REVIEW ARTICLE

The Decade of the Brain : A Brief Review

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Summary

Recognising the huge burden of neurological and psychiatric disorders and prompted by the potentials of new techniques of molecular biology, biotechnology, genetics and imaging to study these, the 1990s were declared the 'decade of the brain'. This stimulated global scientific efforts to understand the human brain in health and disease. This review summarises some of the major research achievements during the decade. While it is impossible to provide a comprehensive summary of the voluminous data that has been generated, it was decided to provide a bird's eye view of the recent advances in the fields of developmental neurobiology, neurogenetics, neurochemistry and imaging of the brain, which have direct relevance for the clinicians.

Key words : Neurobiology, Neurogenetics, Neurochemistry.

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Introduction

On July 17, 1990, President George Bush, through a Proclamation (6158), declared 1990-1999 as the 'Decade of the Brain'. This was prompted by an earlier document prepared by the National Advisory Council of the National Institute of Neurological Disorders and Stroke (NINDS) in 1988, entitled 'Decade of the brain; Answer through scientific research'. This report provided concrete evidence that many neurological disorders, afflicting vast numbers of people, could be prevented, cured or alleviated if research opportunities were fully exploited with adequate funding. The National Advisory Mental Health Council also prepared a report, 'Approaching the 21st century : opportunities for NIMH neuroscience research' at the same time. It identified '50 important questions to answer in the decade ahead'. In June 1990, NINDS drew up an 'Implementation plan - decade of the brain'. This included fourteen major disease categories for which the field of neurobiological research was considered poised for a break through.

This started a chain reaction all around the world. World Federations of Neurological and Neurosurgical Societies and several national governments and scientific societies adopted the 1990s as the 'decade of the brain'. Neuroscience/brain research institutes and/or major neuroscience research programmes were initiated in different parts of the world. The Government of Japan decided on a new neuroscience initiative investing a total of US $125 million in the year 1997, which could increase six fold over the next five years. This included establishment of a $61 million Brain Science Institute at Riken on the initiative of Prof. Masao Ito, who is the head of this

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new institute.[1] In November 1998, the Chinese Academy of Science approved the establishment of Chinese Institute of Neuroscience (CIN) initially at the preexisting famous Shanghai Brain Research Institute, with the start-up investment of $300,000, plus $100,000 a year.[2] As a result of the persistent efforts of the Indian neuroscience community and the Department of Biotechnology, the Government of India announced the creation of a National Brain Research Centre which is already making rapid strides.[3] A unique new institute, the 'Neurosciences Institute', was opened in October 1995 by the Nobel laureate Gerald Edelman at La Jolla, California, as a retreat where scientists from all over the world could discuss a specific idea with a few colleagues for a few days.[4] It is interesting to note that there has been an explosive growth in the number of neuroscientists during this decade. In the US alone, more than 1000 new members were added to the Society of Neuroscience every year. In a symposium held at the National Academy of Sciences in Washington in April 1999, the Society of Neuroscience reported on progress during the 'decade of the brain' and predicted advances for the future.[5] An attempt has been made here to summarise some of the developments during this decade for the Indian neuroscience community to ponder over and assess their own contributions and decide their future plans. It is meant to provide a glimpse of the neurosciences research and directions in which it is expanding, with the help of some examples in each major area of development with which the author is acquainted.

The contributions of Indian neuroscientists, till 1989, i.e. just prior to the 'decade of the brain', have been well documented in a monograph, 'Neurosciences in India : Retrospect and Prospect'.[6] An updated account of some of the significant contributions is in the press.[7] The Department of Biotechnology, Ministry of Science and Technology, Government of India has brought out the 'Proceedings of the Interactive Session on Vision for Neurosciences in the Next Millennium' held in March 1998. A brief review of the important gains of the decade achieved globally will be useful to the neuroscientists in the country to plan their future activities for the coming years.

Developmental Neurobiology

Genes and Neural Development : Great progress has been made during the last decade in understanding the genetic basis of development of intricate neural circuits during embryonic and foetal development.[8] It had been known that a variety of neurons arise from the proliferation of so called 'neural progenitor' cells. Multipotent cells have been identified in the vertebrate central nervous system. Factors that control the differentiation of foetal stem cells to neurons and glia have been defined.[9] Animal experiments have demonstrated the ability of such cells to transform into neurons when implanted into the adult brain, raising new hopes for neural transplantation. Specific protein factors instruct the progenitor cell to make each kind of neuron. Several of these factors have been isolated in the past few years. As an example, a specific protein called sonic hedgehog (Shh) was found to cause particular types of neural progenitor cells to generate dopaminergic neurons. Techniques have been developed for isolating and multiplying large populations of neural progenitors, making it possible to generate particular type of neurons in a test tube. This raises new hopes for therapeutic use of such cells to replace neurons lost due to pathological conditions like trauma, degeneration, stroke etc. Similarly, specific proteins have been identified, which guide the axons of the developing neurons to reach the specific target. This information is likely to help in developing strategies for permitting the growth of fibers across a damaged area in the spinal cord. One such mechanism, originally identified in drosophila, is the notch signalling pathway. It has been shown to mediate 'lateral inhibition' in which undifferentiated cells basically compete with their neighbour cells to decide who will become neural progenitor. It has now been demonstrated that a number of human neurological disorders are associated with derangement in notch signalling. These include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL syndrome) and Algille syndrome (mild mental retardation with multiple developmental disorders).[10]

Plasticity in Brain : Recent observations using MRI on human subjects illustrate the extent to which the patterned activity of early life can produce changes in the circuitry of the developing human brain. For example, in individuals deaf from childhood, who use sign language instead of spoken language, the visual sensory modality takes over many of the perceptual tasks normally performed by the auditory system. Similarly in individuals blind from birth or early childhood, the area of tactile representation in the brain enlarges.[11] Researchers during this decade have revealed far greater plasticity in the brain than believed hitherto. As a matter of fact, the myth that the adult brain has no capacity to regenerate has been exploded.[12-14] While most of the plasticity resides at the level of the synapses, recent evidence reveals that

it may involve other structures e.g. spines of the dendrites, change in circuitry, new circuit formation and even new neuron formation. In addition, it has been demonstrated at least in rats, tree shrews and monkeys that during memory imprinting in adult life, new neurons appear in the hippocampus.[14] The glutamate receptor (NMDA) plays a key role in this process. During the last few years it has been established that the NMDA receptor is essential for early development. Mice experimentally mutated to lack functional NMDA receptors die within a day of birth. In the mature (adult) brain, functional cooperation between two classes of glutamate receptors, the AMPA and NMDA, has been repeatedly implicated in learning. We now know that the genes that code for the NMDA receptor change during development so that the receptor actually lets Ca^{++} enter into the neurons as the brain matures.

Once the molecular mechanisms responsible for development of brain circuits are fully understood, it would be possible to selectively activate the dysfunctional brain circuitry of sensory deprived individuals in adult life by selectively targeting genes to the appropriate region of the brain or spinal cord.

Molecular Genetics

The decade has seen an explosion in our knowledge of the molecules of the brain and their function. The revolution in genetics and recombinant DNA technology has led us to genes that control the development and functions of the nervous system, as well as genes whose mutations cause brain disease. 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. Knowledge of the molecular basis of genetic diseases that affect the nervous system is rapidly expanding. DNA mutational analyses are becoming commercially available for diagnosing many disorders such as mitochondrial disease and disorders associated with expanded trinucleotide repeats.[15] During the past 10 years, genetic factors responsible for a number of the primary neurodegenerative diseases, which include Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, prion disease and many ataxic syndromes have been found.[16] The past decade has witnessed great strides in our understanding of the molecular mechanisms involved in the functioning of the inner ear. Numerous molecules that participate in the cochlear operations have been identified. Use of molecular genetics has led to the identification of genes involved in almost 30 forms of hereditary human deafness. This knowledge is being utilized to explore the possibility of inducing regeneration of the hair cells in the cochlea.

Cloning of gene responsible for Fragile X-syndrome : This is the most common form of inherited mental retardation. In 1991, an international group of collaborators identified the gene for fragile X mental retardation B1 (FMR1). The study of FMR1 gene uncovered a previously unrecognized form of mutation i.e. the dynamic mutation. Within the FMR1 gene sequence, a repeated CGG triplet was identified.

In fragile X syndrome, it is now known that when the triplet expansion exceeds about 230 CGG repeats, FMR1 gene is turned off. The absence of the protein product of this gene, called FMR protein (FMRP), is responsible for the symptoms. A great deal of knowledge has been gathered over the past few years regarding the function of FMRP, a first member of a previously unknown family of proteins. It is hoped that a better understanding of the FMRP's function will not only provide knowledge for designing appropriate therapy for fragile X syndrome, but will also provide novel insight into the process of learning and memory. There are a number of other neurodegenerative diseases like Huntington's disease, Kennedy's disease, dentatorubralpallidoluysian atrophy (DRPLA), myotonic dystrophy etc., which are associated with DNA triplet repeats.[17]

Molecular Genetics of Alzheimer's Disease : Molecular genetic studies of autosomal dominant familial Alzheimer's disease (FAD) have led to the identification of four distinct genes associated with this disorder : APP gene on chromosome 21, Preseniline 1 gene on chromosome 14, Preseniline 2 gene on chromosome 1 and Apolipoprotein gene on chromosome 19. Another gene on chromosome 12 (gene for macroglobulin and the low density lipoprotein related protein LRP1) has also been proposed as a reasonable candidate. Further studies based on this information suggest that abnormalities in the processing of APP protein is a common feature in most forms of AD, resulting in over-production of A-peptide. Currently attempts are being made to design treatments, which will modulate the production and/or disposition of A-peptides and presenilins.[18-21]

Genes and Movement Disorders : Using the tools of genetics and molecular biology, it has been possible to identify 11 varieties of spinocerebellar ataxias. Genes responsible for 8 of these have been identified. Mutational mechanism responsible for the

pathogenesis of these disorders has been elucidated. It is now possible to diagnose these disorders accurately through genetic testing. It offers patients and their children an opportunity to plan for their future.

A gene which encodes a brain protein called α-synuclein, when defective, causes a hereditary form of Parkinson's disease.[22] In addition, Perlmann and Olson[23] have demonstrated that a molecule called Nurr 1 plays a critical role during embryonic development of the dopaminergic neurons and it may also play a role in keeping those cells active throughout life. This raises the possibility that boosting or restoring Nurr 1 activity in failing nerve cells may delay or prevent the onset of parkinsonian symptoms.[24] Mutations in the α-synuclein gene on chromosome 4, and parkin gene on chromosome 6 have been identified in families showing autosomal dominant and autosomal recessive parkinsonism respectively.[25-26] A defective gene on chromosome 2 causing autosomal dominant parkinsonism with low penetration has been considered to be implicated in sporadic disease.[27]

Mutations are now known for many neurodegenerative diseases. However, we still have to learn a lot about the precise mechanism related to the disease manifestation.[28] In the meanwhile, efforts are being made to explore the possibility of gene therapy in several neurological disorders.[29]

Genes and Epilepsy : Today more than 40 genes have been shown to be associated with epilepsy in mouse and man. Mutant genes found in rare forms of epilepsy encode for proteins involved in a variety of ion channels, voltage gated sodium or potassium channel or ligand (neurotransmitter) activated channel. A number of genes encoding the ion channels of the nervous system have been identified and more recently the first three-dimensional structure of an ion channel (potassium) has been determined. The epilepsy gene map has been refined and extended with new information concerning benign familial neonatal convulsions, Unverricht-Lundborg disease with progressive mental retardation and juvenile myoclonic epilepsy. The role of mutations in genes for neurotransmitter receptors, GLRA1 and CHRNA 4, and a voltage-gated potassium channel KCNA1, as causes of inherited neurological disorders has been explored.[30] This information promises to provide new molecular targets for anti-epileptic drugs.

Molecular mechanisms responsible for brain damage following infarct in strokes have been extensively studied in the 1990s. Excessive release of neurotransmitter glutamate triggers release of nitric oxide, which in turn causes a major portion of the neuronal damage.[31-33] Drugs that block the formation of NO have been shown to diminish stroke damage. A large part of research on NO, its role as a neurotransmitter on one hand and neurotoxicity on the other, has been carried out during this decade.

One of the mechanisms responsible for neural damage following cerebral trauma, ischaemia and spinal injury that has been extensively investigated during the 'decade of the brain' is the glutamate induced excitotoxicity - resulting in large amounts of calcium entering the nerve cells. This calcium overload results in generation of free radicals capable of destroying many cellular structures leading to cell death. In addition, more recently it has been demonstrated that besides destroying neurons, it can also damage oligodendrocytes and consequently the myelin. The damage mediated by glutamate and calcium overload may be augmented by zinc. Therapeutic strategies based on this knowledge are undergoing experimental and clinical trials.

Neurotransmitters, Receptors and Cytokines in Brain Disorders

A major finding over the past decade has been that the human brain uses only a few small molecules as neurotransmitters, but uses a huge diversity of different neurotransmitter receptors, which send very different signals to the receiving nerve cell. The diversity of chemical coding accessible to nerve cells is very large and complex.[34,35] The same neuron may synthesize and liberate several different chemical messengers subserving specific functions. Chemical maps of the brain are now becoming available.[36] The interplay of a myriad of interactive and qualitative factors that govern signalling and modulation of a host of highly specialised transmitters responsible for its functioning is now becoming possible owing to the availability of sophisticated techniques using microelectronics and analytical chemistry, which can monitor changes in extracellular concentrations of neurotransmitter *in vivo* at physiologically relevant concentrations as often as 200 per second from several sites simultaneously. Hundreds of neurotransmitter receptor genes have been isolated, cloned and studied in detail. This has paved the way for the pharmaceutical industry to develop new very specific drugs to target specific receptors and nerve network encoded by these genes, raising the hope for treatment of mental illness and neurodegenerative diseases

without the unpleasant side effects associated with the currently used drugs.

Variety of cytokines have been found to play an important role in the pathogenesis of a number of inflammatory and degenerative disorders. These include thrombospondins, β-chemokines, ICAM, TNFα, IL10, IL1, IFNγ etc.[37] They seem to contribute to most, if not all, acute and chronic CNS pathologies.[38] Over-expression of cytokines is observed in the brain of patients suffering from viral infection (for example AIDS), multiple sclerosis, Alzheimer's disease. There is growing evidence that pro-inflammatory cytokines induce glial cells to produce neurotoxic factors. Another area of burgeoning activity is the isolation and characterization of a variety of neurotrophic factors like nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), brain-derived neurotrophic factor (BDNF), glial cell-line derived neurotrophic factor (GDNF). These have led to the discovery of a family of genes - the neurotrophins. Their role in the neural development has been elucidated. At the same time their potential use in therapy is being explored. Thus, already clinical trials with CNTF and BDNF in patients with amyotrophic lateral sclerosis have been initiated.[39-43] We have ourselves demonstrated the effect of co-transplantation of Schwann cells with embryonic substantia nigra in better growth and survival of the transplanted neurons.

The demonstration of neurotransmitter receptors on peripheral blood platelets reflecting their status in the brain has provided an opportunity for using these as markers for the diagnosis of brain disorders (Parkinson's disease, biphasic disorders) and monitoring the therapy. PET studies have revealed reduced levels of D1-like dopamine receptors in the frontal cortex of patients with schizophrenia.[44]

Imaging the Brain

An interdisciplinary cooperation between the cognitive scientists and imaging experts has provided a wealth of information about the functioning of the normal human brain.[45-52] Contrary to earlier belief of localization of specific functions in discrete regions of the brain, it is now known that most functions are widely distributed. As an example, atleast three dozen areas have been identified to be involved in visual function alone. The more complex functions like language and memory emerge from simultaneous activity in many widely separated areas of the brain. Even more surprisingly, areas as yet unsuspected have been found to play a significant role in a variety of functions. Thus cerebellum earlier believed to be solely concerned with equilibrium and coordination of motor activity has now been found to contribute substantially to memory, speech and thought processes as well. Already a vast amount of information has been generated regarding the brain areas and neuronal circuits involved in higher mental functions like memory, attention, emotion, language etc. utilizing such diverse techniques as PET scan, functional MRI, magneto encephalography and event related EEG.[53-59] It is obvious that utilizing diverse imaging techniques, with specific advantages of spatial and temporal resolution, in future one would get a more comprehensive picture of functioning of human brain in health and disease.

Brain imaging studies have revealed anatomical areas of difference between those who do or do not suffer from certain kinds of depression. This may prove to be of significance in differentiating those likely to commit suicide or not. These types of studies while still in their infancy, promise that brain imaging techniques may help improve both the diagnosis and treatment of mental disorders. A major pilot project involving scientists from different parts of the world has been initiated through the support of a consortium of US funding agencies. This 'human brain project' aims to create integrated data bases on all aspects of neurosciences - from molecular to behavioural level, in an accessible manner. This has given birth to a whole new discipline of neuroinformatics.[58,60,61] It is expected that this effort will ultimately lead to three dimensional computerised maps and models of the structures, connectivity, physiology, pharmacology, biochemistry and molecular biology of human, monkey and rat brains, and to make these data available via computer net works in combination with cutting edge informatics research.[60]

Computational Neuroscience

As experimental data continues to amass, it is becoming increasingly clear that the detailed anatomical and physiological data is not enough to infer how neural circuits work. The last few years have seen the birth of a new discipline - 'computational neuroscience' - which brings together computer modelling experts and experimental neuroscientists.[62-64]

Therapy

Information gained from basic research has already

provided promising leads for development of better therapy.[65] Intensive research on the mechanism of interneuronal communication has provided valuable information on a variety of neurotransmitters, neuromodulators, neurohormones and neurotrophic factors involved in growth, development and health of the neurons. The study of their synthesis, storage, release, degradation and recycling not only provides a fascinating picture of the chemistry of the brain but also new insights regarding their role in pathogenesis of many brain and mental disorders. This knowledge has provided valuable information on possible therapeutic targets and modelling of new drugs. A number of neuroprotective agents, acting on various receptors, like aptiganel, ZD9379, GV 150-526A (NMDA receptor blocker) or SNX III (calcium channel blocker), lobeluzole which interferes with the adverse effects of nitric oxide or tirilazad, are under trial. Similarly, a number of neuropeptides like cholecytokinin CCK 8 (for schizophrenia), melanostatin MIF-1 (for depression) or vasopressin (for memory) have shown promise as therapeutic agents on the basis of animal experiments. Efforts to develop new drugs to treat mental illnesses, behaviour disorders and neurodegenerative disorders, rely in large part on detailed knowledge of receptors, ion-channels, transporters, membrane and protein structure of the involved molecules. Some of these are already in various stages of experimental and clinical trials. For example, considering that GABA is deficient in some forms of epilepsy, drugs targeted on enzymes involved in synthesis of GABA, proteins that bind GABA or enzymes that break down GABA have been developed. Similarly, the discovery of a new molecule called Nurr 1, which is believed to play a critical role during embryonic development of dopaminergic neurons, raises the possibility that boosting or restoring Nurr 1 activity in failing nerve cells may delay or prevent the onset of parkinsonian symptoms.[66]

Researchers have now isolated the enzymes β or γ secretase that make β-amyloid that is believed to be responsible for neuronal degeneration associated with (or responsible for) Alzheimer's disease. Several pharmaceutical companies, like Amgen, Elan and Smith Kline Beecham, are already working to develop drugs based on this knowledge.[67] A new drug that lowers the brain levels of glutamates has been found to block schizophrenia like symptoms in rats, without apparent side effects.[68] No doubt we are still a long way away from a specific drug, but these are indicative of a strategy to develop more specific therapy for a variety of neurodegenerative disorders.

Restorative and Augumentative Neurology

The last decade has witnessed a variety of approaches based on developments in molecular biology, biotechnology, solid state electronics, new materials and computer science to replace or help in regeneration of the damaged nervous tissue or substitution of the impaired function by artificial prosthesis.[69] The excitement generated by the initial experience with neural transplantation, in the later half of the 1980s, led to intense research in this field in the 1990s.[70-74] These studies unequivocally established the feasibility of foetal neural transplant in adult brain surviving and providing symptomatic relief in patients of parkinsonism. The final confirmation of this comes from Curt Freed and his associates from the University of Colorado, Denver. In a double-blind placebo controlled study involving forty patients with advanced Parkinson's disease, the control group hadn't improved one year after the operation. But the foetal tissue was seen to hold in patients who received a transplant. Positron emission tomography scans showed a 20% or better increase in dopamine activity in putamen in two-thirds of the treated patients. Patients aged 60 or below showed a marked reduction in parkinsonian symptoms, while older people improved only slightly as compared to the controls.[75] A single patient who had received nigral transplant in putamen ten years earlier has recently been reported to have surviving neurons and substantial symptomatic relief, indicating long term survival of such transplants.[76] Technical and ethical problems associated with the use of human foetal tissue has prompted search for alternatives. Based on animal studies which revealed relatively mild immune response to neural cell xenotransplantation,[77-79] foetal pig neural cells have been used for transplantation. One of the 12 patients so treated revealed graft survival and the presence of pig dopaminergic neurons at post mortem 7.5 months after implantation. Attempts have also been made to transplant genetically engineered cultured cells to act as a source of neurotransmitter dopamine.[42,80-82] The recent discovery of persistence of stem cells in adult brain, ability to selectively separate them, grow them *in vitro* and modify them into desired neuronal type, has raised new hopes as an alternative strategy for replacement of lost neural tissue.[9,14,83-88]

Use of gene therapy for treatment of a variety of genetic and neurodegenerative disorders is being actively pursued in animal models of these disorders.[28,29,42,89-92]

The 1990s have witnessed impressive advances in the understanding of spinal cord injury, pathogenesis of the secondary cell death, factors preventing axonal growth across the damaged segment, molecules that can stimulate and perhaps guide the growing axons to their target. It is now reasonably established that agents that selectively block glutamate receptors (AMPA subtype) help in limiting the final extent of the secondary lesion. Methylprednisolone, besides its antioedema activity, is now known to diminish the release of glutamate and the accumulation of free radicals. A number of other neuroprotective agents are also under trial for minimising damage in stroke patients (see above). Whether some of these will also be of use in patients with head and spinal cord injury is not known. A variety of neurotrophic factors have been identified which promote neuronal and glial survival. GM-1 ganglioside (syngen) is already under human trial for limiting cord injury. An inhibitor-neutralising molecule IN-1 has been shown to promote axon growth of some interrupted axons in rats. Similarly, neurotrophin 3 (NT3) selectively encourages the growth of axons that descend into the spinal cord from the brain. Genetically engineered fibroblasts, which produce NT3 and other growth promoting molecules like human foetal tissue transplants and implants of tube packed with Schwann cells have demonstrated that the injured spinal neurons and tracts, atleast in case of partial injury, retain the potential to grow if provided with an appropriate environment. Therapy with NT3 and 4-aminopyridine is already under trial. This is not to say that as of today we can make a paralysed person, following spiral injury, regain normal function but we have road maps charted which may help in achieving this goal.[93-97]

A variety of electronic prosthesis are in various stages of development and trial to supplement or augment lost neuronal function. The cochlear implant is already in the clinics, a bionic ear for the deaf and a bionic retina for the blind, a neural amplifier for the spinal injury patients are being experimented upon in a host of laboratories around the world. A whole new field of molecular electronics, 'brain computers', or biochips, has emerged as a result of advances in neuroscience, solid state electronics and computer science which may help the neurologically damaged in future.[98]

Concluding Remarks

It is not possible, in this review, to summarise the vast amount of neuroscience knowledge generated during the 1990s, which according to some authorities is far greater than that accumulated in the previous 50 years or more. This article provides a glimpse of some developments the author has been acquainted with. The 'decade of the brain' generated an explosive growth of neuroscience research all over the world, mostly in the US, UK and Europe. This was helped by simultaneous development of a host of techniques and technologies permitting investigations from the molecular level to the study of intact human brain. It improved our understanding of the development, structure and function of the normal brain, pathogenesis of a host of diseases and provided basis for rational therapy. It gave birth to new disciplines of neuroscience like developmental neurobiology, neurogenetics, computational neuroscience, neuro-informatics, cognitive neuroscience, neural transplantation etc. The foundations laid down during this decade would, undoubtedly, provide an invaluable insight into the most elusive riddle of brain-mind relationship on one hand and appropriate therapy for a large number of incurable neurological disorders afflicting mankind. We, in India, could take advantage of these developments and chart out our strategies keeping in mind our needs, resources and opportunities and our desire to become a recognised vital player in the field.

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