstem. Topography and functional relations of the main connecting fiber systems were demonstrated by precisely interpreted clinicopathological observations. These studies resulted in the cellular architecture and regional differentiation of the cerebral cortex as a basis of cytoarchitectonics and cortical localisation theory. It has been said that all subsequent cytoarchitectural studies rest on Meynert's pioneering observations. August Forell (1848–1931), a Swiss neuroscientist trained under Meynert in Vienna, worked on Thalamus opticus in mammals for his doctoral thesis. Later, working in Murich under Gudden, he published papers on the tegmental region.

Through his brother-in-law, G. Scheithauer (1832–1894), an assistant to the pathologist C. von Rokitansky (1804–1878), he came in contact with the latter. Meynert later became interested in the anthropological and philosophical implications of brain research in respect to problems of human behavior in the context of ethics and religion.

In 1888, he delivered a lecture on "Brain and Moralization '' at the meeting of the scientists and physicians at Cologne.

Among his Austrian followers were H. Obersteiner (1847–1922), G. Anton (1858–1933), C. Mayer (1862–1936), and F. Chvostek (1864–1944). Sigmund Freud worked with him for a period as a trainee. Other foreigners included C. Wernicke (1848–1905), A. Forel (1848–1931), B. von Gudden (1824–1886), H. Waldeyer (1836–1921), l. Edinger (1855–1918), and the German neuropathologist Paul Flechsig (1847–1929).

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9. John Hughlings Jackson (1835–1911)

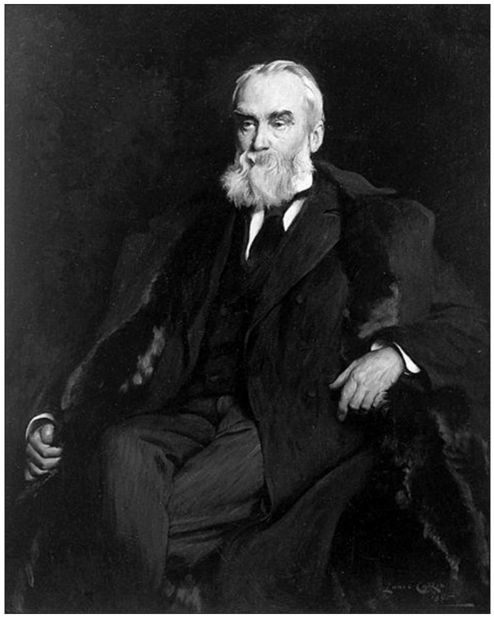

Figure 27: John Hughlings Jackson (1835–1911)

He was the son of a Yorkshire farmer, his mother being of Welsh descent.

It is said that "For Jackson, there were the customary years of indifferent schooling and an apprenticeship at York Medical School and ST. Bartholomew's Hospital before he qualified as a physician in 1856".

Early in his career, he wanted to quit medicine for the field of philosophy. He was prevented from doing so by Jonathan Hutchinson, who prompted him to come to London. Encouraged by Brown–Sequard, Jackson interested himself in neurology. He joined Queen Square and was attached to Moorfields Eye Hospital. It was because of the latter that he introduced the ophthalmoscope to neurology.

Between 1861 and 1909, in a series of over 300 addresses, papers, and discussions, he covered an enormous field which included epilepsy, speech, vestibular vertigo, localization of functions in the brain, and classifying CNS functions at three levels – the lowest representing movements in their most simple form and made up of medullary and spinal centers, the middle consisting of the motor cortex, and the highest residing in the pre-frontal area; the last one was endowed with the greater capacity for differentiation, specialization, integration, and cooperation.

Although *Bravais* in 1827 was the first to describe (focal) convulsions of a limited range and deliberate onset, Jackson further de-lineated the pattern and pointed out the common relationship to focal disease in the brain – the basis of Jacksonian epilepsy. From his clinical observation, Jackson conceived the idea that discharges from cerebral convolutions produced movements of different parts of the body.

Within a few years of Jackson's epoch-making view on cortical localization, it won direct confirmation by the experiments of Fritsch and Hitzig in Germany and of Ferrier in Great Britain.

He grew up with such brilliant co-workers as Gowers, Ferrier, Gall, and Victor Horsley, and his pupils included Henry Head, Gordon Holmes, James Collier, and Kinnier Wilson among others.

He married at the age of 30 years to his talented cousin, Elizabeth Dade, who died 11 years after marriage, without children, from cerebral thrombosis.

Jackson expired in 1911.

Suggested readings:

1. In Selected Writings of John Hughlings Jackson (ed) and James Taylor, Hodder Stoughton, London 1931.

10. Eduard Hitzig (1838–1907)

Figure 28: Eduard Hitzig (1838–1907)

Eduard Hitzig was a native of Berlin, Germany. His Father was one of Europe's most renowned architects. Initially, he studied law and later moved to medicine. He received his doctorate from Berlin in 1862 and was called to Zurich in 1875, where he became the Professor of Psychiatry and the Director of the Burgholzli Asylum. In 1879, he moved to the University of Halle as a faculty member and was later appointed as the Director of the Neuro-Psychiatric Clinic. He was influenced by Romberg (neurology), Virchow (pathology), du Bois-Reymond (physiology), and Westphal (psychiatry).

His pioneering studies, along with Theodore Fritsch (1838–1927), were on the electrical excitability of the cerebral cortex, initiated around the 1860s. The initial studies were on dogs carried out on his wife's dressing table. This was the beginning of a new era of study of brain physiology. Their findings were published in 1870,

stating that they had found the place where "the spirit enters the body." What they had performed was to prove that there is within the brain a separate mechanism that must go into action during the animal's voluntary use of the leg, a motor mechanism in which the activating energy is electrical (Robert Bartholow of Cincinnati, Ohio, is reported to be the first to apply electric current to the human brain in 1874). Hitzig defined the limits of the motor area in the cerebral cortex of a dog and monkey. He described hemiplegia because of pre-central and post-central gyrus lesion. Through his influence, psychiatrists became increasingly aware that the brain is the instrument of the mind. His colleague Fritsch's only scientific contribution was the work performed with Hitzig. According to Penfield,[1] these experiments by Hitzig paved the way for a rapid expansion of neurophysiology.

"Thus, physiologists could now proceed to localize, little by little, discrete functional mechanisms, electrically activated, within the brain. Thus, Charles Sherrington could identify the involuntary reflexes that served the overall integration of functions within the brain, and Ivan Pavlov could show that new skills were learned by the establishment of acquired or conditioned reflexes within the nerve circuits of the cerebral cortex"[1] (this applies to Wilder Penfield's own mapping of the human brain).

Almost 80 years after discovery of electricity, two German Physiologists exposed the brain of a dog under light anesthesia and touched the cerebral cortex, in what we now call the motor convolution with an electrode that delivered a gentle electric current. Behold! The dog moved its paw on the opposite side of the body as if it was making a voluntary gesture. The experimenters Gustav Fritsch and Edouard Hitzig published their findings in 1870, stating that they had found the place where "The Spirit enters the body".[1]

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11. Camillo Golgi (1843–1926)

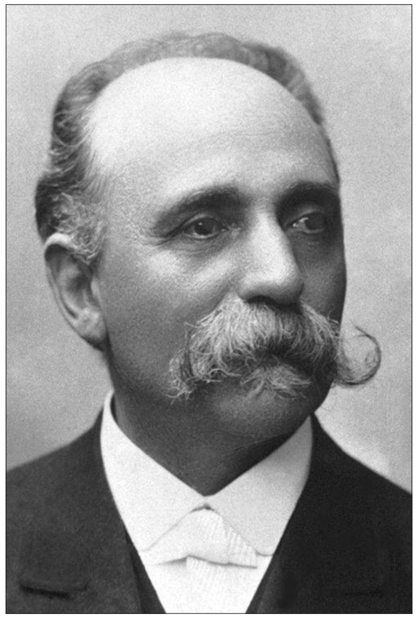

Figure 29: Camillo Golgi (1843–1926)

Camillo Golgi was born at Cortina, Italy, on July 7, 1843, a son of a medical practitioner. He studied at the University of Pavia, graduated in medicine in 1865, and continued to work there for some time, influenced by Prof. Bizzozero. He married Donna Lina Aletti, the niece of Bizzozero.

Initially, he worked on Pellagra, but reading Virchow's Die Cellularpathologie induced him to dedicate himself to study the structure of the nervous system. Initially, his investigations were on insanity and lymphatics of the brain.

His earlier studies in 1870–1871 were carried out on the neuroglia of the cerebral gray and white matter.

In 1872, financial compulsion forced him to take a position as the Chief Resident Physician in a small-town hospital for the chronically ill. His love for science forced him to develop a laboratory in his kitchen, with only a microscope and few instruments, working mostly in candlelight at night. Here, he discovered the chromate of the silver method for staining of the nervous tissue in 1873.

He was invited by the University of Pavia in 1881 as the Chair of General Pathology, where he spent the rest of his academic career until 1918. He became Rector of the University. He also founded and directed the Instituto Quimioterapico-Vaccinogen of the Province of Pavia.

Fridtjof Nansen, the Norwegian explorer, was his student and is credited with having introduced Golgi's method of staining to the rest of Europe.

It is interesting to note that even though Golgi first stained an individual nerve cell in 1873, it was Wilhelm von Walder Hartz who introduced the term neuron in 1891. It was 3 years earlier that Wilhelm His had demonstrated that axons are outgrowths of the primitive nerve cell.

Golgi's monumental work "Sulla fina anatomia degli organi centraI E Del Sistema Nervosa" was published in 1885–1886, and his "Opera Omnia" with beautiful drawings was published in three volumes in 1903.

He then changed his direction and worked on malaria, 1890. He must be credited for having determined the three forms of parasite and three types of fever.

He persistently refuted the Neuron Theory of Cajal even in 1906, when he was awarded the Nobel Prize along with Cajal.

In his later years, he became Rector of the Pavia University and a Member of the Royal Senate. His most revolutionary work was developing the method of staining individual nerve and cell structures using silver nitrate. It was for this contribution that he received the Nobel Prize in Physiology or Medicine in 1906 along with Santiago Ramon y Cajal. However, the two aggressively differed on the interpretation of their observations on neurons. Golgi believed that the neurons formed a network by anastomosis of the axonal fibers supporting the so-called reticular theory. As a matter of fact, already in 1871, the German Josef Ivon Gerlach had put forward the "reticular theory." Golgi believed in this theory with minor modifications. The anastomotic network theory was defended by Meynert and generally believed by most neurologists at that time. Cajal, using a modified Golgi technique (for which he gave due credit to Golgi), observed that the terminal and collateral fibers in the gray matter did not form a diffuse network but remained free, establishing simple contacts with the neuronal cell body and the dendrites of the adjacent nerve cell, thus enunciating the now generally accepted "Neuron Doctrine."

In addition to developing the staining technique for nerve cells, Golgi had many other important contributions, for example, description of the 'Golgi apparatus' in neurons (1898); two fundamental types of nerve cells, Golgi type 1 (motor) and Golgi type II (sensory) neurons; Golgi tendon rrgans; and Golgi Mazzoni corpuscles found in fingertips.

He was a recipient of many awards and honors. The Historical Museum at the University of Pavia dedicated a hall in his honor, where more than 80 certificates of honorary degrees and diplomas awarded to him are exhibited. During his Nobel lecture, Golgi insisted on his reticular theory notwithstanding Cajal's unmistakable demonstration of the findings that led him to propose the 'Neuron Doctrine'. In a paper published in 1917, Cajal referred to this discrepancy as "What a cruel irony of fate to pair, like Siamese twins united at the shoulders, scientific adversaries of such contrasting character."[1] He died at Pavia on January 21, 1926.

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12. Ivan Petrovich Pavlov (1849–1936)

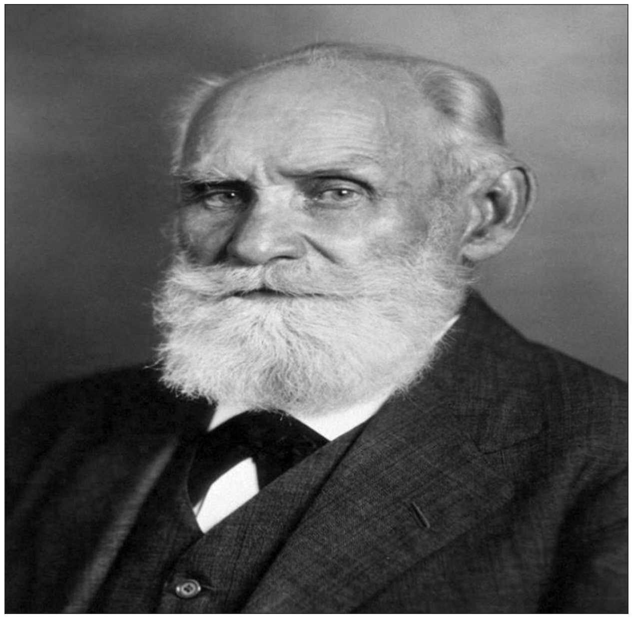

Figure 30: Ivan Petrovich Pavlov (1849–1936)

Ivan Petrovich Pavlov was born in 1849, a son of a peasant, in the village of Riazon in central Russia.

He was educated first for the priesthood, but later in 1870, he changed to study medicine in the University of St. Petersburg. He then studied with Carl Ludwig at Leipzig and Heidenhain at Breslau. He returned to St. Petersburg to work with the clinician Bodkin in experimental pharmacology.

His contributions dealt with cardiac physiology, digestion, CNS, and psychopharmacology.

His Nobel prize in 1904 was for his investigation of the digestive glands. His use of the salivary and gastric fistula (Pavlov Pouch) for the long-term study of secretion in healthy animals led to the discovery of the conditioned reflex.

However, around 1900, aged 54 years, the main line of his research was concerned with the higher nervous activity as determined by the conditioned reflex.

At the age of 80, he began the study of psychiatry using physiologic techniques.

His book "Reflexes and Psychiatry", published in English Translation in 1941, has been called the greatest book ever written on psychiatry.

Notwithstanding the untimely death of his son, which affected him a great deal, he continued to work in his lab until a week before his death at the age of 86. According to one of his biographers, "Pavlov is a star which lights the world shining down on a vista hitherto unexplored."

Pavlov's home is preserved as it was at the time of his death as a museum in Leningrad. The author was privileged to visit this "memorial" in honor of one of the greatest scientists of the 19th –20th century.

Pavlov's Will

"From the very beginning of your work, train yourself to strict consistency in the acquisition of knowledge."

"Learn the ABC of science before you attempt to scale its peaks."

"Learn to do the heavy work that science involves, study, compare, accumulate facts. Without facts, your theories are labor in vain."

"Do not turn yourself into a museum, custodian of facts. Try to penetrate the secret of their origin."

"Never think that you already know everything."

"Do not allow pride to take possession of you."

"Remember that Science demands a man's whole life."

Some Important Publications

1. Lectures on Conditioned Reflexes. London Lawrence 1928 (translated by W.H. Gantt)
2. Conditioned Reflexes and Psychiatry. New York. International Public Co., 1941 (translated by WH Gantt).

13. John Newport Langley (1852–1925)

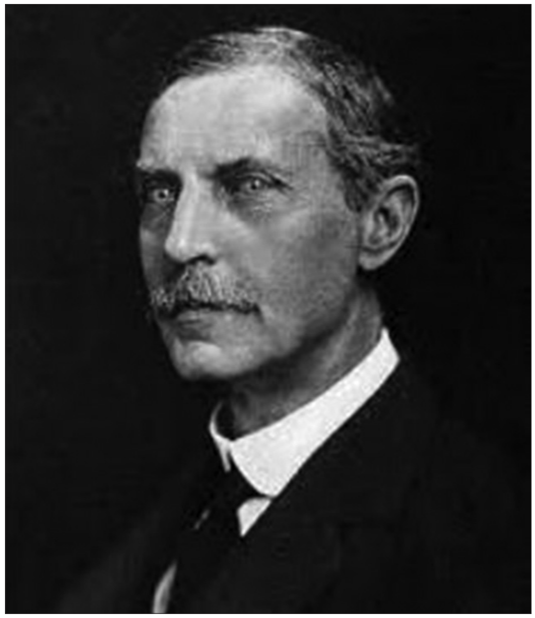

Figure 31: John Newport Langley (1852–1925)

John Newport Langley was an English physiologist born at Newbury on November 2, 1852. His father was a schoolmaster. He matriculated at St. John's College, Cambridge, in 1871 and graduated with honours (1874).

He got interested in physiology because of the influence of Sir Michael Foster (who was also a teacher of Henry Head). He worked with Sir. Michael for 9 years beginning in 1875 and later succeeded him in the Chair. He was the Editor of J. Physiology for 30 years.

Langley's career at Cambridge, starting as a demonstrator and rising to the position of a Professor in Physiology, lasted for 50 years.

His research career could be divided into two periods. The first one from 1875–1890 was devoted to glandular secretions, and the second one was devoted to the study of the autonomic nervous system.

As a matter of fact, his pioneering works in this field, published in his book "The Autonomic Nervous System" in 1921, entitle him to be considered the founding father of this field of neurosciences. It may be mentioned that Walter Holbrook Gaskell (1847–1914), who was educated at Trinity College, Cambridge, and later worked there, is said to have established the histological foundation of the autonomic nervous system. He mapped the nerve supply to visceral organs including the carotid vascular system. This was published as an exhaustive review in J. Physiology 7, 1-80, 1886. No doubt this would have been of help to Langley in his studies. He introduced the terms "pre-ganglionic" and "post-ganglionic" nerves in 1893. He studied the re-generation of nerves and the autonomic nervous system, a term which he introduced in 1898. It was in 1905 he coined the term parasympathetic system.

He was a Fellow of the Royal Society, London (FRS) (1883), at the young age of 31 and its Vice President (1904). President Neurological Society, Great Britain (1893) Received: Retzius Medal of the Swedish Society of Physicians. His pupils included Rudolph Magnus, Elliot Smith, Henry Dale, A.V Hill, Barcroft, Adrian, and Sherrington. It is interesting to note that three of his students, Charles Sherrington, Henry Dale, and Edgar Adrian, were awarded the Nobel Prize.

He died following a brief illness at his home in Cambridge on November 5, 1925.

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14. Santiago Ramón y Cajal (1852–1934)

Figure 32: Santiago Ramon y Cajal (1852–1934)

Cajal was born on May 1, 1852, at Petilla de Aragon in the Pyrenees of northern Spain. His father, to start with an unqualified surgeon in a small town, ultimately became a Professor of Applied Anatomy in the University of Saragossa. Cajal's father wanted his son to become a doctor, but the young boy was interested in drawings and wished to become an artist. His early schooling was unhappy, subjected to 'reign of terror', flogged repeatedly, and deprived of food to improve his scholarship.[1] An attempt to educate him in another school also failed; his father attempted to teach osteology to him at home, for which the father and son surreptitiously obtained bones from a nearby cemetery. One of his biographers summarized Santigo's early life in rather unflattering terms, "rude schooling in which he has thrice pronounced a failure, apprenticeships in barbering and shoemaking, transient flings at sundry hobbies, army life in Cuba, and a rest cure for tuberculosis: his love for drawing ultimately led him to anatomy and later to medicine most likely as a result of persuasion by his father. He, therefore, entered medical school." Thus, in 1873, he took his licentiate in Medicine at Saragossa (Zaragoza) and served as a regimental surgeon in Cuba. He returned to Spain after he contracted tuberculosis. He was appointed assistant and then a professor at his *alma mater*. It was here that he began the histologic studies, which became his life-long passion. In 1879, on an income of 35 euros a month, he married Dona Silveria Fananas Garcia. The couple had four sons and three daughters. From Zaragoza, he moved to Valencia as a professor of anatomy (1884), then to Barcelona (1887), and finally to Madrid (1892). In 1900–1901, he was appointed the Director of the Instituto Nacional de Hygiene and the Investigaciones Biologicals.

Initially isolated by language and local traditions from the main current of science, he led a somewhat leisurely tempo of life, a practice in Latin countries. He was himself conscious of these limitations, which he recorded as follows:

He wrote, "It has been said many times that the problem of Spain is a problem of culture. It is necessary, if we would enrol ourselves with the civilized peoples, that we must cultivate intensively the desert of our land and brain, thus rescuing by prosperity and mental vigor all those national riches that we have lost in the sea, and all those talents which have been lost in ignorance."[2] It was only after recognition he received following a demonstration of silver-impregnated sections before a meeting of the German Anatomical Society at Berlin (1889), presided over by Prof. Rudolf Albert von Kolliker, that his research studies started to receive wider recognition. It was after this meeting that Kolliker, the patriarch of German histology, remarked, "I have discovered you, and I wish to make my discovery known in Germany."[3] This meeting was also attended by such renowned scientists as His, Retzius, Waldeyer, van Gehutchten, and Swalve. Cajal, who until recently published his research studies in Spanish and French, got an instantaneous recognition by the German neuroanatomists.

He had published 237 scientific papers and 11 other books by the time his autobiography was revised in 1923. The Histology of the Nervous System, (two volumes), published in 1913–1914, is considered his crowning achievement.

He published more than 100 articles in French and Spanish Scientific periodicals dealing with the fine structure of the brain and spinal cord. His books were translated into German and English. The illustrations for all his papers and books were drawn by himself. The clarity and beauty of his figures based on his observations using a relatively poor-quality microscope then available are a tribute to his extraordinary skill. What is even more remarkable is the fact that in these pictures, he could visualize dynamic features of the functions of the nervous system from the histological preparations of the fixed nervous tissues. All this led him to formulate the "Neuron Doctrine," which challenged the reticular theory vehemently defended by Golgi, Gerlach, and Meynert.

It was around the 1880s that Cajal began to publish his scientific work dealing with histology of the cells in the CNS utilizing a modification of staining techniques earlier developed by Golgi. The first nervous structure studied by Cajal is reported to be the developing cerebellum of the birds. He soon extended his studies to the entire nervous system, staining not only the individual neurons but also their processes, the axons and dendrites, their ascending and descending branches, and their interconnection. His studies included different parts of the nervous system in different stages of development. His personal drawing of his microscopic observation is simply amazing. Even more than the pictures, his interpretation of their functional significance is mind boggling.

The 'Neuron Theory' was in a sense an extension of the 'Cell Theory', the result of a large number of anatomists beginning in early 1880, including Karl Rudolphi, Johann Purkinje, Ernst Weber, and Theodore Schwann. It is to the credit of Schwann to have one of the first descriptions of the cell structure[4] (Zellentheorie) in animal tissues. However, it is Rudolf Virchow's famous statement "Omnis Cellula e Cellula (i.e., cells can multiply only from themselves)" and that "life is essential cellular activity" provided an authoritative seal on this concept.[5] "He enunciated the neuron theory of cellular independence and defended it all through his life, the theory that we, today, take for granted in histology." "So it was that Ramon y Cajal became what Sir Charles Sherrington called him after his death: 'The greatest anatomist of the nervous system.'"[6]

Wilhelm His (1831–1904) had in 1887 established that axons are outgrowths from primitive nerve cells and by 1889 demonstrated the individuality of nerve cells and reported the terms dendrites, neurite, neuropil, neuroblast, and spongioblast. As a matter of fact, Cajal in his Nobel acceptance speech mentioned His work. However, Cajal's great contribution to the history of science is undoubtedly the postulate of "Neuron Theory". One hundred years later, the majority of Cajal's postulates laid out in his lecture to the Swedish Academy continue to be of remarkable scientific currency and have made Cajal the most cited classical scientist in history.[4]

Although Cajal is generally admired for his remarkable contributions to the structural anatomy of the human brain and identified as the proponent of the "Neuron Theory", his insight about the development of the nervous system and the theories about its physiology derived from the "fixed," stained microscopic pictures were personally drawn by him, although less well known, are a true reflection of his unique genius. These include the development of the growth cone of the axon, its possible biochemical basis, the so-called "chemotactic "or" neurotrophic" hypothesis, work on neurogenesis, and the migration of developing neurons to attain their specific position under their mature conditions, which were some of the first descriptions of these fundamental features of the nervous system. It is noteworthy that it was decades later with the advent of advanced techniques that these found their confirmation.

Cajal was the first to introduce the principle of connectional specificity, that is, the idea that a given neuron will not connect randomly to another during development. It is remarkable that in his Croonian Lecture to the Royal Society, London, in 1894, he suggested that "mental exercise facilitates a greater development of the protoplasmic appendix and nervous collaterals. But the pre-existing connections could also be reinforced by the formation of new collaterals and protoplasmic expansions."

This presumption, which was ultimately confirmed by animal experimentations decades later, in principle referred to plastic properties of synapses, and the functional basis of memory is another evidence of Cajal's unique ability to ascribe functions to fixed morphological structures.

In a recent publication, "The Beautiful Brain: The Drawings of Santiago Ramon Cajal," Cajal is reported to have claimed that, "Neurons generate electrical signals and are responsible for many functions of the brain, receiving sensory inputs, processing this information, storing memories, learning, and controlling our muscles."

Although most of his investigations were concentrated on neurons, Cajal contributed a great deal on the glia and synapses. In his flowery language, he wrote, "My attention hunted in the flower of the gray matter cells with delicate and elegant forms, the mysterious butterflies of the soul, the beating of whose wings may someday clarify the secret of mental life."[5] In two of his publications, "Something about the physiological significance of neuroglia" (1897) and "A contribution to the understanding of neuroglia in the human brain" (1913), Cajal postulated that neuroglia regulate and control neuronal and synaptic functions on one hand and regulate brain micro-circulation on the other. Recent experimental findings are a confirmation of Cajal's stipulation based purely on morphological data.[7]

The Neuron Doctrine proposed by Cajal implied that neurons serve as the functional signaling units of the nervous system and that neurons connect to one another in precise ways.[8] He further proposed that nerve cells communicate with one another only at special points of apposition (which Sherrington later called synapses). With his uncanny insight, Cajal proposed the principle of dynamic polarization, that is, the unidirectionality of neural signals. He is reported to have verified the synaptic hypothesis proposed by Sir Charles Sherrington.[9]

Cajal, not surprisingly, received many awards and recognitions, He received honorary degrees from Oxford and Cambridge and Wurzburg and Clark University Worcester, USA. He was honored by a number of medical and science academies, for example, Academy of Medicine, Paris; Swedish Academy of Sciences; Royal Academy of Sciences, Berlin; The Royal Society London; and to top it all the Nobel Prize in 1906. The rivalry between Golgi and Cajal is legendary. Even during their acceptance speeches for the Nobel Prize, the two proposed different theories. It is to the credit of Cajal who gave credit to Golgi for his contributions, but the latter totally ignored Cajal.[3]

Cajal was conscious of these recognitions, not just for his own sake but for the honor of Spain. However, he commented, "Fame bruises while it caresses, it kisses, but it crushes."[5]

Notwithstanding all these recognitions, Cajal at 82 continued to labor in a modest laboratory in his own home. Among his many disciples were del Rio-Hortega, Fernando De Castro, Villi Verde, Sanchez Perez, and his own son Ramon Fananas.

In 1952, a volume of 651 pages was published in honor of the centenary of his birth by members of a research group in neurophysiology at the Caroline Institute, Stockholm, Sweden.[10] The Institute Cajal at Madrid stands as a glorious monument in honor of one of the most outstanding neuroscientists a gift of Spain.

Cajal breathed his last on October 17, 1934.

Some Quotations from Cajal

Cajal warned his pupils against extreme admiration of one's teachers, "It drains the personality and clouds the understanding."

There is no teacher more zealous than he who studies in order to instruct.

Fame bruises while it caresses, it kisses, but it crushes."

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15. Emil Kraepelin (1856–1926)

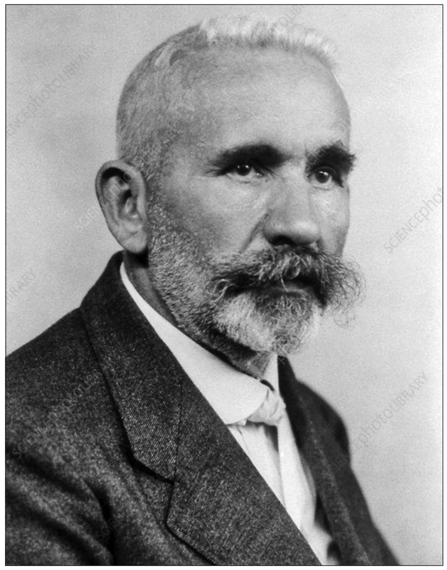

Figure 33: Emil Kraepelin (1856–1926)

Emil Kraepelin was born on February 15, 1856, at Neustrelitz, German confederation. His medical studies started at the University of Leipzig in 1874, where he studied neuropathology under Paul Flechsig and psychology under Wilhelm Wundt. He got his medical degree in 1878 from the University of Wurzburg.

After his graduation, he worked with Bernhard von Gudden, the famous neuroanatomist, at the University of Munich for 4 years. Returning to Leipzig, he completed his thesis – under Wilhelm Erb – "The Place of Psychology in Psychiatry." He completed his doctorate (Umhabilitation) in 1883 at Munich. The same year, his "Compendium of Psychiatry" for the use of students and physicians was first published and was later expanded into "A Textbook: Foundations of Psychiatry and Neuroscience." It was in this book that he argued that psychiatry was a branch of medical science and initiated the foundation of the modern classification system of mental disorders, the precursor of DSM.

Initially starting as a Professor of Psychiatry at the University of Dorpat at the age of 30, within 4 years, he became the Professor and Head at the University of Heidelberg and later moved to Munich as the Professor of Clinical Psychiatry, where he founded the German Institute of Psychiatric Research. Rejecting the prevailing psychoanalytic theories of mental illness, he introduced clinical and neuropathology-based research. As a colleague of Alzheimer, he was a co-discoverer of AD.

He proposed a new classification of mental disorders, distinguishing these into two major groups – manic and depressive and dementia praecox or what is now known as schizophrenia. In addition, his textbook highlighted psychopathic personalities as a disorder of the emotions or moral sense calling these moral insanities. In his last years, Kraepelin was pre-occupied with his teachings.

In the sixth edition of his book "Foundation of Psychiatry and Neuroscience," he included a section on Moral Insanity. In 1925, he published a "Text and Atlas on the Cytoarchitecture of the Adult human Cortex." His fundamental theories on the diagnosis of psychiatric disorders form the basis of major diagnostic systems today, including DSM and ICD.

Kraepelin mentored a number of future leaders of neuroscience, which included Alzheimer, Nissl, von Economo, Brodmann, Achucarro, and Spielmeyer.

He was married to Ina Marie Wilhelmine Schwabe. They had two sons and six daughters. He died on October 7, 1926 at Munich.

Some interesting facts regarding Emil Kraepelin

Founded Deutsche Forsungsanstast fur Psychiatrie at Munich (1902).

Considered to be the "Linnaeus of Psychiatry."

Director of the Institute of Psychiatry at Heidelberg (1895).

Was an associate (or teacher) of Achucarro Nicolas (favorite pupil of Cajal) who worked with Kraepelin and Alzheimer at Munich, co-discoverer of AD and its pathological basis; Korbinian Brodmann and Constantin Von Economo visited Kraepelin in Munich.

Alfons Maria Jacob of Creutzfeldt–Jakob's disease fame, on graduating from Strassburg in 1900 (who had earlier trained with Golgi), joined Kraepelin.

Spielmeyer joined Kraepelin in 1962 as a successor.

Published a text and atlas on the cytoarchitecture of the adult human cortex (1925).

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16. Sir Charles Sherrington (1857–1952)

Figure 34: Sir Charles Sherrington (1857–1952)

Sir Charles Sherrington was born on November 27, 1857, at Islington, London (1857). His father died when Sherrington was a young child. His mother was a noted archaeologist. He was educated at Queen Elizabeth's School Ipswich and developed interest in geology, archaeology, poetry, and painting. He was brought up in a highly cultured home.

In 1876, he began medical studies at St. Thomas's Hospital, London and went to Cambridge to study Physiology under Sir Michael Foster, and in 1880, he entered Gonville and Caius College there.

In 1883, he became the Demonstrator of Anatomy at Cambridge under Sir George Humphrey. In 1884, he obtained his MRCS and in the next year Natural Science Tripos, First Class with Distinction, and later his MB degree from Cambridge. Soon after his medical degree, he went to Spain along with CS Roy to study cholera in that country. Here, he met Cajal, which led to a lasting friendship and evolution of the synaptic doctrine elaborated in his book "The Integrative Action of the Nervous System (1906)". Next year, he went to Italy, apparently to continue the study on cholera. The pathological material collected there was taken by him to Berlin to the lab of the renowned pathologist Virchow, who directed him to Robert Koch's lab, where he stayed for nearly 1 year.

Engaged in research during his undergraduate years, his first short paper was written in association with J.N. Langley, "On Section of the Right Half of the Medulla Oblongata and the Spinal Cord of the Dog." His second paper, also with Langley, was entitled "Secondary Degeneration of Nerve Tracts Following Removal of the Cortex of the Cerebrum in the Dog."

Under his mentor Sir Michael Foster and his senior Langley, he got interested in neurophysiology, which remained his interest life-long.

Upon returning to London, Sherrington was appointed at St. Thomas's Hospital, and in 1891, he was made the Professor–Superintendent of the Brown Institute for Advanced Physiological and Pathological Research. It was the same position Sir Victor Horsley had occupied earlier.

During the decade between 1885 and 1895, Sherrington visited the physiologist Goltz in Strasbourg in Germany. Progressively, his research was concentrated on neurophysiology.

The focus of his work was to investigate the degeneration of the ascending and descending tracts in the spinal cord following lesions of the cerebral cortex and spinal nerve roots. In addition, he studied several other neuronal systems, optic nerves of the rabbit, the sympathetic nervous system of the monkey, the nerve supply of the bladder and anus, the localization of the knee-jerk, and the peripheral distribution of posterior roots. Many of these studies were aimed at understanding the physiology of the spinal cord and the reflex functions. Much of this work on spinal reflexes was summarized in his Croonian Lectures of the Royal Society, entitled "The mammalian spinal cord as an organ of reflex action," and later as Marshall Prize Address, "On the Spinal Animal."

In 1895, he became the Professor of Physiology at the University of Liverpool, where he stayed for nearly 2 decades. It was during this period that he described decerebrate rigidity and published "The Correlation of Reflexes and the Principle of the Common Path." Based on his Silliman Lectures delivered at Yale, he published one of his most famous books, "The Integrative Action of the Nervous System." Notwithstanding his intense pre-occupation with neurophysiology research, he contributed a large number of chapters in several textbooks of Physiology and Medicine, such as those of Foster's, Allbutt's, and Allchin's and chapters for the encyclopedia Britannica and even a Manual of School Hygiene. Taking a lead from the work of his friend Ramon y Cajal, Sherrington introduced the concept of "synaptic hypothesis" in 1898.

In addition to his publication on neurophysiology, he published a number of papers on other subjects such as a preliminary report on the Pathology of Cholera Asiatica as observed in Spain (1885); note on the anatomy of Asiatic Cholera as exemplified in cases occurring in Italy in 1886, Varieties of leucocytes (1885), The History of Trypanosomes in Man (1901), Observations with anti-tetanus serum in monkeys (1917), and The effect of chloroform on the heart (1904).

In 1913, Sherrington accepted to move to Oxford as the Waynfleet Professor of Physiology and remained there until his retirement in 1936, aged 79 years. It was here that he wrote another classic book entitled "Mammalian Physiology: A Course of Practical Exercise." In the relaxed environment here, he enjoyed more personal interactions with his students, who were offered the friendly hospitality of Lady Sherrington at their home, a tradition earlier introduced by Sir William Osler.

The large list of his students includes some of the most distinguished neuroscientists of the 20th century, namely, John Fulton, D. Denny Brown, Harvey Cushing, Wilder Penfield, JC Eccles, and Rudolf Magnus.

It was during the Oxford period that he received the highest recognition. He became a Fellow of Magdalen, the President of the Royal Society (1920), the Order of Merit (OM) 1924, and the Knighthood (1922) and received the Nobel Prize (1932) along with Edgar Adrian. There were many other awards including honorary doctorates from nearly 20 universities, from not only the UK but also other European countries and Canada.

Although during this somewhat relaxed phase of his life his neurophysiology research output had slowed down, his other interests were reflected in the publications such as "Man on his nature," "The Endeavour of Jean Fernel," "The Brain and its Mechanism," and a book of verse entitled "The Assaying of Brabantio and other Verse."

After some years of frail health spent in a nursing home, crippled to some extent with rheumatism, but with an alert mind, Sherrington died suddenly of heart failure on April 3, 1952.

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2. Elvidge AR, Penfield W. Sir Charles Sherrington. In Neurological Biographies and Addresses. London: Oxford University Press; 1936.
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17. Franz Nissl (1860–1918)

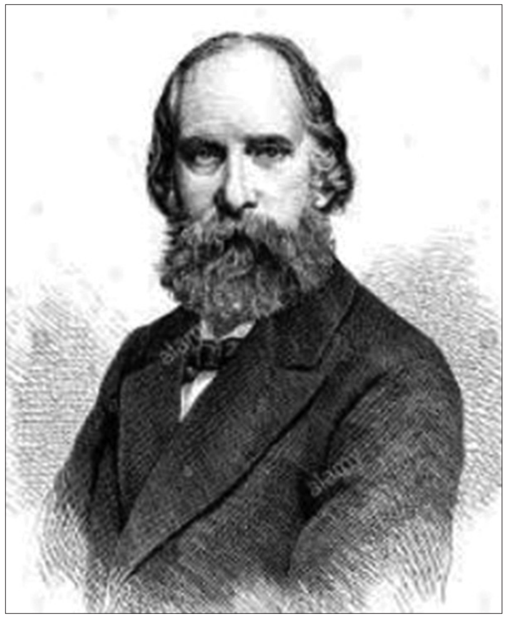

Figure 35: Franz Nissl (1860–1918)

Franz Nissl was born at Frankenthal in Bavaria in 1860. He was a student at Munich and received MD in 1885, reportedly after great difficulty and perseverance. On the recommendation of Bernhard Gudden, he was appointed as an assistant in the district insane asylum at Munich, where he carried out his research particularly on the normal histology of the cerebral cortex. According to Karin D Barron,[1] microglia were first recognized by Nissl in 1899. He named these as "Stabehenzelten" (rod cells) and considered them to be reactive neuroglia. He suggested that they had a capacity for migration and phagocytosis.

Franz Nissl became an assistant at Munchen Kreis Irrenanstalt, moved to Städtische Irrenanstalt at Frankfurt am Main in 1889. It was here that he met Alzheimer of French birth with research interests akin to his. They worked together off and on for 25 years.

Their book "Histologische und histopathologic Arbeiten über die Grosshirnrinde" in six volumes was published between 1904 and 1918. It contained a critical analysis of dementia paralytica by Nissl and Alzheimer's conception of neuroglia and the histopathology of disease later named after him. Nissl was the first person to describe the rod cells in dementia paralytica, whereas Alzheimer described the senile plaques, changes in intra-cellular fibrils, and other microscopic changes in the cerebral cortex of senile dementia.

In 1895, on the invitation of Kraepelin, he moved to Heidelberg. Following Kraepelin's move to Munich in 1904, Nissl succeeded him to the Chair of Psychiatry and Directorship of the clinic. It was at the Heidelberg that he completed his book on The Neuron Theory and its Adherents.

Once again in 1918, on the invitation of Kraepelin, he accepted a research position in the newly founded Deutsche Forschungsanstalt fur Psychiatrie at Munich. By staining techniques developed by him, he demonstrated the till then unknown Nissl granules in the nerve cells. Indebted as we are to Golgi, Cajal, and Hortega for developing staining techniques for various brain cells, it was Nissl who provided staining techniques to provide clear, simple, and constant pictures of the chromodial structure of the cytoplasm. He demonstrated the reaction in the nerve cell body following interruption of the axon. His epic work was on histology and histopathology of general paresis, along with Alzheimer. He initiated the study of cytoarchitectonics of the corticothalamic projection systems in developing the cortex of new-born rabbits. Unfortunately, his premature death prevented this work from being completed. It is said that his days belonged to the patients and the nights to his research, but time was always found for music. He never married.

He is reported to be full of good-humored mockery, particularly toward his chief Kraepelin. Nevertheless, it has been said that a kinder man than Nissl never lived. Having suffered from kidney disease from a young age, he died on August 11,1918, at the age of 58.

Kraepelin in the obituary of Nissl said, "He possessed a thoroughness in research which was stopped by no obstacles, by no difficulty, but above all, an almost cruel self-criticism which could not be corrupted and which controlled all his thinking and a boundless caution in regard to all conclusions. Because of this, he could hardly do enough to satisfy himself in objections, reservations, and repeated testing." (Quoted by Arthur W Young in Neurological Biographies and Addresses. Oxford University Press, London, 1936).

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1. Barron KD. The microglial cell. A historical review. J Neurol Sci 1995;134:57-68.

18. Alois Alzheimer (1864–1915)

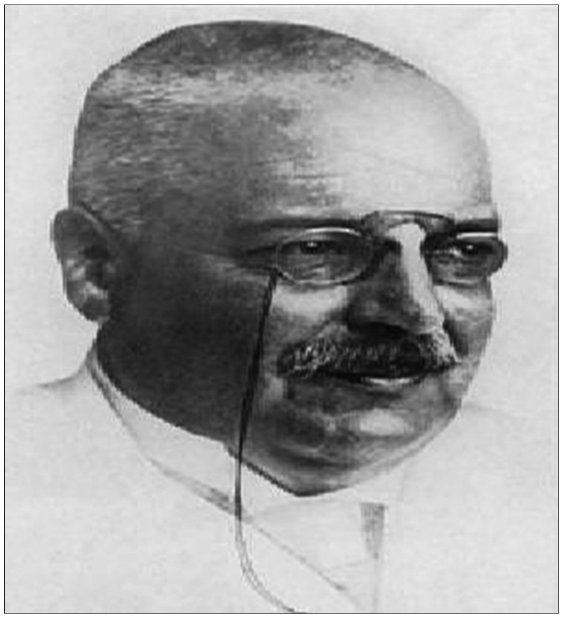

Figure 36: Alois Alzheimer (1864–1915)

Alois Alzheimer was born in Marktbreit, a small town in Bavaria. He attended the Medical School of the Universities of Wurzburg, Tubingen, and Berlin from 1882 to 1887 [**Figure 36**].

He took a position at the Städtische Irrenanstalt in Frankfurt am Main (1888), where he was joined by Franz Nissl. The long collaborative work between the two resulted in "Histologische and histopathologic. Arbeiten über die Grosshirnrinde (Nissl-Alzheimer) Jena, 1904, 1:315-494. Alzheimer is reported to be the chief disciple, collaborator, and friend of Franz Nissl.

Not being selected as the Director of the State Institute, he accepted Emil Kraepelin's invitation (considered the Linnaeus of psychiatry) to Heidelberg in 1902 and later moved with him to Munich, where he worked in the Anatomisches Laboratorium der Psychiatrischen und NervenKlinik. In 1912, Alzheimer was appointed to the Chair of Psychiatry at the University of Breslau. His contributions combined the clinical and pathological approaches to brain disease, including those on general paresis, senility, arteriosclerosis, and acute delirium among others. He is best known for his description of the pathology of senile dementia and its variants to which Kraepelin gave the name of "Alzheimer's Disease."

Alzheimer was introduced to brain histopathology by Franz Nissl at the Municipal Institution for Mentally Disturbed and Epileptics in Frankfurt. Alzheimer's use of the silver staining method, developed by Max Bielschowsky (1902), was crucial for identifying neuritic plaque and neurofibrillary tangles, the defining neuropathological characteristic of the disease. Although the plaques had been described earlier by P. Blocq and G Marinesco in 1892 in an elderly patient with epilepsy, Alzheimer was the first to describe the tangle pathology. In 1911, he described a different type of nerve cell inclusion in two cases with focal degeneration of the cortex, which is now known as the Pick Body after Arnold Pick, who described the clinicopathological entity now known as Pick's disease (1892), which is a part of the spectrum now known as frontotemporal lobar degeneration (FTLD).

During his lifetime, Alzheimer was best known for his clinicopathological studies of neurosyphilis.

He contracted rheumatic endocarditis and died at the young age of 51.

On November 3, 1906, at the 37th Meeting of the Society of Southwest German Psychiatrists in Tubingen, Germany, Alois Alzheimer presented a clinical and neuropathological characteristic of the disease that Emil Kraepelin subsequently named after him. Now, this is the most common neurological disease with 20 million cases worldwide.

Alzheimer was the head of the Anatomical Laboratory at the Royal Psychiatric Clinic of the University of Munich.

Suggested reading:

1. Goedert M, Spillantini MG. A century of Alzheimer's disease. Science 2006;314:777-80.

19. Harvey Cushing (1864–1939)

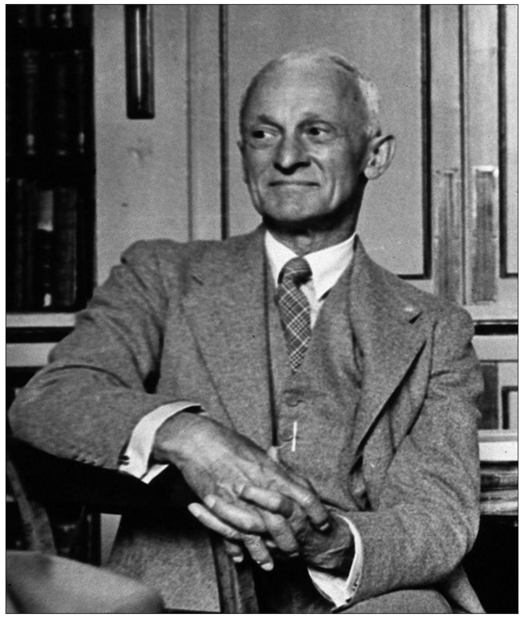

Figure 37: Harvey Cushing (1864–1939)

Born in Cleveland, Ohio, as the ninth child of Henry and Betsey Cushing, his father, grandfather, and great grandfather were all doctors.

He received his education at Yale and Harvard Medical School, where he interned at

Massachusetts General Hospital. He got the degree of Master of Arts and Doctor of Medicine in 1895.

He spent 4 years (1896–1900) at the Johns Hopkins Hospital in General Surgery under William Halsted. Here, he met founders of Johns Hopkins – Welsh, Osler, Howell, and Kelly.

It is interesting to note that during these years, Cushing's attention was drawn to Roentgen's successful demonstration of the use of X-rays for imaging. Along with a couple of other colleagues, he tried to rig up on X-ray equipment. His first paper, dealing with the account of a case of a gunshot wound of the spine, included plates showing the location of the bullet. During these 4 years, in addition to the heavy duties as a surgeon, he experimented on production of gall stones, the bacteriology of the alimentary canal, and the development of cocaine anesthesia.

However, by this time, his interest had turned toward the field of the nervous system. He therefore decided to go to London to visit Victor Horsley and then to Kocher in Berne, Switzerland, and later to the physiology laboratory of Prof. Mosso in Turin.

On the suggestion of Kocher, he initiated studies on the physiological response to intra-cranial tension, which he continued at Turin. The Cushing reflex, that is, the rise of systemic blood pressure in response to an increase in intra-cranial pressure, was described. The last 4 months of this 1-year trip to Europe ended in the laboratory of Charles Sherrington. On return to Baltimore in 1901, he applied for a post as a neurosurgeon. Halsted advised him to take up orthopedics, "a subject which in his opinion covered practically all neurologic maladies having surgical bearings…………"

Cushing thus continued to do general surgery for the next few years, "but contrary to all expectations, neurologic cases began to accumulate in such numbers as to guarantee a living."

From 1901 to 1913, Cushing remained in Baltimore and created the special field of neurosurgery. In addition to his clinical work, he worked in the Hunterian laboratory, developing a teaching course in surgical anatomy using animals as subjects.

It was in Baltimore that he did pioneering work on the blood pressure in man, developed the sub-temporal decompressive operation, perfected the technique of hemostasis using silver clips, and established the value of galeal suture for scalp closure.

He started removing brain tumors in 1902. In 1908, following a visit of Edward Schafer to Baltimore, he undertook the study of the functions of the pituitary gland and developed, both in dogs and man, a successful surgical approach to it.

It is believed that the removal of a meningioma from Major General Leonard Wood in 1910 was regarded as Cushing's first complete extirpation of an intra-cranial tumor. The tumor recurred some years later, and the General died during the second operation. It may be mentioned that most of the cranial operations in the early years were miserable failures.

In 1912, he published the monograph "The Pituitary Body and its Disorders." On the basis of 50 well-studied cases, he enunciated the concept of hyper versus hypo pituitarism. The same year, he accepted the invitation from Boston to become the Moseley Professor of Surgery at Harvard and the Surgeon-in-Chief to the Peter Bent Brigham Hospital. During the First World War, he joined the army and ultimately became the surgical director of the U.S Base Hospital No 5. He developed peripheral neuritis during this period.

In 1919, he returned to Boston and guided the destiny of neurosurgery until 1933, when he accepted the invitation from Yale, the University of his undergraduate studies, to become the Sterling Professor of Neurology.

Among his numerous contributions to neurosurgery (besides the work on the pituitary) are Tumours of the Nervous Acoustics and Syndrome of the Cerebello – Pontine Angle (1917), Intra-cranial Tumors (1932), and Meningiomas and their classification (1938).

More important than these books and a large number of papers was the number of outstanding students to whom he introduced the attention to meticulous details of the evolving surgical techniques and the habit of maintaining detailed records of individual patients.

Amid his busy service and research commitment, on the request of Mrs Osler, he compiled the work of this great physician and published in two volumes "Life of Sir William Osler" (1925), which was awarded the Pulitzer Prize in 1926.

In an address at the time of opening of The Montreal Neurological Institute (MNI), he stated, "So, the measure of this fine Institute will not be what one can outwardly grasp of a carefully planned body, for that is a matter of morphology – of its soma. The real measure will lie in its psyche, the intangible spirit of the laborers within, and for this, as we have seen, there is no standard yardstick. History has repeatedly shown that an institutional esprit, however widely spread throughout a group, is primarily distilled from the ventricles of one of them. So, we may well expect that under the widely trained and many-sided Director (Dr. W.P.) of this new institute neurology will receive a new impetus, making this place still another mecca for workers in the great subject in which we all feel so vitally interested."

This quote does not apply to MNI but to all such academic institutions.

Suggested reading:

John Fulton –A distinguished Neurophysiologist published Cushing's biography, "Harvey Cushing: A Biography", Charles C Thomas Springfield, Illinois, 1946.

Other Publications of Cushing

1. The Pituitary Body and its Disorders, Philadelphia, Lippincott, 1912.
2. Intracranial Tumours, Springfield, Ill, Thomas, 1932.
3. Meningioma; Their Classification – 1938 (With Eisenhardt).

20. Korbinian Brodmann (1868–1918)

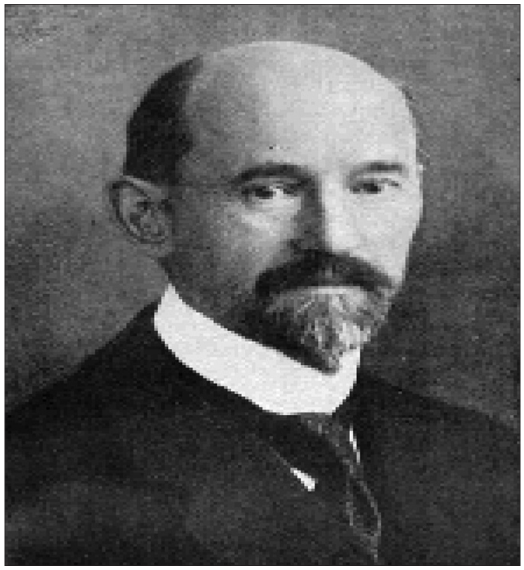

Figure 38: Korbinian Brodmann (1868–1918)

Korbinian Brodmann was born in 1868 in Liggersdorf, Hohenzollern, Germany. He studied medicine in Munich, Wurzburg, Berlin, Freiburg, and received his license to practice medicine in 1895.

Korbinian Brodmann wanted to settle down as a General Practitioner but developed diphtheria. To recuperate from its sequelae, he took a position in a sanatorium for nervous diseases directed by Oskar Vogt, who induced him to devote himself to the study of neurology and psychiatry. In 1898, he received the M.D degree at Leipzig.

In 1900, he met Alzheimer at the State Institute at Frankfurt am Main, under whose influence he became interested in neuroanatomy. In 1901, he moved to Berlin (Neurobiologisches Institut) to work with Vogt – where he developed the present-day science of Comparative Cytoarchitectonics.

Based on his extensive comparative anatomy studies, he established that the cerebral cortex is organized anatomically along with the same basic principles in all mammals. His famous map of the human cortex based on cytoarchitectonic studies appeared in 1908 and his famous book Vergleichenende. Localisations Lehre der Grosshirnrinde in 1909 [Figure 39].

It is unbelievable that he charted the position of some 50 distinct cortical zones devoted to specific cortical functions. These outstanding, unique contributions aroused a lot of opposition to his work, and the University of Berlin refused to admit him as a *privatdozent*, which resulted in a strained inter-personal relationship in the Institute.

He left Berlin in 1910 to join Prof. Gaupp at Tubingen, where he was made a titular professor. Later, when the Deutsche Forschungsanstalt fur Psychiatrie was established at Munich, Brodmann moved there to join Kraepelin, Nissl, and Spielmeyer. Unfortunately, he died shortly after, of acute sepsis.

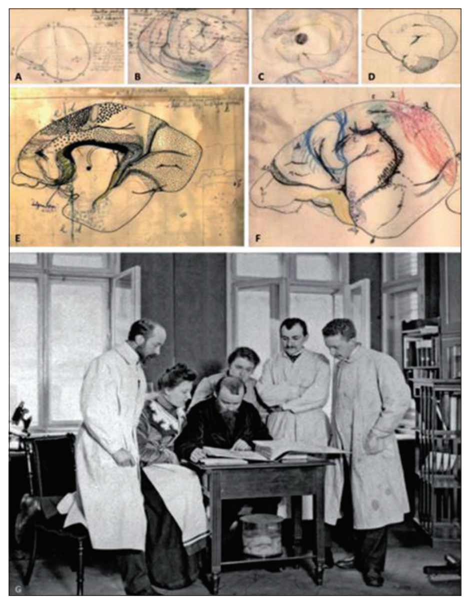

Figure 39: (A–F) Hand drawings of Brodmann (Courtesy-Brodmann Museum, Hohenfels-Liggersdorf, Germany). (A) Lateral view of the left hemisphere of a platypus (Ornithorhynchus paradoxus, Monotremata). (B) Lateral view of the right hemisphere of a spiny anteater (Echidna, Monotremata). (C) Mesial surface of the right hemisphere of a common brushtail possum (Trichosurus vulpecula). (D) Mesial surface of the right hemisphere of the Kinkajou (Cercoleptes caudivolvolus). (E) Mesial surface of the right hemisphere of a prosimian (Lemur niger). (F) Lateral view of the left hemisphere of a kangaroo (Macropus penicillatus). Blue contour primary motor cortex (BA4), red primary visual cortex (BA17), and yellow olfactory cortex. (G) Brodmann together with Ce´cile and Oskar Vogt in the ‘Neurobiological Laboratory’ of the University of Berlin. From left to right: Korbinian Brodmann, Cecile, and Oskar Vogt; the technician Louise Bosse; and the scientific collaborators Max Lewandowski and Max Borchert. Photo taken around 1905. (Courtesy C. & O. Vogt Archive, Institute of Brain Research, University Dusseldorf, Photograph No. 272)

21. Johannes Hans Berger (1873–1941)

Figure 40: Johannes Hans Berger (1873–1941)

Johannes Hans Berger was born in Neuss near Coburg (Thuringia), Germany, in 1873. His father was a physician, and his mother was a highly learned lady. He joined the Psychiatric Clinic in Jena in 1900, made an Ausserordentlicher Professor in 1906 and a Physician in Chief in 1912. Although not a "true psychiatrist," he succeeded Otto Binswanger in 1919 and later became a Rector of the University in 1927–1928 and a Proctor in 1935–1938 when he became Professor Emeritus.

His main interest was the Physical Basis of Psychic Function, although his publications dealt with intra-cranial circulation, bodily manifestations of psychic functions, the temperature of the brain, and psychophysiology. However, his greatest contribution was the innovation of the electroencephalogram. His paper announces that variations in voltage emerging from the brain could be recorded through an intact skull, which was published in Arch. Psychiatry Berlin in 1929.[1]

Initially, the importance, even relevance, of his work was generally unrecognized and even ridiculed. His fellow psychiatrists considered him an unimaginative plodder. He himself lamented that "In Germany, I am not so famous," considering that in 1937, he was invited with Adrian to preside at a Symposium on Electrical Activity in the Nervous System held in Paris.

Distressed by Hitler's destruction of lives and property during World War II, he decided to end his life in a fit of melancholia on June 1, 1941. One of his regrets was that his own country failed to recognize his work, for which he was felicitated abroad. Looking back to what EEG contributed to neurological diagnosis at a time when no other non-invasive techniques were available, it is surprising that Berger did not receive a Nobel Prize, notwithstanding the immense use of EEG in both clinical practice and basic research. It is true that it failed to serve the primary purpose of revealing the physical basis of mental functions, which motivated Berger to initiate this research.

The EEG records the electrical oscillations arising in the brain recorded from the surface of the head. The oscillations vary in frequency over the range of 1–100 Hertz and from a few hundred to few microvolts in amplitude.

Berger's studies began in 1902 in attempts to record from the brains of dogs. From 1924 on, he succeeded in recording the electrical activity of the human brain using string galvanometers without amplification. From 1931 to 1938, with amplification, he continued the intensive studies that established him as the pioneer of human EEG. [Pierre Gloor has collected Berger's 14 papers. This is published in Electroencephalography and Clinical Neurophysiology 18 (1969) Supplement].[2]

Berger discovered the alpha rhythm (10–13 HZ) of the resting brain and its block by the onset of alertness or cognitive activity. The EEG pattern of physical states such as sleep and wakefulness and coma are now well known. Its utility for diagnosis of various types of epilepsy, brain tumors, other pathological states, and brain death has proved to be invaluable in clinical practice. Berger attributed the manifestations of sleep, generalized epileptic seizures, anoxia, and hypoglycemia to an interference with the function of a hypothetical thalamic regulatory center. Over the years, the use of computers and allied technologies have diversified the use of a variety of electrodiagnostic techniques for both basic research and clinical diagnosis.

Berger died as a disappointed scientist in 1941, even though officially he had progressed to the position of a Proctor of the University and as an Emeritus Professor.

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1. Berger H. Uber das Elektrenkephalogramm des Menschen. Archiv Psychiat Nervenkr 1929;87:527-70.
2. Gloor P. Hans Berger and the discovery of the electroencephalogram. Electroencephalogr Clin Neurophysiol 1969;Suppl 28:1-36.

22. Henry Dale (1875–1968)

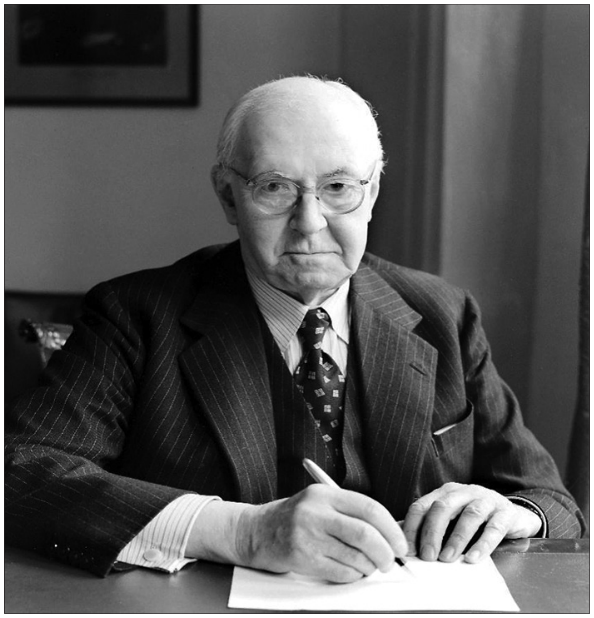

Figure 41: Henry Dale (1875–1968)

Henry Dale was born in London on June 9, 1875. He studied at Trinity College, Cambridge, Natural Science Tripos (Physiology and Zoology), and worked under JN Langley. He attended Medical School at St. Bartholomew's Hospital, London, receiving MD in 1909.

He started research under Prof Starling at University College London and spent 4 months with Paul Ehrlich in Frankfurt. He worked as a pharmacologist at the Welcome Physiological Laboratories (1904) and became its Director (1906). He was appointed in the Department of Biochemistry and Pharmacology at the National Institute of Medical Research, London (1914), and later became its Director in 1928.

After retirement in 1942, he became the Professor of Chemistry and the Director of the Davy–Faraday Laboratory at The Royal Institute. He was the Chairman of Wellcome Trust Board, 1938–1960.

His earlier research was on the pharmacology of ergot alkaloids. He discovered the oxytocic action of the pituitary extract. His later research on histamine led to studies on anaphylaxis and shock. Dale identified acetylcholine and its action as a neurotransmitter, thus establishing the basis of the chemical transmission of nerve impulses. It was established that synaptic transmission depends upon the release of a transmitter from the active pre-synaptic nerve terminal into the synaptic cleft. This acts on the post-synaptic cell membrane.

During the 1960s and 70s, a large number of amino acids, peptides, and other molecules such as norepinephrine, serotonin, dopamine, and GABA were identified as neurotransmitters. With the advent of molecular biology, these chemical processes were further elaborated in the second half of the 20th century. Although the diversity of different neurotransmitters and receptors became very large and complex, it became obvious that the human brain uses only a few molecules as neurotransmitters but uses a huge diversity of neurotransmitter receptors. Soon, the chemical maps of the brain were available.[1]

In addition to many scientific papers, Dale was the author of "Adventures in Physiology'' (1953) and "An Autumn Gleaming" (1954).

He was the President of the Royal Society in 1940–1945 and the President of the Royal Society of Medicine in 1948–1950.

He was Knighted in 1932 and awarded the Nobel Prize in 1936, Order of Merit (OM), 1944. Among innumerable other prizes, he was elected to the Fellowship of US, French, Belgium, Denmark, Sweden, and several other academies.

He was married to Ellen Harriet Hallett in 1904. Their eldest daughter Allision Sarah was married to Lord Todd, Nobel Laureate in Chemistry, under whom several Indian scientists worked. He died on July 23, 1968.

Reference

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23. Pio Del Rio Hortega (1882–1945)

Figure 42: Pio Del Rio Hortega (1882–1945)

Born in Portillo, Spain, he received medical education at Valladolid, graduating in Medicine in 1908.

After practising medicine for 2 years and not liking it, he accepted a position as an auxiliary professor of anatomy at his *alma mater*. He extended his studies in France, England, and Germany and then joined Cajal in Madrid.

Although Cajal's work was concentrated on neurons, Hortega's was devoted to glia. He introduced the silver sodium carbonate method of staining and thus described the "microglia" and "oligodendroglia". Because of some unfortunate misunderstanding with Cajal, he was asked to resign. Hortega, a devoted pupil of Cajal, revered him like a father, even though the latter warned his pupils against the extreme administration of one's teacher.

It is unfortunate that because of an intriguing porter, the two separated, but this did not diminish Hortega's admiration for his teacher until his end.

He established his own laboratory in Madrid, where Dr. Penfield worked for some time. Penfield, who was interested in studying wound healing in the brain, attempted to use the staining method of the Spanish scientists and observed, "The Spanish scientists use silver and gold to impregnate cells selectively. In their hands, its like depth photography. I have tried to make Hortega's method work on the brain scars, and Percival Bailey has tried it on the brain tumor material in Cushing's collection. Neither of us can produce anything to compare with the brilliance of the pictures of Del Rio Hortega publishes[1] Penfield felt that it was clear that if one desired to throw new light on the effect of disease, or injury, and on the process of healing in the brain, the best hope lay in the study of non-nervous cells using Hortega's little tried method."

It is for this purpose that he went to Hortega's Lab in Madrid. It was here that Penfield first stained oligodendroglia in their entirety. When he showed his slide to Hortega, he remarked, "Cesi mejor que yo '' (almost better than I could do).[1]

It may be noted that Hortega's pupil Collado had already performed so for microglia, but no one had performed so for oligos. As a matter of fact, the Germans and the Dutchmen called microglia the "Hortega Cells".[2] According to one of Hortega's biographers, "The microglia danced to him and revealed their graceful limbs. The astrocytes scintillated in their peculiar firmament of the ground substance. Under the microscope, he found a world of beauty which pleased his artistic soul and fed his inquisitive mind."

During the Spanish Civil war, his lab was burnt, and he was sent to Paris to work in the lab of Clovis Vincent and later to England (Oxford) to the Hugh Cairn lab.

In 1940, he left England and accepted the invitation from the Institution Cultural Espanola in Buenos Aires. It was here that he demonstrated the glia of the sympathetic nervous system. He developed cancer and expired in 1945, at the young age of 63.

References

1. Penfield W. Oligodendroglia and its relationship to classical neuroglia. Brain 1924;47:430-52.
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24. Edgar Douglas Adrian (1889–1977)

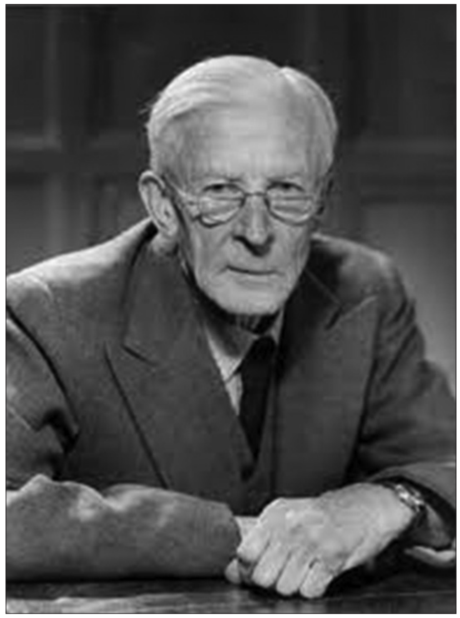

Figure 43: Edgar Douglas Adrian (1889–1977)

Edgar Douglas Adrian was born in London; he was a son of Alfred D Adrian, Legal Adviser to British Local Government. His schooling was at Westminster School, Trinity College, Cambridge (Natural Science Tripos with Physiology) [**Figure 43**]. Along with Elliot Smith and AV Hill, he was one of the distinguished pupils of John Langley who made pioneering contributions to the physiology of the autonomic nervous system.

He graduated BA (1911), was made a Fellow of Trinity (1913) for his investigations on the "all-or-none" principle in nerve, studied clinical medicine at St Bartholomew's Hospital, and received a Medical Degree in 1915.

After working for some time in clinical neurology, he returned to Cambridge in 1919, where in the Department of Physiology, a galaxy of famous scientists such as JN Langley, Walter Fletcher, A.V Hill, and FG Hopkins were doing pioneering work.

He initially worked in the laboratory of Keith Lucas, which he took over in 1919. Here, using sophisticated equipment (Cathode ray tube, Capillary electrometer, etc.), he succeeded in setting up a preparation in a frog consisting of a single end organ in a muscle together with a single nerve fiber to study neuromuscular nerve conduction. He also studied electrical impulses caused by pain. It was during 1928–1932 that he described the method of recording from single sensory and motor axons. This enabled neurobiologists to relate neuronal signaling directly following a stimulus. During the First World War, he worked on patients suffering from nerve injuries. Following his return to Cambridge, he pursued his interest in sensory and motor nerve conduction. He demonstrated that the nerve fibers which conduct pain impulses end in the thalamus and do not directly reach the cerebral cortex. Adrian demonstrated that all neurons use the same mechanism of signaling, that is, the action potential, which manifested the all-or-none phenomenon. This extended from the initial segment of the axon to the pre-synaptic terminal. In addition, he studied the sense of smell and electrical activity of the brain.

His significant contributions were published in numerous papers and three books—The Basis of Sensation (1927), The Mechanism of Nervous Action (1932), and The Physical Basis of Perception (1947). He contributed to "Factors Determining Human Behaviors" (1937).

He was elected the Master of Trinity; the Fullerton Professor of the Royal Society, 1951; the President of the Royal Society, London, 1950–1955; the President of the Royal Society of Medicine, 1960–1962; and the President of the British Association for Advancement of Science. He was the Knighted Baron of Cambridge in 1955.

He was awarded the Nobel Prize with Sir Charles Sherrington (1932) for their work on the function of neurons.

He was married to Hester Agnes Pinsent (a relative of philosopher David Hume), who later became a Justice of Peace and was an enthusiastic social worker. They had one son and two daughters. Adrian expired on April 8, 1977.

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25. Wilder Graves Penfield (1891–1976)

Figure 44: Wilder Graves Penfield (1891–1976)

Wilder Penfield was born on January 26, 1891, in Spokane, Washington, in the north-western frontier of the United States. His father and grandfather were physicians. His mother, who was the leading light of his life, was a school teacher. His father, who left his medical practice owing to his love for deep woods and big game hunting, had practically lost contact with his family.

Penfield studied at Princeton University, where besides his academic pursuit, he became a footballer and later its coach. He excelled in wrestling. It was his biology teacher there, Professor EG Conklin, who prompted him to study medicine. He started at Oxford, UK, as a Rhodes Scholar in 1914.

It was here that he came under the influence of Sherrington and Osler and was initiated in Physiology. During the ongoing World War 1 at that time, his studies were interrupted, and he was injured while travelling in a ship, which was torpedoed. However, he obtained a BA in Physiology from Oxford in 1916. He finished his medical course at the Johns Hopkins Medical School in Baltimore, USA, in 1918. He returned to Oxford in 1919 and got his MA and B.Sc. in 1920. During this visit as a Beit Fellow, besides Oxford, he went to the National Hospital, Queen Square London, where he worked in clinical neurology under Gordon Holmes, in neuropathology with SG Greenfield and in neurosurgery under Percy Sargent.

It was during his second stint in Oxford that he worked along with Cuthbert Bazett on Sherrington's decerebrate animals in the acute and chronic conditions. The results were published in Brain in 1922. In addition, he also published his studies on the changes in the Golgi apparatus of neurons after the axonal section.

On return to the US, he first worked as a surgical intern at the Peter Bent Brigham Hospital in Boston in 1918–1919 when Cushing was initiating neurosurgery. Penfield observed Cushing during this period but did not work with him.

During the next 7 years (1921–1928), he worked in New York as an Associate in Surgery at Columbia University and as an Associate Attending Surgeon at the Presbyterian Hospital and later as an Assistant Professor. The surgical department here was headed by Allen Whipple, who was a real supporter of Penfield's desire to investigate the cause of post-traumatic epilepsy at the cellular level. William Cone joined him in 1924.

Thus, with Whipple's help, Penfield managed to go to Madrid in 1924 to work with Hortega and learn the newly developed staining techniques for brain cells. He managed to apply this technique to study oligodendroglia cells (published in Brain in 1924).

On return to New York, he finally founded the Neurocytology Laboratory (along with William Cone, who had now joined him) in 1924.

Sometime in 1927, Prof Edward Archibald from McGill University, Montreal, visited New York and persuaded Penfield to join him at the Royal Victoria Hospital to start neurosurgery there. After much discussion and "soul searching," Penfield decided to move to Montreal in 1928. With the help of McGill University and a Rockefeller Fellowship, he once again went abroad for 6 months. This was to visit Otfrid Foerster in Breslau to study his technique for surgery for post-traumatic epilepsy. This gave Penfield an opportunity to observe operations on conscious patients as also the use of electrical stimulation to identify the sensory-motor cortex. He also obtained the excised brain tissue to apply the new technique of staining learnt at Madrid. During these 6 months, he visited Prof Leriche in Paris to learn his technique for surgery on the sympathetic nervous system. He also visited the research institute of Oskar and Cecile

Vogt in Germany. Thus, in 1928 (the year of the present author's birth), Penfield moved to Montreal with Cone and joined Colin Russel, a neurologist (who had worked with Victor Horsley). They established the combined Department of Neurology and Neurosurgery at McGill University. With the support of the local authorities, Principal Arthur Currie, Dean CF Martin, and Chief of Surgery Archibald, he, along with Cone, initiated the dual task of establishing a clinical neurosurgical service and a research laboratory to continue their work in the field of neuropathology and cytology, especially to unravel the pathogenesis of post-traumatic epilepsy.

This was helped because of Penfield's training in surgery under Whipple in New York in neurophysiology under Sherrington in Oxford, clinical neurology under Gordon Holmes in London, neurocytology under Rio-Hortega and Cajal at Madrid, and the technique of surgery for epilepsy under Foerster in Germany. Cone had expertise in pathology. With his personal skills, Penfield was able to get full cooperation of the existing French–Canadian neurologists in the town. Soon, they attracted bright young trainees in both neurosurgery (such as Arne Torkildsen, Arthur Elvidge, and Joseph Evans) and basic science (such as Dorothy Russell and Jerzy Chorobski).

All this only further stimulated the real goal of establishing a comprehensive clinical center with state-of-art research laboratories. The story of the creation of the "Institute" is detailed in his autobiography, "No Man Alone". However, with skillful management and support of the state authorities and the University, he was able to get a munificent grant from the Rockefeller Foundation. Thus, the Montreal Neurological Institute, an eight-storey building, was formally opened on September 27, 1934. At that time, it had 50 beds for patient care, two operation theaters, and a number of well-planned research laboratories. Although acknowledging the influence of the British, American, and French traditions, Penfield emphasized that, "……. This inauguration is not a colonial branch of London's National Hospital, not a lesser Salpetrier, springing up in the new world, not an upshoot from an aberrant American root which has tunneled its development way across the unguarded border. We dare to hope that this is the inauguration of an institute of medicine that is characteristically Canadian, the birth of a Canadian School of Neurology." Penfield, the founding Director of this Institute guided its destiny for 26 years, until his retirement in 1960.

He managed its extension to a 135-bedded hospital with some more research laboratories in 1954. Over the years, he managed to add distinguished colleagues such as Francis McNaughton, Reuben Rabinovitch, Herbert Jasper, KAC Eliott, Brenda Milner, and Donald Mc Ray. During this period, the Institute certainly acquired the status of one of the most famous neuroscience enters globally.

Scientific Contributions: Beginning with his earlier pioneering contribution in the field of neurocytology and brain-healing and some other subjects such as vasomotor control of cerebral circulation and classification of brain tumors, Penfield's maximum contribution was in the field of epilepsy. This has been well documented in a large number of papers and six books (list attached). Starting with surgical management of post-traumatic epilepsy, it extended to other focal epilepsies. It led to the identification of temporal lobe epilepsy as one of the most common forms of epilepsy and establishing its treatment. This promoted the development of electrical stimulation of the cortex in conscious adults undergoing surgery for epilepsy as also of electrocorticography along with Herbert Jasper, himself a pioneer neurophysiologist. This provided new insights into the localization of cerebral functions outlining the "Homunculus," identification of the new functional areas such as the supplementary motor area and secondary sensory area, and the role of amygdala and the hippocampus in memory functions. A number of studies were devoted to memory, speech, language, and other psychic phenomena such as automatism, fear, and illusion of familiarity. Similar to many other distinguished neuroscientists, Penfield also got interested in the philosophical aspect of brain–mind relationship.

In his last contribution on the subject published in the book "Mystery of Mind," he ultimately concluded that our being consists of two fundamental elements, "because it seems to be certain that it will always be quite impossible to explain the mind on the basis of neuronal action within the brain" and "I am forced to choose the proposition that our being is to be explained on the basis of two fundamental elements." Several of his colleagues wished that he should have avoided entering this controversial field, having always relied on scientific observations. Another area which led to the unpleasant controversy was his description of a hypothetical "Centrencephalon," a term he coined in 1950. He defined it as that central system within the brain stem which has been or may be in future, demonstrated as responsible for the integration of the function of two hemispheres. On this basis, he even categorized grand mal and petit mal epilepsy as "centrencephalic epilepsy." It was severely criticized by the British neurologist Sir Francis Walshe in 1957. Although one may disagree with Penfield and over the years the term, once quite commonly used, has virtually disappeared from neurological literature, it will be generally agreed that we are still searching for a central integrating mechanism in the brain to explain higher mental functions and consciousness.

Earlier, also in 1931, the two of them (WP and FMRW) had a somewhat "unpleasant" correspondence on one of Penfield's papers, "On the scope of neurology ".[1] Penfield was honest enough to publish this correspondence in "No Man Alone" under notes (pages 371–375).

Recently, an editorial in the British Journal of Neurology, Neurosurgery, and Psychiatry by G.D. Schott has provided an interesting critique on "Penfield's homunculus" and all those following him.[2]

Following his retirement in 1960, he began what he called his "Second Career" (the title of his book published in 1963). On the request of the wife of Alan Greg, an officer of the Rockefeller Foundation who initially was connected with the establishment of MNI, Penfield agreed to write a biography which was later published as "The Difficult Art of Giving" in 1967. He received a Guggenheim Fellowship for this project. In 1965, he became the first president of the Vanier Institute of the Family. Based on his lectures and ideas on this subject, he published a book called Man and His Family in 1967.

Besides these and other scientific books, he wrote two historical novels – No Other God (1954), based on the life of Abraham and Sarah, and the Torch (1960), based on the life of Hippocrates. To collect material for these books he, along with his wife, undertook extensive visits to the Middle East, the site of Ur of the Chaldees for the former and the islands of Cos and Cnidus for the latter. On the persuasion of Theodore Rasmussen, his student and then a successor as the Director of the Institute, he agreed to write his autobiography, "No Man Alone," which in a sense is also the biography of MNI. He worked on it until his last days suffering from cancer.

Penfield expired in April 1976 after submitting the manuscript of this book, which was published in 1977.

Having been a beneficiary of one of his programs, teaching and training of neuroscientists and its promotion globally, a brief mention is made here of another contribution. Penfield had from the beginning an international perspective of his activities, especially this. Himself a product of training in the UK, Spain, and Germany besides USA, he opened the door of his enterprise to others from its start. He arranged for a variety of fellowships for this purpose. Trainees came from all corners of the world.

Donald Baxter, one of his successors as the Director of MNI, writing a foreword to a book by Preston Robb in 1989, commented, "This book will be read with delight by over 2000 neurologists, neurosurgeons, and neuroscientists who have received speciality training in McGill since 1930." The first neuroscientists in several countries including India, Norway, Poland, Chile, and China were trained at MNI, besides a large number from USA. On return to their countries, they spread these disciplines at home.

Awards and Recognitions:

He was a recipient of a large number of national and international awards and recognitions, which included the following:

Fellowship of the Royal Society Canada; the Royal Society, London; the Royal Society of Medicine, London; the American Surgical Association; the Royal College of Surgeons; and the Royal College of Physicians (Eng.).

Honorary Degrees: Princeton, Yale, Toronto, Oxford, Paris, Edinburgh, and Melbourne.

Order of Merit

Cross of Legion of Honor (France) and many others.

Additional note on Homunculus

Starting in the 1930s, Penfield electrically stimulated the brain of epilepsy patients during surgery and found that the cortex, whose stimulation caused movement of various parts of the body, was arranged in an orderly way that roughly reflected the body plan. He depicted his findings in the form of a drawing or a cartoon (or homunculus) draped across the surface of the brain.

He thus showed that there are broad areas of the primary motor cortex devoted to controlling the various parts of the body, leg, torso, arm, and head. He then proceeded to do the same for the sensory cortex and later extended this to other areas, especially the temporal cortex. This generally correct depiction on a 2D cartoon has since been expanded to represent the 3D movement into more detailed maps.[2]

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Footnote: The biography has become somewhat lengthier as the author was trained at MNI and hence had personal contact with Dr. Penfield and interest in his exceptional life.

26. John Eccles (1903-1997)

Figure 45: John Eccles (1903-1997)

John Eccles was born in Melbourne, Australia. He was a son of Mary Carew and William J Eccles, both of whom were teachers. He graduated in Medicine from Melbourne University in 1925 with first class honours. As a Victorian Rhodes Scholar, he went to Oxford, UK, to work under Sir Charles Sherrington at Magdalen College. After obtaining D. Phil (Oxon) in 1929, he continued to work at Oxford until 1937, when he returned to Australia as the Director of a Medical Research Unit in Sydney.

During the Oxford period, his work was devoted to synaptic transmission in the CNS, sympathetic ganglion, and smooth and cardiac muscles using recently developed techniques of electrophysiology at a time when there was controversy regarding electrical versus chemical transmission (proposed by Henry Dale) at the synapses. At Oxford, he also collaborated with Ragnar Granit (who received the Nobel Prize in 1967). He continued his work on synaptic transmission in Australia along with Bernard Katz (NL 1970). He developed the technique of micro-electrode recording of intra-cellular activity. Later, as the Professor of Physiology at the University of Otago, New Zealand, from 1944 to 1951, he resumed the study of synaptic transmission of CNS nerve cells.

In 1951, along with Brock and Coombs, Eccles succeeded for the first time in inserting electrodes into CNS neurons and elaborated the excitatory and inhibitory synapses. These studies led to the publication of the Neurophysiological Basis of Mind in 1953.

Between 1950 and 1960, using intra-cellular recording, Eccles established the ionic mechanism through which motor neurons generate the inhibitory and excitatory action potentials that permit them to serve as the final common pathways for neuronal integration (Albright *et al*. 2000). This in a way elaborated and confirmed the ionic hypothesis Hodgkin, Huxley, and Katz had proposed in 1952.

From 1952 until 1966, Eccles became the Professor of Physiology at the Australian National University, where he studied biophysical properties of synaptic transmission, which is the work cited in his Nobel Prize (1963). Before this, in 1957, he published “The Physiology of Nerve Cells,” although “The Physiology of Synapses” was published in 1964.

In 1966, Eccles moved to the US, first to the Institute of Biomedical Research in Chicago and then to the State University of New York at Buffalo. It was during this period that he published “The Cerebellum as a Neuronal Machine” with Massao Ito of Japan and J. Szentagothai from Hungary. His Sherrington Lectures were published as “The Inhibitory Pathways of the Central Nervous System” in 1969. As a result of prolonged interactions with the philosopher Karl Popper and a dialogue with him, “The Self and its Brain” dealing with brain–mind consciousness was published in 1977.

Eccles was a recipient of a large number of awards and recognitions, which included Knighthood, Fellowships of a number of science academics including the Royal Society London, the Royal Society of New Zealand, and President Australian Academy of Sciences. He was also an Honorary Fellow of the Indian Academy of Sciences. He was awarded the Honorary Doctorate of many universities including Oxford, Cambridge, Melbourne, British Columbia, and Charles University Prague among others.

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27. Rita Levi-Montalcini (1909–2012)

Figure 46: Rita Levi-Montalcini (1909–2012)

Rita Levi-Montalcini was born in Turin, Italy, on April 22, 1909. Her parents were highly cultured and accomplished; her father was an electrical engineer and a gifted mathematician, and her mother was a talented painter. However, both were very conservative with traditional attitudes against a professional career for women. Hence, her twin sister became a painter, one of the most outstanding women painters in Italy. With great difficulty, Rita obtained their father's permission to engage in a professional career and graduated from school at the age of 20. She graduated in Medicine in 1936, enrolled for specialization in Neurology and Psychiatry in Turin.

A victim of Mussolini's dictate, "No Professional Career for non-Aryan Italian Citizens," moved to Brussels.

She returned to Turin after the German invasion and built a small research lab at home in her bedroom. Following Anglo-American invasion in 1941, she moved to Piemonte and later to Florence living underground. She was hired by the Anglo-American Headquarters as a medical doctor for a refugee camp.

At the end of the war, she returned to Turin and assumed an academic position at the University.

She was invited by Prof. Viktor Hamburger to ST. Louis USA, where she ultimately became an Associate Professor and then full Professor in 1958, a position she occupied until 1977.

Owing to the love for her country, she established a research unit in Rome and divided her time between St. Louis and Rome between 1969 and 1978 and also held the position of the Director of the Institute of Cell Biology in Rome. She retired in 1979 but continued her research.

The nerve growth factor (NGF) is the first neurotrophin discovered by Levi Montalcini. The other three are brain-derived neurotrophic factors (BDNFs) characterized by Y.A Barde *et al*.,[1] Neurotrophin 3 (NT3) and Neurotrophin 4 (NT4). They are known to control cell fate, axon growth and guidance, dendrite structure and pruning, synapse formation, and synaptic plasticity.

A large number of growth factors, which promote survival and growth of neurons and those which are responsible for programmed cell death (apoptosis), have since been identified. These discoveries have greatly helped our understanding of neuronal connectivity, selectivity, and development of specialized circuitry.

She was awarded the Nobel Prize for Control of Nerve Cell Growth.

Two other friends, Salvador Luria and Renato Dulbecco, also received Nobel Prize in Medicine and Physiology, earlier than her. All three were inspired by their teacher Levi Giuseppe, a famous Italian histologist working in Belgium.

Reference

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28. Bernard Katz (1911–2003)

Figure 47: Bernard Katz (1911–2003)

Bernard Katz, a son of Russian Jewish parents, was born on March 26, 1911, in Leipzig, Germany. He received most of his education until his MD degree in Leipzig in 1934. In 1935, he moved to work with Professor AV Hill at the University College, London. He was awarded a Ph. D (1939) and D.Sc. (1942) by London University. After a brief period of work with Eccles at Sydney, Australia, he re-joined AV Hill as the Assistant Director of Research and Henry Head Fellow. In 1950, he was appointed as a reader in Physiology and 2 years later professor of Biophysics at the University College, London.

His major area of research was in the field of the physio-chemical mechanism of neuromuscular transmission (for his work with Huxley and Hodgkin, see their biographies). He provided further evidence for the generality of the ionic hypothesis and found that the synaptic receptor for chemical transmitters was a ligand-gated and not voltage-gated ion channel.

Katz was elected Fellow of the Royal Society, London (FRS), in 1952, and its Biological Secretary in 1968; Fellow of the Royal College of Physicians (1968); and Fellow of the Royal Danish Academy of Sciences and Letters (1968) and in the Americana Academy of Arts and Sciences (1969). He was knighted in 1969 and received the Nobel Prize for release of neurotransmitters from nerve terminals, along with Julius Axelrod and von Euler in 1970.

He was married to Marguerite Penly. They had two sons. He expired on April 20, 2003.

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29. Roger Walcott Sperry (1913–1994)

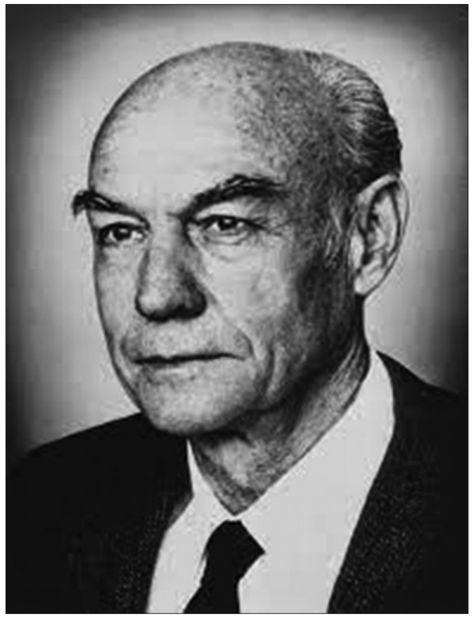

Figure 48: Roger Wolcott Sperry (1913–1994)

Roger Walcott Sperry was born in Hartford Connecticut to Francis Bushnell and Florence Kraemer Sperry on August 20, 1913. He did his early schooling in Elmwood, a suburb of Hartford, and later education at Oberlin College – AB in English 1935. He obtained his MA Psychology in 1937. He also obtained PhD in Zoology under Prof. Paul Weiss at the University of Chicago. He performed 1-year post-doctoral research at Harvard University under Prof. Karl Lashley.

It is interesting that his first major scientific work, lasting nearly a decade, resulted in disproving a widely accepted theory of his mentor Prof. Weiss. This established that the circuits of the brain are hard – wired in early development. Studying regeneration of severed optic nerves in fish, salamander, and frogs, he observed that the fibers of the severed nerve grew back into the brain and made the same connections they had before.

He established the chemical individually of each nerve fiber, resulting in "axonal guidance" during development and regeneration. Taking leads from the work of Cajal, Sperry experimentally showed the radial cortical connections. This was before Mountcastle's discovery of cortical columns.[1]

Notwithstanding the significance of these early research studies, Sperry, however, is best known for his work on "split brain".[2] The first published description of his studies on the result of the corpus callosum section in cats appeared in 1953 as an abstract in collaboration with his doctoral student, Ronald Myers.[3]

This work was later extended to patients undergoing this operation for the treatment of epilepsy by J E Bogen and PI Vogel.[2] M. S Gazzaniga was an active collaborator in these studies. Without going into the details of these studies, it is best to summarize the conclusions in Sperry's words, "the left hemisphere was more geared towards language, abstract, and analytical thought and calculation. The right hemisphere was more important for understanding spatial patterns and complex sounds like music." The experiments confirmed that the operation did not affect intelligence (as measured by IQ) but interrupted inter-hemispheric transfer of information".[4] In his own words, the right hemisphere was not mute but "indeed a conscious system in its own right, perceiving, thinking, remembering, reasoning, willing, and emoting, all at a characteristically human level, and both the left and right hemispheres may be conscious simultaneously in different, even in mutually conflicting, mental experiences that run along in parallel."[5]

In his later life, Sperry became increasingly interested in quasi-philosophical aspects of the unanswered question, which has interested religious seers, philosophers, and scientists of all hues, that is, the brain–mind consciousness relationship and the related theories. He felt that the brain mechanisms would never be understood safely on the basis of the chemistry and biophysics of the single nerve cell.[1] In his views, as expressed in a discussion at a Josiah Macy Conference in 1959 on the Central Nervous System and Behavior, he stated, "I have never been entirely satisfied with the materialistic or behaviorist thesis that a complete explanation of brain function is possible in purely objective terms with no reference whatever to subjective experience, that is, that in the scientific analysis we can confidently and advantageously disregard the subjective properties of the brain process." He favored the concept of emergence as postulated in quantum physics. In his Nobel lecture, he posited, "the events of inner experience, as emergent properties of brain processes, became themselves explanatory causal constructs in their own right, interacting at their level with their own laws and dynamics." It is not surprising that these philosophical views were not easily understood by neurologists and many neuroscientists.

Sperry concluded, "The inner sensation, feelings, precepts, concepts, and mental images or the likes cannot be wedged or measured, photographed, or spectrographed or chromatographed or otherwise recorded or dealt with by any known scientific methodology."[6] Three decades later, Raichle, Frackowiak, and Churchland -expressed the possibility of assigning anatomic specificity of the embodiment of mind, whereas Francis Crick and Koch proposed that, "all aspects of mind, including its puzzling attribute-consciousness awareness, are likely to be explainable in the more materialistic way as the behavior of large sets of interacting neurons."[7-10]

Sperry was a multi-faceted personality with diverse interests such as collecting live wild pets during his school, a variety of athletics in college, sculpture, ceramics, American folk dance, boating, fishing, and collection of fossils later in life.

The list of honors and awards received by him from various universities and academies is not surprisingly enviable, ending with the Nobel Prize received in 1981, along with David Hubel and Torsten Wiesel, for his work on "Split Brain." He was married to Norma Gay Dupree. They had one son and one daughter. He died of amyotrophic lateral sclerosis on April 17, 1994, aged 80, never stopping to work until his end.

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30. Alan Lloyd Hodgkin (1914–1998)

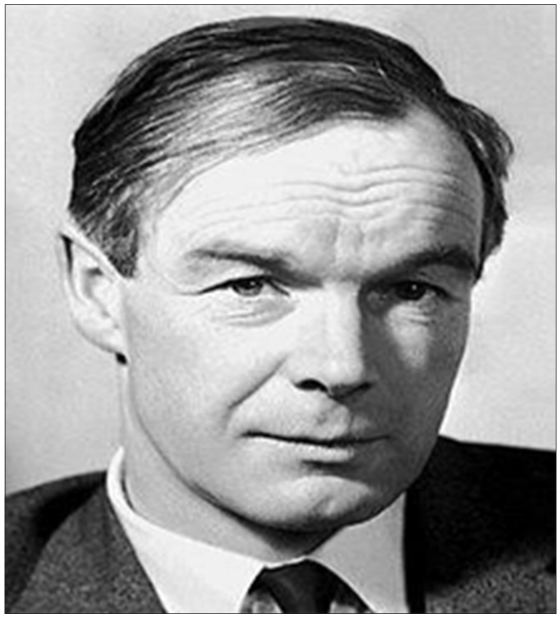

Figure 49: Alan Lloyd Hodgkin (1914–1998)

Alan Lloyd Hodgkin was born in Banbury, Oxfordshire on February 5, 1914. He was educated at Trinity College, Cambridge, 1932–1936. Although a student of biology, on the advice of one of his teachers, he learnt mathematics and physics as well. As an undergraduate, he started experimenting on nerves in the frog, a study he continued for several years, first as a research scholar and later as a Fellow of Trinity.

Based on his Fellowship thesis, he was invited to work at the laboratory of Gasser at the Rockefeller Institute in New York (1937–1938). He returned to Cambridge in 1938 and started his path-breaking association with Andrew Huxley to work on nerve conduction. This collaboration was interrupted during the wartime when Hodgkin worked on airborne radar. After the war, he returned to Cambridge and resumed his studies with Huxley.

Most of his experiments were carried out on giant nerve fibers of squid. This resulted in elaborating the ionic hypothesis. Along with Huxley and Katz, he demonstrated that the resting potential, as well as the action potential, were dependent upon the movement of specific ions, Na, K, and Cl, through the axonal membrane. Along with Huxley and Katz, Hodgkin provided a quantitative account of the ionic currents during the action potential. According to Albright *et al*. (2000), the ionic hypothesis proposed by them remains one of the deepest insights in neuroscience. "It accomplished for the cell biology of neurons what the structure of DNA did for the rest of biology."

However, notwithstanding such path-breaking work on the ionic basis of action potential, controversy persisted up to 1950 whether transmission between neurons in the CNS occurred by electrical or chemical means. Around this time, Eccles, the key proponent of electrical transmission, produced evidence that synaptic transmission was mediated by chemicals (see Eccles).

He was elected Fellow of the Royal Society in 1948, appointed Fullerton Research Professor (1951). He was knighted in 1972 and awarded the Nobel Prize in 1963 along with Sir Andrew Huxley and Sir John C Eccles for elaborating the ionic mechanism of the nerve cell membrane.

He was elected to the Royal Danish Academy; American Academy of Arts and Sciences; Leopoldina Academy, Germany; and the Indian National Science Academy (INSA). He was awarded honorary degrees by a number of universities.

He married Marion, the daughter of the renowned pathologist Peyton Rous. They had three daughters and one son.

Sir Alan expired on December 20, 1998.

Suggested Readings:

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2. Hodgkin AL, Huxley AF. J Physiol 116(1952)49, 473, 497, 117 (1952)500, 121(1953)403.

31. Andrew Fielding Huxley (1917–2012)

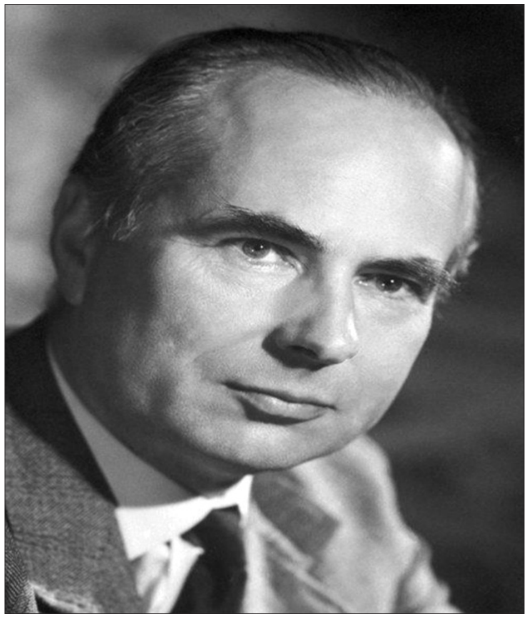

Figure 50: Andrew Fielding Huxley (1917–2012)

Andrew Fielding Huxley was born in Hampstead, London. He was a grandson of Thomas Huxley and a son of Leonard Huxley. The biologist Julian Huxley and Aldous Huxley were his stepbrothers. His family was a distinguished family of intellectual giants of England.

Andrew Fielding Huxley was educated at University College School, London, and Westminster School. He then went to Trinity College, Cambridge, UK, in 1935. Inspired by one of his teachers, he started his Tripos in Physics, Chemistry, Mathematics, and Physiology as an additional subject (1935).

Influenced by Adrian, Hodgkin, and Millikan, he got interested in physiology. He spent 1937–1938 doing anatomy and 1938–1939 doing part II of physiology. During this period, he joined Hodgkin at the Marine Biology Laboratory at Plymouth. It was here that he started research on nerve conduction inside the squid giant axon.

This ultimately led to the "Ionic Theory" of nerve conduction. During the initial years of war, he spent time on operational research in gunnery.

He went back to Trinity College in 1946 in the Physiology Department in various positions until 1960, when he was appointed the Head of the Department of Physiology at the University College, London. Initially, he worked with Hodgkin on nerve conduction, especially the ionic mechanisms of the nerve cell membrane. Later, he turned to muscle contraction, which continued to be his research interest.

Huxley was the Editor of the Journal of Physiology (1950–1957) and the Journal of Molecular Biology. He was elected Fellow of the Royal Society in 1955. He was awarded the Nobel Prize in 1963 for the ionic mechanism of the nerve cell membrane.

He was married to Jocelyn Peace, and they had six children. Sir Andrew expired on May 30, 2012.

32. Vernon B Mountcastle (1918–2015)

Figure 51: Vernon B Mountcastle (1918–2015)

Vernon B Mountcastle was born at Shelbyville, Kentucky, on July 15, 1918 (*belonging back to Pocahontas daughter of the Native American)*, to a distinguished Scottish American family, which had migrated to USA. He was proud to trace his ancestry to the Powhatan Chief.[1] His family moved to Virginia when he was 3 years old. His early education was in public schools and a college in Roanoke, Virginia, getting a BS degree in 1938.

He obtained his MD degree from Johns Hopkins University in 1942. He wanted to be a neurosurgeon and spent the summer of 1942 working as an intern under Walter Dandy. He then served as a physician in the US Navy Amphibious Forces during the Second World War.

On returning to Baltimore after the war, he could not find a position in the Department of Neurosurgery and hence joined as a Fellow (1946–1948) in the Department of Physiology under Philip Ward at Johns Hopkins. In his own words, he found the prevailing experience as "the expectation of excellence." He gave up his goal to become a neurosurgeon and opted to be a neuroscientist. He progressively became an Assistant Professor, Professor (1948–1980), and Director of the Department of Physiology (1964–1980), Johns Hopkins University School of Medicine, and ultimately the University Professor of Neuroscience, School of Medicine (1980).

Working with Bard, he initially studied the limbic system, identifying brain structures contributing to rage. This was published in 1948.[2] He, along with Rose, and others completed the first functional mapping of the thalamic areas representing physical body sensations and then using state-ofthe-art micro-electrode studies.[3] Extending these studies, he produced a detailed representation of the body in the cerebral cortex. However, the most path-breaking work of Mountcastle was the documentation of the columnar organization of the cortical neurons initially in the cat and later in the monkey. Initiating these studies in the primary sensory cortex, that is, the post-central gyrus, in anesthetized cats, these studies were extended to conscious primates, which was at that time a newly emerging technique. Continuing with the somatosensory system, touch and flutter, and later response to stimuli from mechanoreceptors, carefully quantifying the results, he established the direct correlation between the physical stimulus, the neural signals, and the perceptual correlates. The studies involved recordings from the thalamus besides the primary sensory cortex and were later extended to the parietal cortex.

The concept of a columnar vertical organization of cortical neurons established that all cells in a vertical column had a special association and were engaged cooperatively in signal processing and that every recorded neuron responds to the same sources of inputs identified by body location. Furthermore, every neuron has shared properties over a short distance; then, there is a shift to a new population in which every neuron has a new set of properties. He thus concluded that the several hundred million "cortical minicolumns," each comprising 100 neurons, are the basic functional processing units of the cerebral cortex.[4] Fully aware of the distributed nature of the cortical functions, he suggested that local columnar organization is part of this distributed representation that includes columns in other areas of the cortex.[5]

It is surprising that this revolutionary concept evolved as a result of years of painstaking work by him, and his colleagues did not find unreserved approval of the collaborators who declined to be co-authors of this paper.[3] According to Sejnowski, even at an earlier stage when Mountcastle was not yet 40, "cortical columns were considered the musings of an old man."[6]

Besides the studies on the somatosensory system, in later years, these were extended to the posterior parietal cortex, which explored a new field, for example, directed visual attention. This included coding of the depth of perception and other aspects of visual perception in awake monkeys; neural control of eye movements; and oculomotor action planning, command, and control. Mountcastle not only developed the Department of Physiology, which he inherited from Philip Bard, but also created a new Department of Neuroscience and another Brain Research Center, the Zanvyl Krieger Mind/Brain Institute at Johns Hopkins.

He was the first elected President of the Society for Neuroscience in 1969 (presided over its inaugural session in 1971), which has now grown into a mammoth scientific body with researchers from all conventional and newly developed sub-fields of neuroscience. A large number of scientists worked under him and later distinguished themselves as leaders in the field. These included Charles Duffy, WH Talbot, Darian Smith, Apostolos Georgopoulos, RA Anderson, Sten Skoglund, Edward Glaser, Michael Merzenich, Ed Connor, Gian Poggio, and Tom Powell.

It is surprising that Mountcastle and his group do not seem to have much interaction with David Hubel and Torstein Wiesel, who worked at the Wilmer Institute at Johns Hopkins in a similar field, for example, single-cell recordings from the visual cortex. They later moved to Harvard Medical School and got the Nobel Prize. In the author's opinion, Mountcastle deserved the prize no less. In addition to a long list of research publications, he edited the Journal of Neurophysiology and the Textbook of Medical Neurophysiology. He wrote two books, "Perceptual Neuroscience: The Cerebral Cortex" in 1995 and "The Sensory Hand: Neural Mechanisms in Somatic Sensation," at the age of 87 in 2005.

It is not surprising that he received some of the most prestigious awards (except the Nobel), which included the Lasker Award, the Lashley Award, the Sherrington Gold Medal, the Helmholtz Medal, the Cajal Medal, the Fidia Medal in Neuroscience, and the National Medal of Science in addition to six honorary degrees.

Mountcastle married Nancy Clayton Pierpont, a school teacher, in 1946, the same year in which he joined Philip Bard at Johns Hopkins. He died on January 11, 2015, at the age of 96. He had two sons and a daughter.

References

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2. Bard P, Mountcastle VB. Some forebrain mechanisms involved in expression of rage with special reference to suppression of angry behaviour. Res Publ Assoc Res Nerv Ment Dis 1948;27:362-404.
3. Menzerich Michael M, Vernon B. Mountcastle: A Biographical Memoir. US: A National Academy of Sciences; 2019. Available from: http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/mountcastle-vernon.pdf.
4. Mountcastle VB. The columnar organisation of the neocortex. Brain 1997;120:701-22.
5. Andersen RA. Obituary: Vernon B Mountcastle (1918-2015) Curr Biol 2015;25:R310-3.
6. Sejnowski TJ. Vernon Mountcastle: Father of Neuroscience. PNAS 2015;112:6523-24.

Suggested reading:

1. Connor Ed. Vernon B Mountcastle: In memoriam. Neuron 2015;85:899-900.

33. Godfrey N. Hounsfield (1919–2004)

Figure 52: Godfrey N. Hounsfield (1919–2004)

Godfrey N. Hounsfield was born and brought up in a village in Nottinghamshire, UK. As a young boy living on a farm, he became interested in experimenting with farm equipment and constructing an electrical recording machine, a homemade glider, and so forth. He was schooled at Magnus Grammar School in Newark.

During the Second World War, he joined the Royal Air Force as a volunteer reservist and got interested in a course on Radio and later in Radio Communication.

After the War, he got a Diploma from the Faraday House Electrical Engineer College in London.

He then joined the Staff of EMI in Middlesex in 1951, worked on radar and guided weapon programs, and got interested in computers. He led a design team building the first all-transistor computer EMIDEC 1100 in England (1958). He got interested in automated pattern recognition, which led to the idea which was to ultimately become the EMI scanner and the technique of computed tomography between 1967 and 1976. For this, he was awarded the Nobel Prize along with Allan Macleod Cormack in 1979. "As a bachelor, I have been able to devote a great deal of time to my general interest in science which more recently has included physics and biology." He was fond of and played the piano.

34. Torsten N Wiesel (1924 to present)

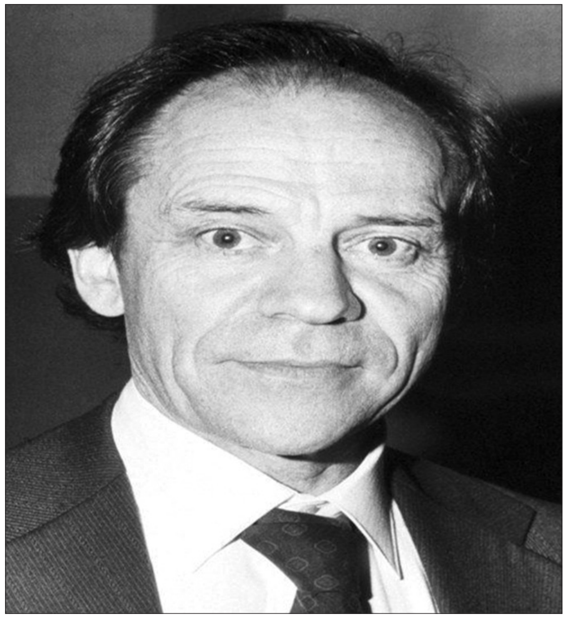

Figure 53: Torsten N Wiesel (1924 to present)

Torsten N Wiesel was born on March 6, 1924, in Uppsala, Sweden, to Anna–Lisa (mother) and Fritz S Wiesel (father) as the youngest of five children. His father was a psychiatrist and the head of a mental hospital on the outskirts of Stockholm. More interested in sports, Torsten was an average student. However, he did reasonably well as a medical student. Because of his background, even as a medical student, he spent 1 year working in different mental hospitals. However, his interest in neurophysiology was stimulated by his professors, Cart G. Bernhard and Rudolf Skoglund. After his graduation in medicine, he joined Professor Bernhard's Neurophysiology Laboratory at the Karolinska Institute in 1954 for doing basic research.

He then moved to Johns Hopkins Medical School to Dr. Stephen Kuffler's Laboratory as a post-doctoral fellow. Here, he was introduced to visual neurophysiology. This was the beginning of his collaboration with David Hubel for many years, devoted to information processing in the visual system. It was for this research that the two of them (along with Roger Sperry) got the Nobel Prize in 1981. Along with Dr. Koffler, he moved to the Harvard Medical School. In 1983, Wiesel became the Vincent and Brook Astor Professor at the Rockefeller University, where he established a laboratory of neurobiology. Over nearly 2 decades, he elaborated the circuitry of the primary visual cortex in collaboration with Charles Gilbert. He was invited to be the President of the Rockefeller University in 1991, from where he retired in 1998. In 2000, he accepted the position of Secretary General of the Human Frontier of Science Program at Strasbourg.

Besides a number of prestigious administrative and policy making appointments in both USA and other countries, he served as the President of the International Brain Research Organization (IBRO 1998–2004); the Board of Governors of the New York Academy of Sciences (2001–2006); the Board of Directors of the Population Council (1999–2008); and the Chairman Committee of Human Rights of the National Academy of Sciences, USA (1994–2004).

In 2007, the Torsten Wiesel Research Institute was established at West China hospital in Chengdu by the world eye organization.

Dr. Wiesel's Interaction with NBRC

Dr. Wiesel visited us at the National Brain Research Center on three occasions (December 2003, May 2006, and November 2010).

Some Important Publications

1. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol 1963;26:1003-17.
2. Ibid. Comparison of the effects of unilateral and bilateral eye closure on the cortical unit response in kittens. J. Neurophysiol 1965;28:1029-40.
3. Katz LC, Gilbert CD, Wiesel TN. Local circuits and ocular dominance columns in monkey striate cortex. J Neurosci 1989;9:1389-99.

35. David H Hubel (1926–2013)

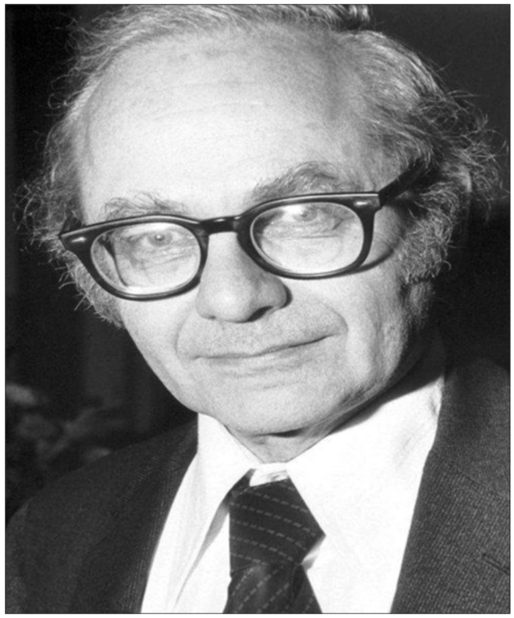

Figure 54: David H Hubel (1926–2013)

David H Hubel was born in Windsor, Ontario, Canada, on February 27, 1926. His parents were born and brought up in Detroit, USA. His father, who was an engineer, later moved to Canada. He gives credit to his Irish history teacher Julia Bradshaw for awakening his interest in learning how to write readable English. He owed much of his interest in science to his father, but to his mother, he quoted "goes much of the credit for encouraging me to work for whatever objectives I set for myself." He grew up in Montreal and was schooled at Outremont. As a child, he was interested in chemistry and electronics and studied mathematics and physics at McGill College. He graduated in 1947.

For no obvious reason, he applied to Medical School at McGill; "Rather to my horror, I was accepted," he had quoted.

Not having done any biology at all, he spent the summer at MNI and became fascinated by the nervous system, impressed by the work of Penfield and Jasper. He spent 2 years' residency in Neurology and 1 year in Jasper's lab, who he describes was "unequalled for his breadth and clarity of thinking in brain science."

He moved to the US for a year of Neurology at Johns Hopkins in 1954. He was drafted by the army as a doctor assigned to the Walter Reed Army Institute of Research, Neuropsychiatry Division, and "there at the age 29, I finally began to do research," he quotes. It was here that Walle Nauta worked in neuroanatomy among several other distinguished biologists. His main project of research initially was "a comparison of the spontaneous firing of single cortical cells in sleeping and waking cats" by recording from the visual cortex. In 1958, he moved to Wilmer Institute, Johns Hopkins Hospital, and there, he began his collaboration with Thorsten Wiesel. This whole lab was moved to Harvard Medical School a year later as a part of the Department of Pharmacology. Five years later in a move unprecedented for Harvard, a new Department of Neurobiology was started, where he worked for the next 22 years. He had a number of hobbies including music (piano and flute), woodwork, photography, and astronomy.

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2. Ibid. Early exploration of the visual cortex. Neuron 1998;20:401-12.
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4. Hubel DH, Wiessel DH. Receptive fields, binocular interaction and functional architecture in cat's visual cortex. J Physiol 1962;160:106-54.
5. Hubel DH, Wiesel TN. Ferrier lecture: Functional architecture of macaque monkey visual cortex. Proc R Soc London (Biol) 1977;198:1-59.
6. Ibid. Receptive fields and functional architecture of monkey's striate cortex. J Physiol 1968;195:215-43.

36. Eric R. Kandel (1929 to present)

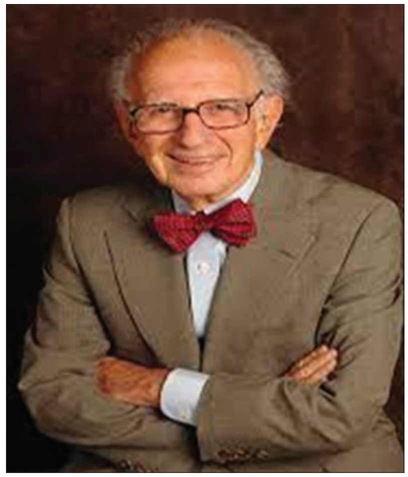

Figure 55: Eric R. Kandel (1929 to present)

Eric R. Kandel was born in Vienna, Austria, more than a decade after the breakdown of the Austro-Hungarian empire. Vienna was still intellectually vibrant, a great cultural center of the world.

Schooled in Vienna and later in Erasmus High School Harvard College, he became interested in Freud. He joined N.Y.U. Medical School to study psychiatry to become a psychoanalyst–psychiatrist under the prominent analysts Ernst and Marianne Kris, the parents of his friend.

He decided to learn about the "biology of mind" and so moved to Henry Grundfest's lab at Columbia University. Influenced by Grundfest, Kuffler, and Crain, Kandel planned to take a reductionist approach to the biology of learning and memory and selected Aplysia (molluscs) for this purpose.

However, he decided to spend a couple of years at the Harvard Medical School, doing Residency in Psychiatry. Here, in his spare time, he could work in the laboratory of Steven Kuffler, who had brought David Hubel and Torsten Wiesel along with him from Johns Hopkins. It was here that Kandel was able to record intra-cellularly from hypothalamic neuroendocrine cells and found these cells to have all the electrical properties of normal nerve cells.

Kandel then went to Paris to work in the lab of Tauc, who had a lot of experience with Aplysia. Here, he observed synaptic changes that paralleled the behavioral changes during habituation, sensitization, and classical conditioning.

He returned to Harvard after 16 months and then moved to New York University to focus on the behavior of Aplysia and start work on the molecular basis of memory storage.

He was invited to Columbia University N.Y to become the founding Director of the Center for Neurobiology and Behavior along with several of his earlier collaborators, James Schwartz, Alden Spencer, and Irving Kupfermann.

Summarizing his work of the last 10 years, Kandel recorded, "During the past 10 years, my career has begun to come full circle. From an initial interest in the complex cognitive problems of psychoanalysis and memory storage, my research on memory led me first to the mammalian hippocampus, which proved too difficult as a first step and forced me to take a more reductionist approach and study initially the simplest forms of memory in Aplysia woodwork, and then only much later, the more complex forms of memory in mice.

I found that despite important differences in details, simple implicit and explicit memories have a similarly short- and long-term storage form.

In each form, short-term storage requires covalent modification of pre-existing proteins leading to the alteration of pre-existing synaptic connections, whereas long-term memory storage requires gene activation, new protein synthesis, and the growth of new synaptic connections."

In short, he relentlessly pursued the question of how memories are formed, preserved, and discarded.

He was awarded the Nobel Prize in 2000 for signal transduction in the nervous system, learning along with Arvid Carlsson and Paul Greengard.

Suggested readings:

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3. Kendel ER, Spencer WA. Cellular neurophysiological approaches in the study of learning. Physiol Rev 1968;48:65-134.
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37. Gerald M Edelman (1929–2014)

Figure 56: Gerald M Edelman (1929–2014)

Gerald M Edelman was the Director of Neuroscience Institute and the Chairman of the Department of Neurobiology of the Scripps Research Institute, USA; Edelman was born on July 1, 1929, in New York. He was a son of a practising physician. He was educated in New York Public School, received the B.S degree, *magna cum laude* in 1950, and attended a medical school at the University of Pennsylvania. He received his MD degree in 1954.

In 1957, he joined the Rockefeller Institute, USA, as a post-graduate student under Dr. Henry Kunkel, wherein he received his Ph. D degree in 1960. He then continued at Rockefeller University in various capacities.

Edelman made significant contributions in biophysics, protein chemistry, immunology, cell biology, and neurobiology. His studies led to the discovery of cell adhesion molecules.

He established that the precursor gene for the neural cell adhesion molecule was responsible for the entire molecular system of adaptive immunity. From the 1970s, he devoted himself largely to the brain and study of consciousness. He founded the Neuroscience Institute in 1981 at Rockefeller University. It moved to the Scripps campus in the LA Jolla section of San Diego. He formulated a theory to explain the development and organization of higher brain functions in terms of a process called neuronal group selection. This he designated "Neural Darwinism". He formulated a biologically based theory of consciousness "including one later elaborated in his four books with Giulio Tanoni entitled "A Universe of Consciousness," "How Matter Becomes Imagination," and "Bright Air, Brilliant Fire," on the Matter of Mind". The other two books were "Wider Than Sky" and "Second Nature: Brain Science and Human Knowledge." He published more than 500 papers.

He received the Nobel Prize for Physiology or Medicine in 1972. This was for his earlier studies on the structure and diversity of antibodies. It was only later that he got involved in neurobiology research. He was a recipient of many honorary degrees and fellowships of various academies including the National Academy of Sciences, USA, and the Academy of Sciences, Institute of France.

He was married to Maxine Morrison in 1950 and had three children. He died at the age of 84 on May 17, 2014.

Some quotations from Edelman

"Can you ask a question in such a way as to facilitate the answer? And I think great scientists do it." (Gerald Edelman, NL 1972).

"The brain of an adult human is about three pounds in weight. It contains about 30 billion nerve cells or neurons. The most recently evolved outer corrugated mantle of the human brain, the cerebral cortex, contains about ten billion neurons and one million billion connections or synapses. Counting one synapse per second, we would just finish counting these 32 million years from now. If we considered the numbers of ways in which circuits or loops of connections could be excited, we would be dealing with hyper astronomical numbers: 10 followed by at least a million zeros (there are 10 followed by 79 zeros, give or take a few, particles in the known universe)."

The brain is inter-connected in a fashion no man-made device yet equals."

"A brain's connections are not exact."

"At the finest scale, no two brains are identical, not even those of identical twins. Furthermore, at any two moments, connections in the same brain are not likely to remain exactly the same."

"The general cellular functions of neurons such as respiration, genetic inheritance, and protein synthesis are like those of other cells in the body. The special features related to neural function are mainly concerned with synapses."

"The different functionally segregated areas are for the most part reciprocally connected. This is why the brain can sense the environment, categorize patterns out of a multiplicity of signals, initiate movement, mediate learning and memory, and regulate a host of bodily functions. We do not presently understand fully how this is done."

"During development and behavior, neuronal groups are formed that consist of local collectives of strongly inter-connected neurons that share inputs, outputs, and response properties. Each group is connected to only certain subsets of other groups and possibly to particular sensory afferents or motor efferents. In a given brain area, different combinations of the group are activated preferentially by different input signals". "To explain brain functions, localizationism "favors specificity" of local brain modules, whereas "holists" stress global integration, mass action, and Gestalt phenomena for analysis of brain complexity suggest that effective brain function arises both from the combined action of local segregated parts having different functions and from the global integration of these parts mediated by the process of re-entry."

Some important publications of Edelman:

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Chapter 7B: BRIEF BIOGRAPHICAL NOTES

1. William Harvey (1578–1657)

Figure 57: William Harvey (1578–1657)

The continuous circulation of blood within a contained system was the 17th century's most significant achievement in physiology and medicine. In Galenic physiology, blood was thought to be produced in the liver, where it received "natural Spirit."

Harvey believed in the circulation of the blood as early as 1615 but did not publish it until 13 years later in his monumental work, "Exercitatio Anatomical de Motu Cordis et Sanguinis in Animalibus" (on the Movement of Heart and Blood in Animals). For 20 years after its publication, it was a subject of controversy. In this initial period, many medical men ignored him.

2. Franciscus Sylvius (1614–1672)

Figure 58: Franciscus Sylvius (1614–1672)

Franciscus Sylvius was born in Hanau in Germany on March 15, 1614, and was initially named Franz de le Boe. He, however, received his medical education and spent the rest of his life in the Netherlands. He practiced medicine in Amsterdam but later moved to Leiden, Germany, as a professor of medicine. He became the Vice Chancellor of the University in 1669–1670. He is credited to have founded the first academic chemical laboratory because he believed that all life and disease processes are based on chemical action. He studied the structure of the brain and described the lateral fissure "a deep fissure or hiatus which begins at the roots of the eyes and runs posteriorly above the temples as far as the root of the brain stem." It divides the cerebrum into an upper larger part and a lower smaller part." This was later named Sylvian Fissure by Bartholin. The connection between the third and fourth ventricles is also named after him as Aqueduct of Sylvius.

From the available information, it does not appear that he attributed any special function of these anatomical structures. In addition to the brain, he contributed to blood circulation and digestion. His book Opera Medica was published posthumously in 1679.

He possessed 190 paintings, some by famous artists (Ref: Wikipedia).

3. Jacob Augustus Lockhart Clarke (1817–1880)

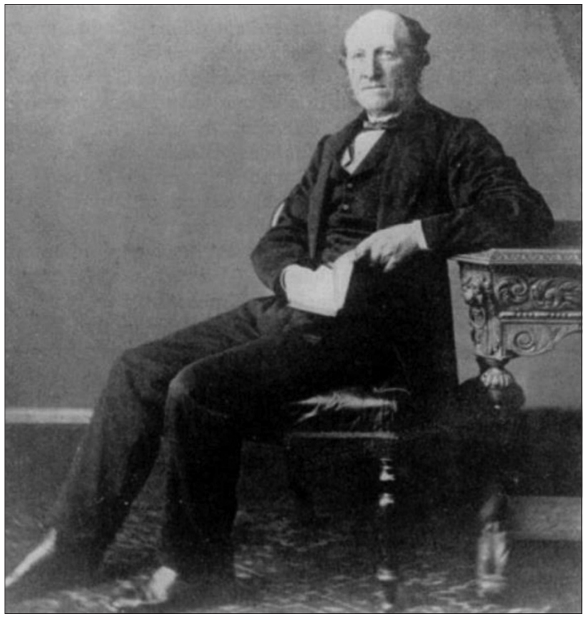

Figure 59: Jacob Augustus Lockhart Clarke (1817–1880)

Jacob Augustus Lockhart Clarke was a British born in London engaged in general practice but better known for his research on the spinal cord, especially those establishing the nucleus dorsalis, "Column of Clarke and the nucleus intermedius-lateralis." He described syringomyelia more or less as it is known today, being preceded by Gall and elaborated by Halfopean, Charcot, Joffroy, and Thedore Simon.

4. Silas Weir Mitchell (1829–1914)

Figure 60: Silas Weir Mitchell (1829–1914)

He was of Scottish descent – USA citizen. He had his medical education at the University of Pennsylvania and Jefferson Medical School and 1-year medical study in Paris.

His earlier studies were on snake venom. He started work in Clinical Neurology in 1863 but was deeply interested in research in neurophysiology, physiology of the cerebellum, cutaneous sensation after nerve injury, and protopathic and epicritic sensation.

He studied gunshot wounds, nerve injuries, and a host of other diseases.His place in neurology is not founded on a single immortal discovery but is rather the result of consistently important controlled works. He was considered the Father of American Neurology.

5. Wilhelm His (1831–1904)

Figure 61: Wilhelm His (1831–1904)

Born in 1831, Wilhelm belonged to a wealthy Swiss Family. He received his medical education at some of the best European schools – Basle (1849), Bern (1850), and Berlin (1850–1852) under Johannes Muller, Remak, Virchow, Kolliker, Brown–Sequard, Claude Bernard, and Meissner.

He proposed a new classification of tissues based on histogenesis and did extensive work on developmental anatomy, especially of the nervous system.

In 1887, he established that axons are outgrowths from primitive nerve cells, and in 1889, he demonstrated the individuality of nerve cells. Dendrites, neurite, neuropil, neuroblast, and spongioblast are terms that he introduced in medical terminology.

He established that the neural parts of the nervous system originate in the ectoderm, whereas the blood vessels arise in the mesoderm. After his lucid explanation, the ectodermal origin of Virchow's neuroglia was never contested.

His son, Wilhelm His, Jr, was also a distinguished anatomist whose name is linked with the cardiac atrioventricular bundle he first described in 1893.

6. Gustaf Magnus Retzius (1842–1919)

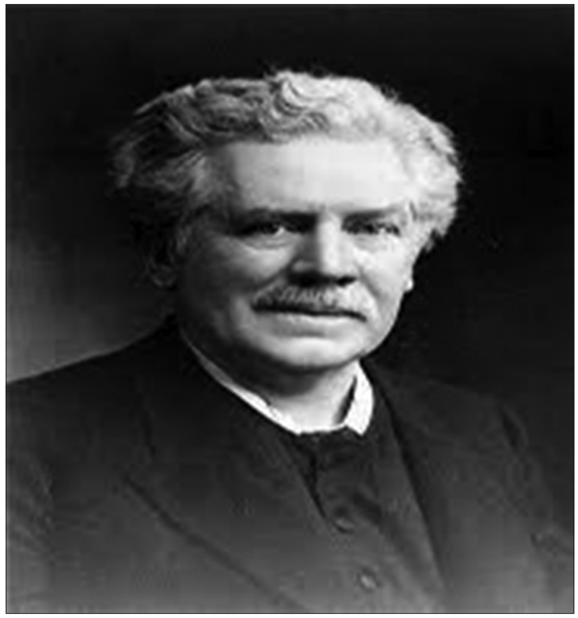

Figure 62: Gustaf Magnus Retzius (1842–1919)

Gustaf Magnus Retzius was born in Stockholm – a son of a Professor of Anatomy at Karolinska Institute. Educated at the University of Uppsala, he received his medical degree in 1871.

He became Docent in Anatomy at the Caroline Institute, where along with Axel Key, he began research on the membranes and cavities of the nervous system.

Experimentally and by dissection, he established the existence of foramina of Magendie (discovered in 1825) and of Luschka (discovered in 1859) and presented the view that CSF escapes from the sub-arachnoid space through the Pacchionian bodies into the sub-dural space and then the venous sinuses.

Interestingly, he took over as the Editor of the national newspaper Aftenbladet, owned by his father-in-law, for 4 years. He returned to Caroline Institute and published 333 scientific papers – dealing with comparative anatomy.

He delivered Croonian Lectures of the Royal Society, London, in 1908.

He donated his brain, which is preserved in the pathology museum of the Caroline Institute.

His book "Biologische Untersuchungen Der Neuroglia des Gehirn beim Menschen und bei Säugetieren," Vol 6, Verlag von Gustav Fischer, Jena, 1894 (Quoted by Matash and Kettenmann in Brain Res Rev 2009) deals with his lesser known contributions on Glia.

7. Walter Halbrook Gaskell (1847–1914)

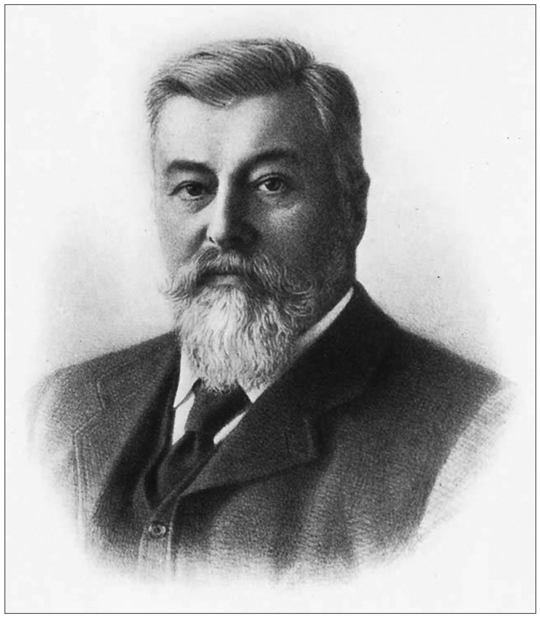

Figure 63: Walter Halbrook Gaskell (1847–1914)

Walter Halbrook Gaskell was born in Naples, Italy, although his family home was in England. He was educated at Trinity College, Cambridge, and University College, London. He later worked as a Faculty of Cambridge University. Gaskell's accomplishments were in the field of the autonomic nervous system. He established the histological foundation of the autonomic nervous system, upon which Langley expanded. His innervation studies in different animals led to the mapping and interpretation of the nerve supply to the vascular system. The results of this study, first announced in 1885, were incorporated in an exhaustive treatise published in 1886 (J. Physiol 7, 1-80, 1886), which was a landmark in the history of the investigation of the sympathetic nervous system.

He delineated the pre-ganglionic outflow to the thoracic segment and the first two lumbar segments. He also published "The Involuntary Nervous System," London. Longmans, Green & Col 1916.

8. Constantin Von Monakow (1853–1930)

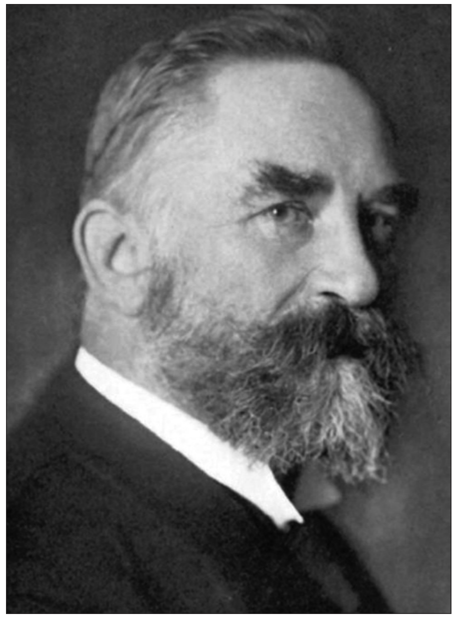

Figure 64: Constantin Von Monakow (1853–1930)

Constantin von Monakow was born in a Russian family in Dresden, Germany, and later moved to Zurich, Switzerland, where he did his primary schooling.

Although he was interested in philosophy and history of art and literature, he still studied histology and embryology with Prof Von Frey and Prof Hermann, who interested him to study Anatomy under Hermann Meyer.

At this time, it was still taught that the site of the soul was in the corpus callosum.

He later got interested in macroscopic and microscopic pathological anatomy as an assistant to Hitzig, who in 1870 had discovered the electrical excitability of certain parts of the cortex. He studied histology of the brain in various types of dementia.

Working with Gudden in Munich, he saw secondary atrophy of the anterior corpus quadrigemina after enucleation of an eye in a cat and also secondary atrophy of the thalamus after partial destruction of the same hemisphere. He showed that the optic nerve took its origin from ganglion cells in the retina.

He studied the nuclei of the thalamus and their projection on the cortex.

He also studied and described many other neuroanatomical structures such as the rubrospinal bundle.

9. Ludwig Edinger (1855–1918)

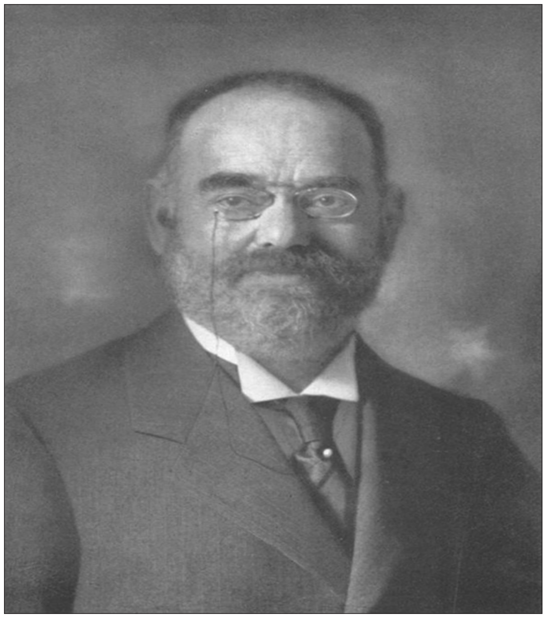

Figure 65: Ludwig Edinger (1855–1918)

Ludwig Edinger was born in Giessen, Germany, and was the Founder of a Neurological Institute in Frankfurt financed by himself. He described the Edinger Westphal nucleus (1885–1887).

He was the first to describe the syndrome of thalamic pain (1891) – verified at post-mortem. In 1911, he proposed that hormones of the anterior pituitary lobe be transported up the pituitary stalk to the hypothalamus.

10. Alfred Walter Campbell (1868–1937)

Figure 66: Alfred Walter Campbell (1868–1937)

Alfred Walter Campbell was born in Australia and practiced as a neurologist and psychiatrist in New South Wales. It has been claimed that although some spadework had been performed earlier, it is safe to say that the architecture of the cerebral cortex started with Campbell in England and Brodmann in Germany.

His magnum opus, "Histological studies on the localization of cerebral function (Cambridge University Press 1905)," became a classic, and his map of the human brain has been reproduced in virtually every textbook on neuroanatomy. His biographer Gerhard von Bonin felt that although Brodmann thought mainly as a comparative morphologist and evolutionist, Campbell thought fundamentally in terms of function.

11. Prof Oskar Vogt (1870–1959)

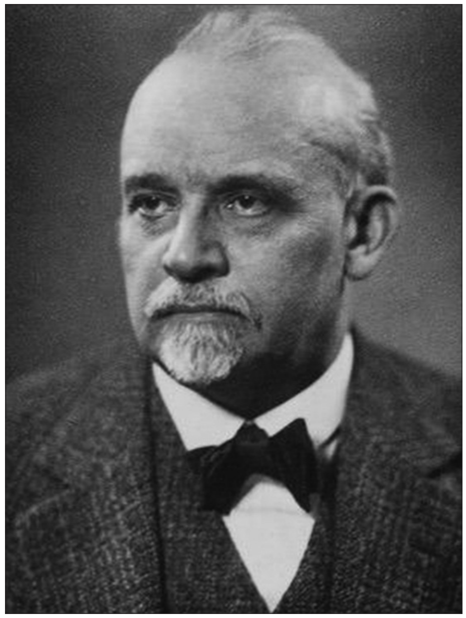

Figure 67: Prof Oskar Vogt (1870–1959)

He was a great neuroanatomist, and by studying the microscopic structure of the various areas of the brain, he had classified the cortical areas according to the cytoarchitectonics. He believed that one could detect the personality of a person by anatomically determining the distribution of different types of nerve cells in different areas of the cortex – Vogt's Areas. He and his wife, Cecile Vogt, are well known for their extensive research on the cytoarchitectonic studies on the brain. The Russian Government had invited him to Moscow to take away "Lenin's Brain" for examination. Vogt was the Director of Kaiser Wilhelm Institute for Hirnforschung at Neustadt in Southern Germany..[1]

Reference

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12. Cornelius Ubbo Ariens Kappers (1877–1946)

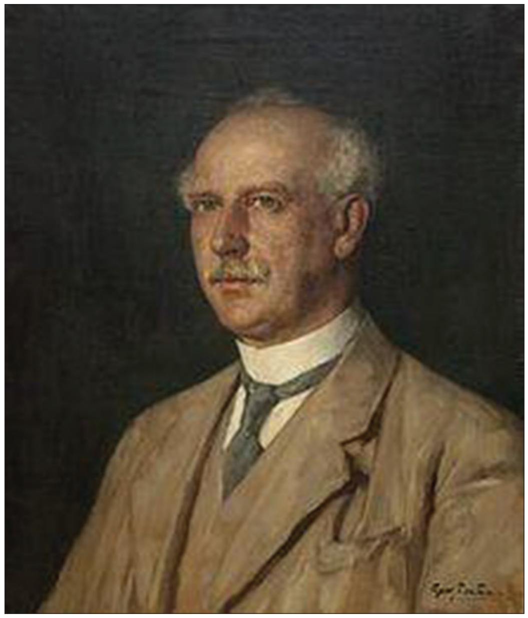

Figure 68: Cornelius Ubbo Ariens Kappers (1877–1946)

Cornelius Ubbo Ariens Kappers was born in Groningen, Netherlands,

and trained at the University of Amsterdam, worked there, and later moved to Germany at the Pathology Institute Frankfurt. He later became the Chief at *Edinger Institute*.

He expanded Edinger's concepts of dividing the brain into the neo, archi, and paleo sub-divisions.

Special contributions: "Comparative Neuroanatomy". Published the Comparative Anatomy of the Nervous System of the Vertebrates including Man 2 vols.

13. Nicolás Achúcarro (1880–1918)

Figure 69: Nicolas Achucarro (1880–1918)

Nicolas Achucarro (1880–1918) was a pupil of Cajal and Pierre Marie in Paris, Kraepelin, in Germany, and his contribution was "Delineation of the nature of the various cell types in the human cerebral cortex (1910)".

Chapter 7C: PATHBREAKERS

1. Central Sulcus was described by **Luigi Rolando** (1773-1831), hence called Rolandic Sulcus. While the fissure separating the frontal and parietal lobes from the temporal lobe was described by **Franciscus Sylvius** (1614-1672) and hence called Sylvian Fissure.
2. **1812: Franz Joseph Gall** (1757-1828) introduced the concept of phrenology i.e., predicting the function of different parts of the brain by the shape and irregularities of the skull. The scientific basis of this was obviously wrong.
3. **1825**: **Foramina of Magendie** (1758-1828) was discovered in 1825 and foramina of **Luschka** in 1859.
4. **1837**: **Johannes Evangelista Purkinje** (1787 – 1869) presented to the German Men of Science and Medicine at Prague a resume of his microscopic survey of the human brain. It included the first adequate description and illustration of the nerve cells with their nuclei and dendrites and myelinated fibres. It was at this meeting that he described a row of "flask shaped ganglionic bodies" in cerebellum which later came to be known as Purkinje Cells.
5. **1850:Augustus Volney Waller** (1816-1870) Dying-back degeneration of axon i.e. degeneration starting at the distal end of axon and spreading retrogradely was first described by Waller in 1850 in Phil Trans R Soc B 140, 423-429, 1850. His method of study of trophic degeneration of nerve fibres i.e. Wallerian degeneration became the standard method of investigating the anatomy of the nervous system.
6. **1851**: **Rudolf Ludwig Carl Virchow** was the first to describe the perivascular space around cerebral arteries – now called Virchow-Robin Space. In a paper in 1854, he described the cellular nature of the cerebral interstitial substance and two years later called it neuroglia..
7. **1852**: **Charles Edouard Brown-Sequard** (1817-1894) was the first to show in 1852 that stimulation of the cervical sympathetic nerve in the rabbit causes blanching of the ear. He also described that hemi-section of the spinal cord resulted in loss of sensation on the opposite side of the body, but retention on the same side (Brown – Sequard Syndrome) Described the decussation of the sensory tract in the spinal cord.
8. **1861**: **Pierre Paul BROCA** (1824-1880) "described the lesions of the left frontal opercular region to be responsible for (motor) aphasia and Ferrier called this as "Broca's convolution". Originally called it aphemia, later designated aphasia by Trousseau in 1861.
9. **1868: Jean Martin Charcot (1825-1893)**: Though the first description of disseminated sclerosis (MS) is attributed to Jean Cruveilhier (1791-1875), real credit goes to Charcot who provided the distinct clinicopathological description of the disease. In 1869, he discovered Amyotrophic Lateral Sclerosis (ALS) also known as Charcot's disease.
10. **1873**: **Camillo Golgi** (1843 – 1926) first stained an individual nerve cell in 1873 using a chromate of silver staining method. He described the so-called Golgi apparatus in 1898.
11. **1874**: **Carl Wernicke** (1848-1904) described word deafness (Sensory aphasia) due to lesion of the superior temporal gyrus.
12. **1881: Theodore Fritsch** (1838-1927) along with **Eduard. Hitzig** (1838-1907) demonstrated motor response following electrical stimulation of the precentral gyrus.
13. **1887**:**Wilhelm His,** (1831-1904) established that axons are outgrowth from primitive nerve cells and in 1889 reported the terms dendrite, neurite, neuropil, neuroblast, spongioblast.
14. **1887: Ludwig Edinger (1855-1918)**: described the Edinger-Westphal nucleus in 1887 and is also credited with description of Thalamic pain and its verification by autopsy in 1891. Founder of a self-financed Neurology Institute at Frankfurt.
15. **1890:Sergei Sergeivich Korsakov** (1853-1900) described alcoholic polyneuritis with a distinct mental symptom, the amnestic confabulatory syndrome known as Korsakoff Psychosis. Also credited with establishing the concept of Paranoia.
16. **1892**: **Albert Pick** (1851-1924) described the first case of the disease now called Fronto – Temporal Lobar Dementia (FTLD) in 1892. It was later named as Pick's Disease.
17. **1892**: **Salomon Eberhard Heschen** (1847-1930) first presented his discovery of the cortical visual centre- This received reservation from Horsley, Beevor and Hitzig. In 1893 and 1894 he described his basic observations of the projection of retina on the calcarine cortex.
18. **1893: Andriezen I**: The neuroglial elements in human brain. Brit. Med J 2:227-230,1893.
19. **1893**: **Joseph Jules Dejerine** (1849-1917) Among his many contributions to clinical neurology e.g., progressive hypertrophic interstitial neuritis, the thalamic syndrome, olivo-ponto-cerebellar atrophy, was the description of word blindness due to lesions of the supra marginal and angular gyri.
20. **1895**: **M Lenhossek** coined the term astrocyte in 1895 in the second edition of his book on the nervous system as a replacement of the term glial cells in higher vertebrates.
21. **1896**: **Rudolf Albert Von Kolliker** (1817-1905) gave the term "Axon" to the axis cylinder described by Wilhelm His (1831-1904) in 1887.
22. **1898**: **John Newport Langley** (1852-1925) introduced the term autonomic nervous system in 1898 and introduced the terms "preganglionic" and "postganglionic". It was in 1905 that he coined the term "parasympathetic".
23. **1903: Franz Nissl (1860-1918)**: It was Nissl who was the first to develop the technique to provide clear, simple and constant picture of the internal structure of the nerve cell cytoplasm including the granules now called the Nissl Granules.
24. 1899- He (Nissl) was the first to describe the "Stabchen. Zellen" (the rod cells) in the brains of dementia patients, these were later recognized as the Microglia by Hortega.
25. **1908**: **Alois Alzheimer** (1864-1915) described the clinical and pathological features of dementia now known by his name Alzheimer's Disease (Name given by Emil Kraepelin)
26. **1911: Henry Head** (1861-1940) Paper with Gordon Holmes in 1911 on sensory disturbances from cerebral lesions, and study of sensory, motor dermatomes.(Ref Posner MI, Petersen SE, FoxPT, Raichle ME Localization of cognitive operations in human brain Science 240,1627-31,1988)
27. **1918**(Air) Ventriculography was first introduced by **Walter Edward Dandy** (1886-1946) in 1918 and Pneumoencephalography in 1919 (Roentgenography of the brain after injection of air into the spinal canal. Ann Surg 70:397,1919)
28. **1920**: **Pio Del Rio Hortega** (1882-1945) along with his pupil Collado was the first to describe the microglia using a modified Cajal stain.
29. **1924: Joannes Hans Berger**: Started his studies for recording electrical activity from the skull in 1902, Succeeded in recording the electrical activity in the human brain in 1924. His paper accounting that variations in voltage emerging from the brain could be recorded through an intact skull was published in Arch Psychiatry Berlin in 1929.
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107:569,1948.

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46. **1964**: **Alf Brodal** provided a detailed anatomy of the brain stem reticular formation and its role in maintaining consciousness.
47. **1969: Pierre, Gloor**: Collected works of Hans Berger (Fourteen papers): Electroenceph Clin Neurophysiology vol 18 (supplement) 1969.
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49. **1973**: **Godfrey N Hounsfield** (1919-2004) developed Computerized Transverse Axial Tomography, the first brain imaging technique to visualize the brain non-invasively. Computerized transverse axial scanning (tomography). Description of system.
50. **1973**: **William Scoville** and **Correll** described loss of memory following lesions of the temporal lobe bilaterally.
51. **1975: ME Phelps**: Introduced the application of annihilation coincidence detection to trans axial reconstruction tomography (Positron Emission Tomography (PET) in 1975 (J Nucl. Med 16:210, 1975).
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ANNEXURE 1

Recent Advances and Future Trends

Unpredictability is essential in the search of new knowledge". But scientists as a rule are poor predictors of the future.

It is well known that scientists, who deal with ignorance, are notoriously bad at prediction. Roentgen, Wright brothers, Rutherford, Edward Purcell could not predict the practical uses of their scientific work. Sir John Maddox, in 1999, acknowledged that "The most important discoveries of the next 50 years are likely to be ones which we cannot even conceive". The following account is therefore based on expectations regarding the development of recent advances and hopes expressed by current leaders. Penfield pronounced the ultimate problem of neurology- "To understand the man himself and to analyse the means by which man, the creator of science, has done what he has done". It is a dream of neuroscientists to recreate the human brain and ultimately to unravel the mystery of mind. Towards the end of the twentieth century, some leaders of neuroscience hoped that "to develop a theory of mind would complete a triumphant hat trick for the century, first the atom, then the gene and now the mind". The individual neurons that make up the brain are well understood (or are they!). The significance of the other cells in the brain- the glia-is currently under extensive investigations. The way they link together in the simple network is becoming clear. The way whole net networks combine to result in higher mental functions and behavior is only poorly understood.

Beginnings have been made to unravel these unanswered questions. Hans Moravec in his essay on "Rise of Robot" (Scientific American 1999), believed that "By 2050 brains based on computers that execute 100 trillion instructions per second will start rivalling human intelligence". Others expected that neurons, electrons, and the chip-the triangle would interact for progress.

Erech De Solla Price of Yale University predicted, "I expect computerized artificial intelligence to team up with the human brain to change the very pattern of human thought". Only a few days ago, Elon Musk, founder of Neurolink, in a recent live stream conference, demonstrated microchips that can be implanted into the human skull with tiny wires that hook up to the brain. Thus, it is evident that the emerging field of brain-machine interaction will attract increasing attention.

Neuroscience would continue to advance in these known and many unknown directions. What knowledge is available about the brain and the nervous system is only a tiny fraction of what we don't know. The Brain Remains the most defiant piece of ignorance and undoubtedly the greatest challenge to humankind. Recent advances in cellular and molecular biology, genomics, genetic engineering, computer science, microelectronics, and in-vivo imaging have revolutionized neuroscience research. Techniques have been developed to study the molecular structure of ion channels, neurotransmitter receptors, transporter systems, and other membrane-bound proteins. For example, *rapid in-vivo electrochemical* detection of neurotransmitters using carbon-fibre microsensor permits direct monitoring of changes in the extracellular concentration of dopamine, norepinephrine, serotonin, etc., at physiologically relevant concentrations, virtually in real-time, simultaneously at multiple sites. Newly developed optical imaging techniques using laser scanning microscope and other fluorescent imaging technologies provide high-resolution optical imaging of ion concentration dynamics, membrane potentials, cortical signal mechanisms, and neuronal circuitry.

Techniques of structural and functional genomics permit the identification, cloning, and sequencing of genes involved in physiological functions and pathological states. In addition, it is possible to produce gene knock-out and gene knock-in animal models to explore the functions of individual genes.

The revolution in genetics and recombinant DNA technology has revealed genes that control the development and functions of the nervous system and genes whose mutations cause brain diseases. In addition, progress in structural biology has given us three-dimensional structures of many of the proteins encoded by these genes, offering new possibilities for drug development.

New techniques currently in use allow rapid whole genome sequencing and identification of location and abnormalities of genes in inherited neurological and psychiatric disorders. These recent advances are changing our conceptual understanding of the brain function at every level from molecule to the synapse, to the neural circuit, and ultimately the intact behaving organism, including the man himself.

As a result of these advances series of new sub-disciplines of neurosciences have already evolved

- Developmental Neurobiology
- Neurogenetics
- Neuroinformatics
- Computational Neuroscience and modelling
- Cognitive neuroscience
- Artificial Intelligence, Neural network, Robotic
- Augmentative and Restorative neuroscience
- Molecular Neuropharmacology
- Glial Biology
- No doubt this is only a list based on current ongoing development. The future remains unpredictable – The future direction of evolution, in neurosciences as unknown as biological evolution in general. "Let it be recognized that we still do not know how the brain creates the mind, or does it!"

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Neurons to Behavior

Address delivered at the Inauguration of the XXXVII Annual Conference of the Indian Academy of Neuroscience at All India Institute of Medical Sciences, New Delhi, 18th November 2019

Oration by Prof P.N. Tandon:

Prof. Randeep Guleria, Director AIIMS, Dr Shashi Bala Singh, President IANS, distinguished colleagues. It is a privilege for me to be given this opportunity to address this prestigious Academy, founded by some of my dear friends – Professors K.P. Bhargava, B.N Dhawan, S.S Parmar, BK. Bachhawat, Mehdi. Hasan, P.K Seth, KC Singhal, VK. Selvarajan. At least one of them, Dr P.K Seth is here with us today. I would like to express my gratitude to those who are no more with us but worked hard to leave this legacy for us.

The initiation and growth of neurosciences in India were delayed and slow. I remember that in 1983, at the first conference organised by the Academy there were only 70 participants. The Secretary's report just informed us about the current strength and activities of the Academy indicating its progressive growth. I am sure that it has a bright future.

I realised that this year the Academy had chosen the theme for this conference Neurons to Behaviour, which permits me a broad scope for this talk. Recently I have been interested in studying the evolution of neurosciences, not only in India but globally. In the short time available to me, I would like to share some interesting highlights from this study. I plan to publish a more comprehensive study later on.

I may add that in respect to India efforts in this direction have already been initiated by Neurology India during the last two-three years. From time to time there have been a number of publications summarising Indian contributions to neurosciences.

Let me first share with you some interesting historical facts about the nervous system, its constituents-the neurons and the glia, its functions, and current efforts to explore its mysteries. This may be of some interest specially for our young audience here.

While there had been keen interest in exploring the psycho-philosophical and religious aspects of "soul", "spirit", "intellect", "mind" etc. since antiquity, it is only from the time of Greek physician Hippocrates (born about 460 BC) that one finds specific mention of brain and its psychological and physiological functions.

In the Edwin Smith Papyrus from Egypt, which dates back to 3000 BC there are four hieroglyphic figures, which according to medical historian Dr. William Francis (nephew of Sir William Osler) represent the word ' brain'.[1] These decorate the ceiling of MNI foyer.

Surprisingly, Vedas and Upanishads, as well as the Ayurvedic literature which are so rich in valuable information on the human body, mind and consciousness do not refer to the brain at all. *Charaka* regards mind *(manas)* as a separate sense *(indriya)* with its object *(artha)* defined as thought. It is however more than other senses and is the conductor of the symphony of senses. In its absence or distraction, pleasure and pain are not felt nor other sensory experiences registered. Soul or Self, on the other hand, are the witness and ultimate subject of all conscious activities. According to *Charaka* the sense objects sense mind, self-complexity is the integrative basis of sensory experience, motor action and life itself. The mind, self and body form a tripod which supports life.

This was more or less similarly re-iterated in Buddhist literature. All sensible doctors in all epochs have been cognizant of the interaction between soma and the psyche.

Psyche was personified as the beloved Greek God Eros. Psychiatry has been a recognized speciality longer than neurology.

In contrast to this Hippocrates provided a very comprehensive statement on the human brain and its functions as summarised in the following quotation:

"Men ought to know that from the brain and from the brain only, arise our pleasure, joys, laughter and tears. Through it in particular, we think, see, hear and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant". However, even his contemporaries and successors of the Hellenic Greek, Roman, Egyptian and European schools continued to highlight the role of soul and spirit and their participation in the vital human activities even as late as the latter part of 18th century.[2] This in spite of the fact that Thomas Willis had ascribed higher cognitive functions to the cerebral cortex as against the prevalent view of Galen who attributed the animal's spirit in the ventricular system to be the source of all intellect.

Soul and its participation in vital phenomena dominated the thinking of philosopher scientists and medical practitioners till the later part of the 18th Century. This was true of the Vedic and Buddhist India, Hellenic Greek, Egypt, Rome or Europe.

Towards the later half of the 18th Century

"Soul" and its participation in vital phenomena was located as below:
In the Pineal Gland by Rene Descartes
In the pit of the stomach by Diogenes
In the Blood by Empedocles
In the Cerebral Ventricles by Galen
In the Septum pellucidum by Digby
In the Fornix by Peyronie

It was the book by Philippe Pinel of Salpetrier in Paris, published in 1801 which opened the door to modern psychiatry.

Let me share with you some little-known historical facts about "Neurons" and other cells in the brain and reference to "Behaviour" in connection with the brain.

1. It was Golgi who first stained an individual nerve cell in 1873 and propounded the so-called "Reticular Theory".

2. It was Wilhelm von Walder Hartz who introduced the term neuron in 1891. It was Purkinje's student, G G Valentine, who published the first microscopic image of the nerve cell in 1836 with its nucleus and nucleolus.[3]
3. It was Cajal (1831-1904) who in 1894 propounded the "Neuron Theory". The discovery of cytoarchitectonic is generally attributed to Theodore Meynert in 1867.
4. William His demonstrated that axons are outgrowths of the primitive nerve cell. He is also credited for introducing terms dendrites, neuropil, neurite, neuroblast.
5. Pio Del Rio Hortega and his pupil Collado were the first to stain and describe Microglia (1919).
6. Wilder Penfield, working in Hortega's lab was the first to stain and describe oligodendroglia (1924).
   7. The word *"neurologie"* first appeared in the translation of the book "Cerebri Anatome: Cui Accessit Nervorum Descriptio et Usus" by Thomas Willis. It was in this book that Willis ascribed higher cognitive functions to the cerebral cortex as against the prevalent view of Galen who attributed the animal 'Spirit' in the ventricular system to be the source of all intellect.
   a. Even though Golgi first stained an individual nerve cell in 1873, the term Neuron was introduced by Wilhelm von Waldeyer Hertz in 1891.
   b. However, the concept that nerve cells serve as independent functional units of the nervous system and connect to one another in precise ways led to the "Neuron Doctrine" by Cajal (1894) as opposed to the prevailing "Reticular Theory" of Golgi, His and Forel.
   c. In his lecture to the Royal Society (Croonian Lecture) 1894, Cajal suggested that "Mental exercise facilitates a greater development of the protoplasmic apparatus and of the nervous collaterals. But the pre-existing connections could also be reinforced by the formation of nerve collaterals and protoplasm's expansions", thus hinting at plasticity of the neurons.

8. Theodore Meynert (1833-1892) dealt in great detail with the central anthropological problems of human behaviour in the context of ethics and religion in his lecture on "Brain and Morality."
9. This was further elaborated by Emil Kraepelin (1856-1926) in his book (6th edition) ``Foundation of Psychiatry and Neurosciences" which included a section on "Moral Insanity".

During the 19th and early part of the 20th century a variety of philosophers, and psychologists, psychiatrists, neurologists and even physical scientists explored the complex, yet one of the most challenging fields of brain, mind consciousness and behaviour.[4] They were classified as; Mentalists, Functionalist, Pan Psychiatrists, Behaviourists, Parallelist, Emergent Materialist, in addition to the earlier Monists, Dualists and Mystics.

Time would not permit me to elaborate on all these "isms"; I would like to conclude with two extracts from my Presidential Address to the Indian National Science Academy (1992), published in 1993, which reflects our current status of "ignorance on the subject".[4]

Extracts from Prof PN Tandon's Consciousness Paper (1993)

During the last couple of decades, the reductionist approach to study the brain at the molecular, cellular, or network level, has undoubtedly provided a wealth of information. Thus, individual neurons, their organelles, their membranes and receptors, their messengers start to get well understood. There is much better information regarding neural networks, their development, variability and plasticity, even with respect to some of the mental functions. The electrochemical parameters involved in such functions start to be known.

Lot more additional information has been added since then with the help of genomic and proteomic studies on the one hand and sophisticated imaging techniques on the other.

However, there are enough unexplained observations which need to be resolved before the answer to the eternal question of brain – mind and consciousness can be found.

We have observed stimulation of various parts of the brain to produce movement but never the coordinated activity resembling even a simple voluntary act, leave aside the graceful movements of the master pianist's fingers. Stimulation of the sensory area of the brain results in crude sensations, numbness or tingling, but not one of a gentle touch of a loved one; a sensation of flashes of light but rarely the vision of beauty, a sense of sound but not even formed words leave aside a message of hope. Stimulation or focal abnormalities in the brain are known to produce fear or anger but not joy, laughter or happiness. Certainly, one has never been told by any patient that any such stimulation, electrical, chemical or spontaneous as in epilepsy, produces a sense of curiosity or adventure, pity or piety, an original thought or intuition, a feeling of compassion, love or faith. And the other way around as yet there is not the faintest clue as to how the identical sensory stimuli in terms of physical characteristics as simple as light touch, one from the loved one and another from a despised one are distinguished by the brain. To understand the mechanism underlying these would be the most challenging task of science, lest it be stated that in the ultimate test science failed!

To summarise

"More may have been learned about the brain and mind in 1990s then during the entire previous history of psychology and neuroscience", but we still know only small fraction of what we need to know.[5]

During the latter part of the 20th century, the study of the brain moved from a peripheral position within both the biological and psychological sciences to an interdisciplinary field called neuroscience.

This realignment occurred because the biological study of the brain was incorporated into a common framework of cell and molecular biology on one hand and psychology (and more recently cognitive science) on the other. The scope of study of the human brain now extends from gene to cognition, from molecule to mind.

Currently:

Neuroscience, the multi-disciplinary all-encompassing discipline concerned with exploring the frontier of brain research globally involves the largest intellectual enterprise ever. A variety of advanced techniques and technologies, now available, are being utilized to unravel some of the mysteries of the structure, development and functions of the brain and the role it plays in higher mental functions, cognition and consciousness. Attempts are being made to create a brain.

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ANNEXURE 3

NEUROSCIENCES IN INDIA: AN OVERVIEW

[Chapter from Neurosciences in India, (ed) BN Dhawan, PK Seth. IAN & CSIR, New Delhi, 2009.]

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Introduction

Neuroscience as a distinct discipline was initiated in India only after our independence even though some isolated examples of work in the field could be found earlier also. The contributions to neurosciences in the country have been a subject of several reviews over the years.[1-7] This write-up is aimed at briefly highlighting the major contributions during 1960-1980. Tribute must be paid to some of the pioneers who laid the foundation of this edifice and are not with us anymore. The names of Drs. Jacob Chandy, B. Ramamurthi, R.G. Ginde, R.N. Chatterji, Ashok Bagchi in Neurosurgery, Baldev Singh, T.K. Ghosh in Neurology, B.K. Bachhawat in Neurochemistry, D.K. Dastur in Neuropathology, B.K. Anand and A.S. Paintal in Neurophysiology, K.P. Bhargava in Neuropharmacology readily comes to mind. Fortunately the other pioneers are still active and with us. There is no doubt that there are others who also contributed to this development. It is not intended to minimize their contributions by not naming them individually. Their contributions find detailed reference in the author's comprehensive volume-Neurosciences in India: Retrospect and Prospect edited by Sunil K Pandya.[3] Similarly the work of pioneers in Psychiatry and allied sciences has been documented in a volume-Mental Health: An Indian Perspective (1946-2003) edited by S.P. Agarwal.[8] Another interesting source of some historical interest is the monograph edited by Prof. K. Rajasekharan Nair- Evolution of Neurosciences in India as also the autobiography of Prof. B. Ramamurthy - Uphill All the Way.[9,10]

Neurosciences comprise a large number of distinct disciplines, fortunately now seamlessly merging into one another. Unlike in the West, the seeds for their development in India were laid by clinicians Neurologists, Neurosurgeons, & Psychiatrists. However, the leaders of these disciplines were deeply conscious of the need for development of the allied basic neurosciences Neuroanatomy, Neurophysiology, Neurochemistry, Neuropharmacology, and Neuropathology.

There have thus been continued additions to these with the emergence of other specialties as Neuroimaging, Neuroanaesthesia, Neuroendocrinology, Neuro Ophthalmology, Neurotology, Neurotraumatology, on the clinical side and Developmental Neurobiology, Neurotoxicity, Neuro-oncology, Neuro-immunology, Neurovirology, System Neuroscience, Computational Neuroscience etc on the basic side. We continue to see new additions like Cognitive Science and Behavioral Sciences in its fold. Over the years we have witnessed the development in all these fields in the country. Individuals, groups, departments and specialized centres have provided nuclei of excellence in all fields of neurosciences in the country. However, it must be mentioned that while clinical neurosciences progressed rather rapidly resulting in creation of a number of specialized centres at Vellore, Chennai, SGPGI, Bangalore, Kolkata, Delhi (AIIMS, GB Pant Hospital), Thiruvananthapuram etc., parallel development of basic neurosciences was relatively slow and patchy and unfortunately remains so even today. Thus soon after the initiation of the first Department of Neurosurgery by Dr. Chandy at CMC, Vellore in later part of 1949, efforts were made to enlarge the scope of neuroscience by adding Neurology (1951), Neurochemistry (1957), Neurophysiology units/departments. Similarly when Dr. B. Ramamurthi joined the Madras Medical College, a department of neurosurgery was established in 1950. Progressively Neurology, Neuroradiology, and later Neuropathology and Neurochemistry were added. This then in a course of twenty years developed into a multidisciplinary distinct Institute of Neurology. Yet it lacks Neuroanatomy, Neurophysiology, and Neuropharmacology even today. The story was repeated at several centres - Bombay (Mumbai), Calcutta (Kolkata), Hyderabad etc. but at none of these institutions all major neuroscience disciplines existed to constitute a comprehensive neuroscience centre. National Institute of Mental Health & Neurosciences which existed as a Mental Hospital earlier wisely planned to add other neuroscience disciplines e.g. Neurology, Neurosurgery, Neuropathology and later Neuro-physiology, Neurochemistry and Neuropharmacology.

All India Institute of Medical Sciences, New Delhi, by a fortunate coincidence, had basic neurosciences strengths in Neuroanatomy, Neurophysiology, Neurochemistry, from its inception to which were added the clinical departments of Psychiatry, Neurology. Neurosurgery, Neuroradiology, Neuroanaesthesia when it was elevated as a Neuroscience Centre. However, the basic neurosciences remained as part of the major disciplines of Anatomy, Physiology, Pathology, and Biochemistry. Recognizing the need to strengthen the basic neurosciences in the country, the Department of Biotechnology, Government of India, decided to establish a comprehensive multidisciplinary Brain Research Centre, which is less than a decade old. The faculty of this centre represents expertise in most basic neuroscience disciplines from molecular biology and genetics to systems neuroscience and computational neuroscience.[11,12] By design it didn't have any clinical disciplines. Recently nuclei of Cognitive Science departments/centres have been established at Allahabad and Hyderabad. Similarly a Behavioral Science Department /Centre has been initiated at Delhi.

Increasing support for these developments has been forthcoming recently from the Departments of Science and Technology, Biotechnology in addition to Indian Council of Medical Research and Council of Scientific & Industrial Research.[5]

The last decade has not only seen the establishment of the National Brain Research Centre for postgraduate education and research but also initiation of comprehensive neuroscience postgraduate courses at the Jiwaji University, Gwalior, NIMHANS Bangalore, and TIFR Mumbai. In addition to the already existing postgraduate courses in Neurology, Neurosurgery and Psychiatry degree courses have also been started in Neuroradiology, Neuropathology, and Neuroanaesthesia. Increasing importance of neurosciences has prompted the Indian Institute of Science Bangalore, to initiate an independent department. Several national laboratories of CSIR e.g. CDRI, ITR, CCMB, ICB and several others like NCBS Bangalore, are actively involved in neuroscience research providing opportunities for Ph.D. degrees.

In parallel with these developments we have witnessed the emergence of scientific societies and academies for promotion of these disciplines. Starting in 1951, the Neurology Society of India was an umbrella body for all neuroscience disciplines. It currently has over 1500 members. Recent years have seen a rapid increase. It has also nucleated several sub-speciality groups like Societies for Paediatric Neurosurgeons, Stereotactic Neurosurgery, Neurotrauma, Skull-base Surgery, Society for Cerebrovascular Diseases etc. Since 1953 it has published its own journal Neurology India. The Indian Psychiatry Association was established in 1947.

Initiated in 1982, but formally registered in 1984 the Indian Academy of Neuroscience was created by the efforts of Professor K.P. Bhargava, B.N. Dhawan, M. Hasan, S.S. Parmar and P.K. Seth. The Academy, which is celebrating its Silver Jubilee currently, has more than 800 life-members. While clinical disciplines are not excluded; its primary objective was to promote basic neurosciences. A detailed write up about the Academy is published separately. It publishes its own journal, The Annals of Indian Academy of Neurosciences.

In the meanwhile an Academy of Neurology was established in 1991. It has about 795 full members and about 250 associate members. It publishes its own journal, Annals of Indian Academy of Neurology since 1998.

From the above account it will be obvious that there has been a progressive evolution of all major disciplines of Neurosciences in the country. This is especially so during the last decade. We have now fully developed clinical centres, staffed by competent clinicians, equipped with state-of-art facilities comparable to the best anywhere. There are a number of institutions where high quality work is going on in practically all branches of neurosciences.

The Indian Academy of Neurosciences decided to put together at one place an update of the status of neurosciences in the country, particularly highlighting the developments during the last decade or so.

While this is being done for individual disciplines by a chosen leader of the field, I would like to take this opportunity to briefly mention some of the most outstanding examples of contributions of the pioneers of Indian Neurosciences for the benefit of the younger generation who may not be aware of the work of researchers of earlier years or not have easy access to the reviews referred to above. Mention is made of what may be considered some landmark contributions, nationally relevant and internationally recognized. Obviously there would be a personal bias in selecting these, which is by no means meant to be a comprehensive catalogue. Such details are available in the references mentioned earlier.[3,4,7] Let me hasten to apologize to those whose work does not figure here even though it may be equally or even more valuable than those included. I have intentionally not included most of the contributions during the last decade or so as these are expected to be covered by the authors of the individual disciplines.

Neurophysiology

The studies of **B.K. Anand** and his group on regulation of food intake and the identification of the hypothalamic feeding and satiety centres would undoubtedly qualify to be among the landmark contributions.[13-17] In addition this group made a number of studies on the functions of the limbic system for regulating affective behaviour and visceral responses in monkeys and cats**.**[18] Also he published an article on neurophysiological problems at high altitudes.[19]

Similarly the seminal work of **A.S. Paintal** on J-receptors and other visceral receptors u like type B-atrial receptors, mucosal mechanoreceptors of intestines and pressure- pain receptors of muscles has got international recognition.[20-23]

A number of students trained by Dr. Anand- **Dua-Sharma, GS Chinna, KN DD Sharma, SK Manchanda, Usha Nayar and T. Desiraju** went on to become leaders in their own right and produced some outstanding researchers. Similarly, Dr. Paintal's students like **Marcus Devanandan, W. Selvamurthy** and **Ashima Anand** continued his traditions.

P. Brahmayya Sastry who in 1957 joined the Department of Physiology of the Andhra Medical College, Visakhapatnam contributed a great deal on factors influencing acetylcholine synthesis, storage and release in nervous tissue.

T. Desiraju who moved from AIIMS to NIMHANS, Bangalore led a very active group working on diverse subjects like neural mechanisms of sleep, organization of prefrontal cortex and thalamo-cortical connections, neuro-physiology of Yoga and theories of consciousness.

V. Mohan Kumar at AIIMS and **BN Mallick** also trained at AIIMS (and later moved to Jawaharlal Nehru University) continued to advance the frontiers of sleep research. The former contributed a series of papers on functions of the preoptic areas. KN Sharma along with S. Dua-Sharma who moved to Bangalore initially continued their interest on feeding behaviour and its regulation later diversified to neural control of reproduction, neural organization in nociception and pain. They produced a stereotactic atlas of the canine brain.

High altitude physiology attracted the attention of a number of investigators - H.S. Nayar, M.S. Malhotra, W. Selvamurthy, S K Roy, Shashi B Singh.

Neuroanatomy

A.C. Das and his colleagues-**Mahdi Hasan, K.K. Bisaria** at K.G. Medical College, Lucknow carried out internationally recognized gross anatomical studies on the intracranial venous Sinuses, the tentorium cerebelli, the tentorial notch, the anomalies of the posterior communicating arteries, the superficial sylvian vein, and grooves on the occipital lobe of

Indian brains which were published in such prestigious journals as Anatomical Record, Journal of Anatomy (London) and Journal of Neurosurgery. **N.H. Keswani** at AIIMS established a virtual school of neuroanatomy, which included **V. Bijlani, Gomathi Gopinath, Shashi Wadhwa** who made (and the Department continues to do so) outstanding contributions on developmental neurobiology.

Some of the most outstanding of their contributions include birth weight and development of cerebellar cortex,[24] the salivatory centres in the brainstem of monkey,[25] and more recently studies utilizing latest techniques of immunohistochemistry, stereology, electron microscopy, and neurochemistry have explored the development of the human brain at different ages of gestation. Some of these studies are first in the world. In the late nineteen eighties and early nineties, under the leadership of **Gomathi Gopinath**, a large number of papers were published on fetal neural transplant in rodents and mammals. Later on this became a subject of research at llTR, Lucknow.

Hasan and his colleagues at Aligarh Muslim University contributed a large number of studies on neuroanatomical changes in ageing brain, as also the effects of a variety of neurotoxins using electron microscopy.

Neurochemistry

It was only in the 1960s that centres devoted to neurochemistry were established at Baroda, Calcutta, Delhi and Vellore. Subsequently these spread to Chennai, Bangalore, Mumbai, Hyderabad and Thiruvananthapuram. The foundation for neurochemistry was laid by **J.J. Ghosh, B.K. Bachhawat, C.V. Ramakrishnan, P.S. Sastry** and their colleagues. **G.P. Talwar** who initially devoted to research on neurochemistry later committed himself to pursue immunology. Other outstanding researchers of the earlier years included **D.K. Basu, A.S. Balasubramanian, P.S. Sastry, M.S. Kanungo, Shail Sharma, P.K. Sarkar, S.L.N. Rao, R. Rajalakshmi, K. Subba Rao.** Some of the most outstanding contributions of these investigators were study of nucleic acid and protein metabolism, lipid metabolism, metabolism of sulfated compounds, studies on brain enzymes (hexokinases, dehydrogenases and oxidases, lysosomal hydrolases, acetylcholinesterases etc.), neurotransmitters and their receptors, especially opiate receptors. Detailed studies were carried on myelin, synaptogenesis and neural membranes. Nutrition and brain development were studied by a number of scientists which included several important events such as cellular proliferation, nucleic acid and protein turnover, dendritic arborization, myelination and synaptogenesis.[26] Most of the contributions in this field were summarized in a monograph by Tandon and Gopinath published by the Indian National Science Academy, New Delhi.[27]

Special mention may be made of one of the earliest studies on enzyme arylsulfatase, lipid peroxidation, enzymatic formation of PAPS (3- phosphoadenosine-5-phosphosulfate). These studies led to the discovery of the etiology of metachromatic leukodystrophy. Original studies were made on biosynthesis of phospholipids components of the myelin membrane specially ethanolamine plasmalogens sulfatides, gangliosides & cholesterol. The Wolfgram protein phosphorylation was another such study. Among the studies on the effect of drugs and toxins in the brain, the pioneering studies on the mechanism of neurotoxicity of Lathyrus sativus deserve special mention. Further elaboration of these and other neurotoxins continues to be carried out at llTR, Lucknow (P. Seth and colleagues) and NBRC, Manesar (V. Ravindranath).

Neuropathology

In 1949, the Indian Council of Medical Research established a Neuropathology Unit at Tata Memorial Hospital, Bombay under the leadership of **Dr. V.R. Khanolkar. CGS lyer and DK Dastur** later joined this unit. Initially studies were carried out on experimental poliomyelitis in monkeys and neural lesions in different types of leprosy. A referral centre for neuropathology was thus established. lyer later moved to Central Leprosy Teaching and Research institute at Chengalpet, Tamilnadu and Dastur established one of most productive Departments of Neuropathology at JJ Hospital and later at Bombay Hospital. A decade later **Dr. S. Sriramachari** started the Department of Neuropathology at the National Institute of Mental Health and Neurosciences, but he soon moved to ICMR. When neurosurgery was started at AlIMS, New Delhi, he provided neuropathology support as an Honorary Professor. In the meanwhile **Dr. Ilona Bubelis** set up a department at KEM Hospital, Mumbai where she trained **D.H Deshpande** who later took over the Department. **Dr. KM Wahal** at KGMC, Lucknow who was trained in neuropathology in the USA provided the service to the Neurosurgery Unit but did not pursue a career in neuropathology. **Dr. Subimal Roy** was persuaded to take up neuropathology as a full time commitment at AlIMS. **Dr. AK Banerjee** devoted himself to neuropathology at Postgraduate Institute at Chandigarh in 1971. **Dr. Sarla Das** after completing her training under Dr. Sriramachari moved to Cuttack in 1971 and later moved to d NIMHANS, Bangalore as Head of Neuropathology. **Dr. Sarasa Bharati** joined the Department of Neuropathology at the Madras Neurological Institute. **Chitra Sarka**r succeeded Subimal Roy and **SK Shankar** took over from Sarla Das and are currently providing leadership at AlIMS & NIMHANS. **Dr. Radhakrishnan** started the Department of Neuropathology at SCTIMST, Trivandrum in 1978.

It is not surprising that the most outstanding contributions in this field are those related to infections of the nervous system leprosy, tuberculosis, cysticercosis, fungal infections and Japanese encephalitis. CGS lyer at Chengalpet, **CK Job** and **KV Desikan** at Vellore, VR Khanolkar, DK Dastur, **NH Antia**, **L Mehta**, **SS Pandya** at Mumbai (Bombay), **MC Vaidya** at New Delhi carried out extensive studies on all aspects of pathology, pathogenesis, electrophysiology and surgery of neural leprosy. **MG Deo and GP Talwar** independently developed a vaccine, while **Indra Nath** studied the immunology of this disease. It is worth mentioning that Barry Bloom, an international authority on mycobacterial diseases, once remarked that research on leprosy in India has become a cottage industry. Dastur, 1955; Khanolkar, 1964; Antia *et al.*, 1970; Dastur, 1978; Dastur, 1983; Job, 1970; Job and Desikan, 1968, are just a few examples of some of the critical studies.[28-34]

Similarly neurotuberculosis-tuberculous meningitis, tuberculoma - was a subject of a large number of studies including its microbiology, pathology, pathogenesis, diagnosis, imaging and therapy. In addition to detailed clinical studies by most of the neurologists and neurosurgeons of the era, a large number of detailed studies on pathology of tuberculous meningitis and tuberculomas, some unique observations on tuberculous encephalopathy, radiculopathy, arteritis, spinal meningitis with myelo-radiculopathy, and tuberculous abscess deserve special mention. It will be difficult to name the large number of contributors to this subject. However, much of the work carried out is summarized in some of the reviews on the subject.[35,36] In a Textbook on Infections of the Nervous System Kocen writing on tuberculosis of the nervous system stated, "In more recent years, the major contributions on both pathology and the varied clinical manifestations of tuberculosis of the brain and spinal cord have come from workers in India in particular Dastur, Tandon and Wadia.[37]

Pathology of Japanese encephalitis has been a subject of detailed investigations at NIMHANS, Bangalore (Deshpande, Shanker and Gouri-Devi). While detailed pathogenetic and virology studies were carried out at KGMC Lucknow and National Institute of Virology Pune by **UC Chaturvedi, Asha Mathur and Kalyan Banerji**. Recently candidate vaccines have been developed at National Institute of Immunology, New Delhi and Indian Institute of Science, Bangalore.

Parasitic diseases, especially neurocysticercosis attracted the attention of a large number of pathologists and clinicians alike. An immunodiagnostic test for neurocysticercosis has been developed indigenously. Clinico-pathological differences between the disease as seen in India and in other parts of the world were highlighted by Tandon.[38] Studies on fungal infections of the CNS aspergillosis, cryptococcosis, mucormycosis and several others have been reported. A recent issue of Neurology India (vol 55,2007) provides a comprehensive review on the subject highlighting the Indian contributions.

Neuro Oncology

A lárge number of pathological studies on brain tumors have been reported over the years. These deal with routine histopathology, electron microscopy, Immunohistochemistry for tumour markers, tissue culture, proliferation index determination, in-vivo cell kinetics, and in-vitro drug sensitivity etc. Correlation of ultrastructural and endocrinological parameters on pituitary adenomas, revealed interesting original observation of great clinical relevance.[39,40]

Neuropharmacology

Drugs acting on the central nervous system have fascinated a number of pioneers of Indian Pharmacology. The most outstanding among them is no doubt **Col RN Chopra,** who was elected as President of the Indian National Science Academy (1939-40). Besides producing the first comprehensive documentation of indigenous plants of therapeutic value, he initiated the work on the hypnotic effect of Rauwolfia Serpentina in 1940. This lead was later pursued by **BB Bhatia** at Lucknow and **JC Patel** at Bombay. Post independence, in addition to the existing pharmacology departments in the medical colleges, the creation of Central Drug Research Institute, Lucknow, and other such centres provided new stimulus to research in neuropharmacology.

Some of the important names of this era include **KP Bhargava** and his associates and students at KGMC, Lucknow, the school established by **BN Dhawan** and **RC Srimal** at CDRI, **RB Arora** and **NK Bhide** at AIIMS. New Delhi, **UK Seth** and **Nilima Kshirsagar** at Mumbai, **PC Dandiya** and **MK Menon** at Jaipur, **C Sarkar** and **DK Ganguly** at the Indian Institute of Chemical Biology, Kolkata, **PSRK Harnath** at Hyderabad, **SK Bhattacharya** and **PK Das** at BHU, Varanasi, **SK Kulkarni** at Chandigarh, amongst others. They contributed extensively on central vasomotor control, chemoreceptor trigger Zone (emetic centre) in medulla, neurotransmitters involved in thermoregulation, stress related gastric ulcer, drug induced stereotypy neuro-pharmacological studies on blood-brain barrier, central nervous system stimulants and depressants, neurotransmitter action and their receptors and factors influencing their regulation, mechanism of action of a variety of analgesics, antiepileptics and other centrally acting agents.[41] Much of these researches have been summarized by Bradley B and Dhawan BN (1976) and PK Das and BN Dhawan in a monograph published by INSA in 1984.[42] Stimulated by the earlier work of Chopra and later GV Satyawati at BHU several scientists explored a large number of plant derived centrally acting compounds like Asarone, Jatamansome, Withania somnifera, Bacoside A & B from Bacopa monnieri.[43]

Several new synthetic drugs were also developed. These include antidepressant Sintamil by Ciba-Geigy (now Novartis), neuroleptic centbutindole, antidepressant centpropazine and local anaesthetic centbucridine by CDRI as well as neuromuscular blocking agent chandonium iodide jointly developed by Punjab University, Chandigarh and CDRI.

In recent years a new impetus has been given to neuropharmacology by some of the major pharma-industries like Ranbaxy, Cipla, Reddy and Wockhardt.

Neurotoxicology

Neurotoxicity has assumed a significant concern in recent years as a large number of drugs, substances of abuse, chemicals, natural constituents of plants affect the nervous system and lead to various types of nervous system disorders.

Industrial chemicals such as lead, manganese, methyl mercury, certain pesticides and several others have been implicated in learning, memory and diseases like Parkinson's, Alzheimer's, ADHD etc. Several institutions all over the country are undertaking studies on the neurotoxicity of chemicals. The major contributions have been made from ITR, Lucknow (earlier ITRC), NIMHANS, Bangalore and NBRC, Manesar. The thrust has been to delineate the basic mechanisms of neurotoxicity of these chemicals and understand the factors influencing the neurotoxicity. Attempts have also been made on protection of the neurotoxicity effects using plant extracts and antioxidants but such studies are confined to experiment levels.

Clinical Neurosciences

In this limited overview it is not possible to even briefly summarize the Indian contributions in this field. Excellent reviews on neurology **(NH Wadia)**, neurosurgery **(RG Ginde & VK Kak)** and neuropsychiatry (**A. Venkoba Rao**) have been provided in Neuroscience in India: Retrospect and Prospect.[3] Additional inputs have been included by Tandon,[4] Tandon and Gouri-Devi,[7] Chopra and Sawhney.[44] To highlight the importance of clinical research examples of a few outstanding contributions by the pioneers are mentioned here. At the cost of repetition it is once more emphasized that this is not a comprehensive review. The examples included here relate to the diseases more frequently encountered in India or where the variations in their incidence, manifestations or course as compared to other regions of the world have been observed. Special attention has been given to interdisciplinary investigations to highlight the value of such cooperation.

During the initial years most clinical researchers were busy highlighting the patterns of CNS disorders and their relative incidence compared to the West, where most of them were trained, for eg. Gourie-Devi's epidemiology paper and Wadia (1987).[45,46]

The high incidence of neurotuberculosis, brain abscess and neurosyphilis (at least in some of parts of the country) was not surprising. Large series of patients with tuberculous meningitis (TBM), its sequelae and tuberculomas were reported from all over the country specially Madras and Bombay. Iheir pathology, pathogenesis, clinical features, problems of diagnosis and strategy for management were investigated by multidisciplinary teams consisting of clinicians, pathologists, microbiologists and radiologists. These contributions have been summarized in a series of critical research papers and reviews published nationally and internationally by various authors.[47-55] Proceedings of a National Seminar, organized by the Indian (now called National) Academy of Medical Sciences were published in 1972. Poliomyelitis, Japanese Encephalitis, Cerebral Cysticercosis, Brain Abscesses, Kyasanur Forest Disease and more recently HIV infection of the brain have been the subject of a large number of publications (Pankaj Seth).[56] It will not be possible to describe these in detail but mention may be made of two unique clinical syndromes of infective origin encountered in India i.e. single 'ring' or 'disc' enhancing lesion producing focal epilepsy and enterovirus 70 disease (acute hemorrhagic conjunctivitis associated with neurological manifestation). The former had been reported from all parts of India soon after the introduction of CT Scan and accounted for nearly 20 percent of all patients presenting with focal epilepsy. It was discovered to be of varied etiology, presenting a peculiar feature of "disappearing" and "reappearing" lesions, without any specific treatment. Ultimately it was established that majority of these lesions were solitary cysticercus cyst.[57-60]

In March 1971 and again in 1981, an epidemic of acute hemorrhagic conjunctivitis affecting several million people occurred in India. Wadia and his colleagues ultimately reported the neurological disorders associated with this infection and along with Kono from Japan confirmed the neurovirulence of the causative virus.[61,62]

As mentioned earlier a number of typical manifestations of well known neurological disorders or some new syndromes constituted several important publications. These included Infantile Tremor Syndrome, Madras Motor Neuron Disease, Tropical Spastic Paralegia, Monomelic amytrophy, Olivopontocerebellar degeneration associated with slow eye movements and peripheral neuropathy, hot-water epilepsy among others. These have already been included in textbooks.

An unusually high incidence of congenital Atlanto-axial Dislocation and Cranio -vertebral anomalies was reported from many centres in the country. Its diagnosis, clinical picture, associated medullospinal compression and surgical management have been a subject of a large number of publications and monographs.[63]

In the field of neurotraumatology special mention needs to be made of pioneering studies on temporal lobe lesions, brainstem pathology, post traumatic brain oedema, cranio-cerebral erosion, brachial plexus injuries and optic nerve injuries.

Among cerebrovascular diseases, unusually high incidence of stroke-in young and cortical venous thrombosis needs special mention.

Brain Tumours - their pathological, clinical and therapeutic aspects - were the subject of a large number of studies. Notwithstanding the high quality of many of these studies there were no distinctive or unique features, which deserve to be recorded in this presentation. It may, however, be mentioned that there are several centres in the country where several hundred brain tumours are operated upon every year with results comparable to the best anywhere.

Another area of major contributions extending over a number of years is one of stereotactic neurosurgery, particularly functional neurosurgery by the group at Madras (Chennai) - B Ramamurthi, V. Balasubramanian, S. Kalyanaraman & T.S. Kanaka. This received much deserved international recognition.

Concluding Remarks

Beginning with very modest but determined efforts of its founding fathers, neurosciences have come a long way in the country. There are some outstanding groups, departments and centres both in clinical and basic disciplines. Last decade especially has witnessed a more rapid growth. As will be observed from the examples quoted here, and many others experts in this volume, it is obvious that internationally competitive and nationally relevant research has been possible, often under very difficult circumstances. However, the environment is rapidly changing with state-of-art facilities available at many centres in the country.

It is expected that there would be a quantum jump both in the quantity and quality of research contributions in future. However, considering the growing importance of the discipline, the availability of newer technologies with vastly improved prospects of exploring the most complex organ of the body, the brain; the overall efforts in the country remain sub-critical. The Academy of Neurosciences has to play an important role in attracting talented young researchers to this ever expanding and challenging field and provide them with a stimulating environment to pursue a gratifying career.

In the end let me once again reiterate that this presentation is not a comprehensive review. It has an undeniable subjective bias dictated by constraints of limited personal knowledge of the vast field under review. I am sure the deficiencies will be covered by other contributors to this volume. The studies mentioned here are just to demonstrate that high quality research had been possible in the country even when resources were limited and with increasing opportunities one has very high expectations for the future.

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ANNEXURE 4

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APPENDIX TABLE 1: The summary of some important contributions by clinical scientists

Sr. No	Name	Nationality	Place of Work	Major Contribution	Collaborators	Comments
1.	Pierre Paul BROCA (1824-1880)	French	Salpetrier, Paris	Concept of the relationship of certain symptoms and circumscribed lesions of the brain (1861), localized (aphemie), motor aphasia (Aphasia) to the left inferior frontal gyrus, later called Broca's convolution by Ferrier.		Initially, the concept was based on clinical and autopsy findings of a single patient. It was criticized by Trousseau, Pierre Marie, and Hughlings Jackson. The idea was elaborated by Hitzig, Ferrier, Charcot, Wernicke, and Dejerine
2.	Jean-Martin Charcot (1825-1893)	French	Salpetrier, Paris (Joined in 1860) (Neurology Clinic)	Laid the foundation of Psychopathology, cerebral localization, disseminated (multiple) sclerosis, ALS, neurosis, and hysteria	Many students who became renowned included Pierre Marie, Tourette, Bekhterev, and Colin	"He entered neurology in its infancy and left at its coming of age, nourished mainly by his own contributions. Laid the foundation of neuropathology.
3.	Theodore Meynert (1833-1892)	Vienna (Austria)	First Psychiatric Clinic at Vienna, established specially for him	Clinical studies along with neuroanatomy, histology constituted the basis of cortical localization. Described several new anatomical structures in the brain not known before this.	Teacher of Freud, Wernicke, Ford, Von Gudden, Edinger, and Korsakov	One of the founding fathers of neurology, also a pioneer in cytoarchitectonics and later on the advocate of the role of ethics and morality in human behavior.
4.	Hughlings Jacksons (1835-1911)	British	National Hospital for the Paralyzed and Epileptics, Queen Square. (Estd. 1859) also attached to Moorfield Eye Hospital, London	Focal Epilepsy, later called Jacksonian epilepsy, constituted the localization of functions in the cerebral cortex.	Colleagues: Gowers, Ferrier, Victor, and Horsley Students: Henry Head, Gordon Holmes, James Collier, and Kinnier Wilson	Considered the Father of British Neurology. Introduced the use of an ophthalmoscope in neurology practice. Considered a neurological philosopher.
5.	William Gowers (1845-1915)	British	National Hospital Queen Square, London	An outstanding teacher and diagnostician. The first successful operation for removing a spinal tumor by Victor Horsley was diagnosed and localized by Gowers and referred to him in 1887.		His "Manual of Diseases of the Nervous System," 2 volumes, published in 1886-1888, was called "The Bible of Neurology." His famous "Manual and Atlas of Medical Ophthalmoscopy" with his self-drawn pictures published in 1904 could not be bettered.
6.	Carl <u>WERNICKE</u> (1848-1904)	German	Private practice in nervous diseases (neurology and psychiatry) for some years later as a faculty member in Breslau in psychiatry	Initially contributed to neuroanatomy, later on to symptomatology resulting from thrombosis of the posterior inferior cerebellar artery. He is most well-known for his description of sensory aphasia (word deafness) because of lesion in the superior temporal gyrus (1874). Description of the clinical syndrome of polio-encephalitis superior hemorrhagica (1881).	Was a student of Neumann in Breslau Meynert in Vienna	His first book on aphasia was published in 1874 when he was 26 years old.
7.	Joseph Jules <u>DEJERINE</u> (1849-1917)	French	Salpetriere and Bicetre in Paris	One of the pioneers in the study of localization of functions in the brain. Along with Vialet, he showed that word blindness might occur because of lesions of the supra-marginal and angular gyrus (1893). His other studies included hypertrophic interstitial neuritis (Dejeriine-Sotta), thalamic syndrome, and progressive muscular dystrophy.	Was a student of Vulpian (1826-1887). His collaborators included Roussy, Andre Thomas, Sottas, and Paul Dubois (1826-1887)	His wife Augusta Klumke (1859-1927) was herself a medical person and a great help in Dejerine' investigations. His famous book was Anatomie des Centres Nerveux (Paris Rueff 1890-1901).

Contd...

Table 1: Contd...

Sr. No	Name	Nationality	Place of Work	Major Contribution	Collaborators	Comments
8.	Sergei Sergeivich KORSAKOV (1853-1900)	Russian	University Psychiatric clinic, Moscow	He studied neurological disorders because of alcoholism, the most famous being "Amnestic Confabulatory Psychosis," which later came to be known as Korsakov's Psychosis (1890), credited with establishing the concept of Paranoia.	A pupil of Meynert in Vienna	Established a Russian Association of Psychiatrists and Neurologists.
9.	Ludwig EDINGER (1855-1918)	German	Initially at Weigert's Senckenbergisches Pathologisches Institute in Frankfurt, later he built a Neurological Institute of his own, financed by himself.	He combined structure, function, and clinical observation. He promoted the study of comparative anatomy. He is best known for describing the Edinger Westphal nucleus (1887). He is credited as the first person to define "Thalamic Pain'' (1891) verified by autopsy.	Collaborators: Van Gehuchten, Ariens Kapper, Gorden Holmes, Wallenberg, each actively collaborated with him in an important area of neuroanatomy.	His book "Zehn Vorlesungen uber den bau der nervösen Central organ des Menschen." Theme (Leipzig, Vogel, 1885) was translated in many languages. He later published a book on the Clinical Application of Neuroanatomy (1909).
10	Joseph Francois Felix BABINSKI (1857-1932)	French	-Salpatrier, Paris -Neurology Clinic, Chief at Hospital de Pitie	Most famous for describing the "Cutaneous Plantar Reflex", which came to be known as Babinski Sign (1896). He also studied Argyll- Robertson Pupil in neurosyphilis and asynergia and adiadochokinesia as signs of cerebellar dysfunction. It is claimed that it was Remak who reported the Plantar reflex 3 years earlier, but it was Babinski who first realized its diagnostic significance.	Worked under Charcot at Salpetriere	In 1912, he published his paper on the localization of the first spinal tumor to be removed in France (Rev Neur Paris 23, 1-4, 1912). According to Wartenberg, "The number of works devoted exclusively to Babinski run into hundreds."
11	Alois ALZHEIMER (1864-1915)	German	Städtische Irren anstatt Institute in Frankfurt, moved to Anatomisches Laboratorium der psychiatrischen under venenKlinik, in Munich., Chair of Psychiatry at Breslau	Clinical and pathological approaches to brain diseases. Best known for his description of the pathology of senile dementia, which was given the name of AD by Kraepelin. He has also contributed to studies on general paresis, senility, and acute delirium.	Worked with Emil Kraepelin, and Nissl	Published along with Nissl "Histologische und histopathologische Arbeiten unter die Großhirnrinde" (Jena, 1904, 1-315-494)
12	Henry HEAD (1861-1940	British	Trinity College, Cambridge University College London, London Hospital	The study of cutaneous pain sensation, sensory dermatomes. Also, contribution to Aphasia was significant, although not as well recognized.	Studied at Trinity College, Cambridge, Colleagues Langley, Sherrington, Gordon Holmes	With the help of River, he made observations on himself after sectioning the cutaneous branch of his radial nerve. He was the editor of Brain from 1910 to 1925. Book on Aphasia and kindred disorders of speech, Vol 2 Oxford University Press, London 1920.
13	James Stansfield COLLIER (1870-1935)	British	National Hospital Queen Square, London.	A detailed description of clinical and pathological features of sub-acute combined degeneration associated with pernicious anemia (1900). Other contributions on cerebral diplegia, myotonia congenital, aphasia, apraxia, and agnosia intracranial aneurysm.	JRS Rusell, FE Batten	

Contd...

Table 1: Contd...

Sr. No	Name	Nationality	Place of Work	Major Contribution	Collaborators	Comments
14	Constantin Von ECONOMO (1876-1931)	Austrian	Psychiatric Clinic of Wagner Von Jauregg at Vienna	Initially, he worked on the physiology and anatomy of Midbrain (1909), Trigeminal Pathways (1911), Tumors of Pons (1911). However, he is best known for his studies on Encephalitis Lethargica (1917). Published his atlas on the Cytoarchitecture of the adult human cortex (1925).	Worked with several well-known neuroscientists such as Pierre Marie, Kraepelin, Von Ebner, and Exner across Europe.	Published Die Cytoarchitektonik Der Hirnrinde des erwachsenen Menschen (Wien, Springer 1925).
15	Wilder PENFIELD (1891-1976)	Canadian/ American Origin	Founder Montreal Neurological Institute, Montreal, Canada	Pioneering work on Cerebral Cytology and Pathology, followed by electrical stimulation of the brain and localization of function, temporal lobe epilepsy, the role of amygdala and hippocampus in memory.	Student of Sherrington, Rio Hortega. Otfrid Foerster, Osler, Gordon Holmes, Percy Sargent. A long list of collaborators, Cone, Elvidge Rasmussen, Feindel, Jasper, Milner, and trainees including Dorothy Russell, Webb Haymaker, Kristiansen, Erickson and many others from across the globe	Published a series of books (see the attached list in his biography)
16	Roger Wolcott SPERRY (1913-1944)	American		Initially studied the regeneration of severed optic nerves of fish, salamander, and frogs. However, his best-known work was on "Split Brain "(1953). He established that the left hemisphere was geared toward language, abstract and analytic thought, and calculation. The right hemisphere was more important for understanding spatial patterns and complex sounds such as music. He later became interested in the brain─mind-consciousness riddle.	Trained under Karl Lashlesy, Paul Weiss Collaborators Gazzaniga, Ronald Myers, his doctoral student.	See the list of refs in the attached biography.

APPENDIX 2: INTERESTING READINGS

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