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Contribution of Neuropathology for Intervention in Neurosciences

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Abstract

Neuropathology has come of age from a simple diagnostic field to a branch in the broad field of neurosciences encompassing functional pathophysiology, molecular biology, immunology and the conventional anatomic pathology. It has provided insight into the normal functioning of the nervous system, highlighting pathology. While the conventional biochemical, pharmacological, molecular biological techniques failed to provide accurate topographic and cellular localisation of the enzymes, reactive proteins and receptors and thus their role in cellular function, the morphological studies highlighted them. The pathological findings in brains of Schizophrenics collected at autopsy has failed to provide insight into psychopathology, but has offered an anatomical correlate to the integration and processing of output from the association cortex and behavioural manifestations. Normal ageing and various neurodegenerataive disorders can now be considered different zones of a continuous spectrum of neuronal degenerative changes, leading to slow death. Neuroimmunology and neuroinfections have now become facets to understand and convert the disease causing organisms into vectors for disease healing genes. An integration of pathomorphology and molecular genetics has offered means to understand tumour biology and predictors of genetic transmission of neoplasia to the next generation. Neuropathological studies have provided a "peeping hole" into the traumatised brain, its reaction to injury and the degree of plasticity with healing, thus an understanding of nature's experiment. In short neuropathology, in the modern era is no more a morbid study but a component to integrate structure with function, in the large field of neuroscience.

Key words -
Neuropathology,
Neurooncology,
Neurodegeneration,
CNS infections,
Muscular dystrophy,
Transgenic animals

From the time Rudolph Virchow coined the word 'Cellular Pathology', in the early part of eighteenth century, Pathology, the study of disease has grown and gained a wider connotation with the advent of newer techniques, thus it has become

broad based.

From the beginning of the 19th century, to date, the 'Decade of the Brain', the field of neuropathology has transgressed the usual boundaries and has become part of neurobiology along with many other specialities. Now, rather than compartmentalising branches of neuroscience, understanding the disease phenomenon by multidisciplinary approach has become important. With this, neuropathology is entrenched as a special branch for the conventional pathologist and has also become a modality of investigation for a neurobiologist. With this concept in mind, neuropathology has entered a grey zone merging with neurochemistry, neuropharmacology, neuroimmunology, molecular biology, computational and mathematical science and cybernetics. The field of neurobiology is too wide and hence we present only a fleeting glance at the broad field, some of which are of relevance to Indian neuroscientist. The subject dealt with is not meant to be exhaustive and has the personal bias in selecting the areas, which may have some relevance in intervention in neurosciences.

Psychiatric disorders

With the mapping of the chemical anatomy of the brain, distinct from classical structural anatomy, it has become clear that most neurotransmitters in the nervous system utilise many receptors than hitherto realised. Molecular biological techniques applied to the tissues have revealed that receptor population, previously thought to be homogenous, in reality consist of many subtypes, than is evident by pharmacological methods. Five cloned subtypes of muscarinic receptors are now evident, though at present there are no drugs that distinguish among them [1]. The antidepressant drugs acting via the monoaminooxidase inhibitor and toxins acting through the MAO mechanism has led to the identification of differential enzyme capabilities of the astrocytes in different anatomical areas. The anxiolytics acting through the serotonergic pathway involving 5-HT1A receptor is considered to mediate the effect by functioning as somatodendritic auto receptor and also postsynaptic receptor, but the exact anatomical locus of anxiolytic activity is not clear [2]. The antidepressant drugs like imipramine and fluoxetine exert their clinical therapeutic effect blocking the serotonin re-uptake but the effect is evident only after 2-3 weeks after the commencement of treatment. The anatomical locus is considered to be the serotonergic neurons of dorsal raphe nucleus. The evidence is rather pharmacological than sturctural. To answer these enigmas, in vivo studies with microdialysis system has come into existence [2], which revealed no enhancement of release of serotonin in the terminal field, frontal cortex after systemic administration of the uptake inhibitor clonipramine, but rather enhanced the release of serotonin at the dorsal raphe nucleus. Since the uptake inhibition occurs rapidly, the question has been why does it takes so long for optimal therapeutic efficiency? Blier et al [3] suggested that in spite of acute inhibition of uptake, the uptake inhibitors also rapidly decrease the 'turnover' of serotonin and the firing rate of serotonergic neuronal soma, in the raphe nucleus, which in turn cause a fall in the release of serotonin in the terminal fields from the serotonergic neurons. Over time, even in the presence of continuous uptake inhibitor, the firing rate of the neuron returns to normal, to exert its pharmacological effect. These illustrate how the increasing knowledge of receptor types, their anatomical locations in the brain, their physiological functions in the health and disease provide us with understanding of the pathogenesis and development of appropriate therapeutic interventions.

While the routine pathomorphological studies in Schizophrenia have shown the end result in the brain, the clue to pathogenetic mechanism has emerged from observation that specific class of drugs like amphetamine (a dopamine agonist) and PCP (a glutamate antagonist) produce clinical symptoms in

normal people that closely mimic symptoms of Schizophrenia. The mode of action of these drugs support the involvement of specific neurotransmitters (i.e. dopamine and glutamate) in Schizophrenia [4]. In search for a structural correlate for the this psychopathology, postmortem studies on formalin fixed brains [5], [7] have revealed preferential, but not exclusive affection of medial temporal lobe structures (parahippocampal gyrus, hippocampus and amygdala), found in all subtypes of Schizophrenia. The structures of the medial temporal lobe are believed to have a crucial role in the integration and processing of the output from association cortex. It is plausible that all Schizophrenias have abnormalities in the medial temporal lobe that differ in degree but not in the kind. Dysfunction of this system could result in clinical symptoms that form the core of Schizophrenic syndrome. Postmortem volumetric studies using stereological methods [7], on brains of Schizophrenics in comparison to controls failed to show significant changes in the cortex and white matter, but for variable increase in basal ganglia. Translating these findings to psychopathology has not enlightened us in the understanding. Neuronal migration defect and developmental anomalies in the brain have been invoked to explain the biological basis for Schizophrenia [8], [9], [10], though not consistently convincing. Lesions around the temporal lobe are commonly associated with psychosis in patients with multiple sclerosis. A study of obsessive compulsive phenomenon is subjects with herpes simplex encephalitis revealed that, nearly 40 per cent of cases develop clear obsessive phenomenon. This emphasises the role of medial temporal limbic structures on repetitive thinking. The psychiatric manifestations in cases of Rabies and Creutzfeldt-Jakob disease, with visual hallucinations, mania, depression, schizophrenia like psychosis, provide probable anatomical correlates to the behavioural manifestations. It is also recognised that brain regions hitherto considered 'silent' have functions that are perhaps curcial to the understanding of mental disorders. These studies have exposed the limitation of conventional neuroanatomaopathological studies and the need for a multidisciplinary study to elucidate the anatomochemical pathology for understanding mental disorders. They have also highlighted the need to undertake the difficult task of mapping neurotransmitter-neurochemical anatomy of the human brain and refrain from extrapolating form studies on lower mammals. This realisation has led to the establishment of Human brain banks, dedicated to various neurological and neuro psychiatric disorders.

A need for holistic and integrative approach to study the brain is achieved now by the newer imaging techniques, filling the yawning gaps in the conventional neuropathological studies, and each became a complement for better understanding. In this context, brain mapping is a remarkable example of technology transfer from the hard and exacting sciences like physics, mathematics and engineering to the rather emperical 'art like' Life Sciences [11].

Down's Syndrome and infantile autism continue to be two important and common conditions in the general population., causing significant psychological and social morbidity thus straining the economy and coping mechanisms of the family. The study of brains in autism has defied clear definition of pathological lesions. Presence of cytogenetic abnormalities have been described although no consistent abnormalities have been noted, so also no consistent association with HLA types [12].

The pathological studies of Down's syndrome has shown the close relationship between the Alzheimer's disease, sharing the gene and gene product, the amyloid b protein. A localisation of cytosolic Cu / Zn superoxide dismutase, interferon receptor, amyloid precursor protein, phosphoribosyl glycinamide synthetase and Ets-2 Protooncogene on the chromosome 21 in man and chromosome 16 in mouse has highlighted the possible mechanisms initiating the neuronal pathology [13], [13b]. By

injecting human SOD gene along with regulatory sequence into the nucleus of the zygote, transgenic mice are generated to study more about Down's syndrome [14]. An earlier attempt by a German pathologist Alfred Gropp, to breed mice with genetic defect on chromosome 16, (homologous to human chromosome 21) has resulted in mice with phenotypic expression of Down's syndrome, but failing to live beyond birth. The transgenic mice interestingly have large protruding tongue and the abnormalities in motor end plates of tongue muscle similar to Down's syndrome in humans. In another model, embryonic stem cells were cultured from preimplantation mouse embryo. Spontaneously occurring or retroviral induced HPRT mutant were selected and injected into blastocyst, to yield chimeric mice, the HPRT mice [15], [16]. Similar HPRT primates are also evolved, an animal model to LeschNyhan syndrome, an X linked mental disorder with self mutilation. Further studies are in progress, both chemical and structural to correlate with the human disease.

Ageing and neurodegenerative diseases

The normal ageing and some of the neurodegenerative disorders share common morphological substrate in the form of neuronal cytoskeletal abnormalities. It is rather the degree of anatomic and chemical pathology rather than the specific cellular pathology, that distinguishes different neurological disorders like Alzheimer disease, Parkinson's disease, Picks disease, PSP, Lewy body disease, etc. A synthesis of neuroanatomical study by Meynert during last century and the pathological study during seventies and eighties of nineteenth century has resulted in identification of nucleus basalis of Meynert (NBM) as the primary source of acety 1 choline in the cerebral cortex [17]. Damage to the NBM in Alzheimer's disease appears to account for the consistent loss of cholinergic markers in cortex associated with the disease. Cholinergic neurotransmission has long been thought to be involved in memory, learning and arousal and their blunting in Alzheimer's disease has lead to the supplementation of acety 1 choline as a therapeutic procedure [18]. Similarly, the involvement of substantia nigra in Parkinson's disease and the recognition that loss of dopaminergic neurons of this anatomical locus lead to the clinical symptoms, resulted in supplementation therapy with Levo dopa. In order to understand the role of the neurotransmitters in the brain and their receptors, one must know the precise sites of synthesis and localisation of the neurotrophins as well as their receptors. The sites of synthesis can be revealed by in situ hybridisation using specific antibodies against the prosequence in the protein. The presence of native protein can only be determined by immunohistochemistry. The biochemical and pharmocological techniques, by the very methodology of homogenising the tissue, will not be able to provide information on cellular localisation.

These morphological approaches have helped to localise four closely related trophic factors, nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3, (NT-3) and NT-4, in the brain. NGF, BDNF and NT-3 are expressed by specific, partially overlapping subset of neurons in the hippocampus and other areas of the brain [19]. Further neurotrophin receptors with differential affinity have been identified. The high affinity receptor for NGF, trk is found specifically located on cholinergic neurons that also contain low affinity receptors. This fits well with the observed effect of NGF on central cholinergic neurons, and therapeutic trials in animal models to improve learning and memory with implications to Alzheimer's disease [20]. Another trophic factor of great promise is ciliary neurotrophic factor (CNTF) which is found to reduce the morphological features of motor neuronal

and axonal degeneration, even when the treatment has been started after the first symptoms of the disease has become manifest. These neurotrophic factors have been seen to be unregulated in different kinds of perturbations in the brain like ischemia, hypoglycemia, excitotoxic lesions, epilepsy treatment and mechanical injuries resulting in reparative responses [21], [22].

Recent studies of synaptic pathology by neuroanatomists and pathologists have offered an understanding of the structural correlate to physiological and psychological manifestations. Masliah et al [23], by quantitative morphometry have shown that loss of synaptic input in the neocortex is an age dependent factor that contribute to the overall synaptic loss of Alzheimer's disease, thus establishing a link between normal ageing process and neurodegeneration. It is interesting to note that here is a constant turnover of synaptic system and with epileptic discharge a massive depletion of synapses occur and this loss progresses unabated, with each seizure. Similarly a single dose of phenobarbitone is found to cause loss of synaptic density in the rat brain [24]. Luckily the generation of new synapses replenish the ones lost, thus equilibrium is established. These observations explain the epilepsy related psychosis and amnesia, and at the same time highlight the dynamic events occurring unlike in the neurodegenerative diseases, with relentless down hill course. In an attempt to understand Alzheimer's disease, recently a 57 kD nuclear protein 'Statin' is identified which modulates the compartments of cycling and quiescent neuroglia in the senescent human brain [25]. In Alzeimer's disease, 'Statin negative neuroglia' are increased in all the regions, except cerebellum. It is not clear if this is a reparative scar formation to fill the gap left by the degenerated neurons or altered equilibrium between neuronal and glial interaction. This finding has great implication in understanding regeneration is CNS and spinal cord following injury. In contrast to earlier thinking, now it is found that oligodendroglia, unlike astrocytes form in a discrete ventral location of the foetal brain, thus control the overall patterning of the brain during development [26]. An aberration in this spatial and temporal patterning by the environmental clues appear to result in anomalous white fibre tracts and the consequent pathophysiology.

Alzheimer's disease (AD) may be either sporadic or familial and the study of the latter has revealed the role of several genes in these cases. β amyloid protein is a major constituent of senile plaques, which along with neurofibrillary tangles are one of the histological hallmarks of AD. The gene for β amyloid precursor protein (β APP) of which β amyloid peptide is a fragment, is located on chromosome 21. Down's syndrome (trisomy 21) has an extra copy of the gene and some familial AD (FAD) cases have point mutatins of the β APP gene, reiterating the importance of β APP and its aberrant processing in the pathogenesis of AD lesions. Recently, the successful production of transgenic mice with V717F mutation and AD lesion has been met with a great deal of optimism and enthusiasm as an animal model for AD [26b]. The apolipoprotein E gene on chromosome 19 is implicated in several pedigrees of FAD [27]. Laboratory evidence suggests that the e4 allele of the Apo E gene accelerates the amyloid fibril formation, at least in vitro. In sporadic AD, individuals homozygous for e4 allele have a higher risk for AD and an earlier age of onset [28]. Two other genes, presenilin 1 (PS-1) and presenilin 2 (PS-2) on chromosomes 14 and 1 respectively have been linked to FAD [29]. Currently, the role of these genes is still unclear. Thus although lacunae still exist in our understanding of AD [30] and in a therapeutic approach to AD, major strides have been made in the last few years.

The transplantation technology has advanced and now both genetically engineered cell transfer and transplantation of foetal tissue in the treatment of Parkinson's disease is a possibility [31]. The other line of thinking is to transfer genes alone, with the help of herpes or adenoviral vectors but into the

preexisting relatively subnormal neuronal and glial elements, but not grafting cells or tissue. The neuropathological studies have helped to appreciate the limitations of the techniques, and the extent of connectivity of the neuronal circuits [31b] in transplantation experiments.

Neuroimmunology and neuroinfection

The field of neuroimmunology is too vast to be dealt with here. However, some of the recent observations mentioned below have great relevance to the understanding of neurological disorders.

a) Some of the immune responses in CNS are noninflammatory,
b) Some of the neuronal antigens are immunosuppressive, hence do not elicit detrimental autoimmune reaction,
c) The transforming growth factor (TGF) in CSF acts on macrophages causing antigen specific suppress [32] and
d) The NGE and catecholamines in the CNS alter the proliferative response of the lymphocytes and thus [33].

Evidence is accumulating that large DNA viruses encode proteins with significant homology to a variety of molecules involved in host defense, including cytokines and cytokine receptors, now referred as 'Virokines' and 'Viroceptors'. For example ECRF-3 protein of Herpes simplex virus is a functional receptor for chemokines such as IL-8 because of structural homology and thus can transmit a signal to cytoplasm of a normal cell [32]. Both HSV and EBV share properties that they use to persist in sympathetic ganglia and B Lymphocytes respectively but rarely cause fatal infections in people not immunocompromised. This has brought to light the capacity of viruses, by molecular mimicry subvert some component of the host immunity, thus establish a stable relationship between the virus and host, allowing long term and sporadic virus shedding and thus resulting delayed neurological and psychiatric symptoms [34].

In case of HIV, earlier it was thought that HIV infection remains dormant and only after being activated the virus reaches high levels of replication causing CD4+T-cell depletion and disease. Now it is realised that there is no latency, but a dynamic interaction between HIV and host immune system from the beginning. Gradual perturbation of the immune system, frustrating the initially effective response along with constant evolution of the virus population, seems to result in uncontrolled overt HIV replication [35]. It is not clear how these changes modulate the immunity to associated opportunistic infections. With the emergence of the psychoneuroimmunology, and interdisciplinary field concerned with the study of behavior-neuroendocrine-immune interactions and their potential health consequence, data has accumulated showing association between stress and pathogenesis of infectious disease. This mechanism is exemplified by the reactivation of tuberculous lesions and latent herpes viral infection and the evolution of HIV infection and their role in neuropsychiatric disorders and neurooncology [32]. The identification of the spongiform change in CJD, Kuru and Scrapie and the AIDS encephalopathy based on pure morphological studies is a tribute to conventional neuropathological study. In CJD and Scrapie, the spongiform change doubted initially as an artefact of fixation, has emerged into the diagnostic criterion. The topographic distribution of these lesion has brought out the anatomopathological correlates with the clinical features.

Neurooncology

In order to predict the biological behavior and clinical prognosis of CNS Tumours, several technical approaches in estimating tumour growth potential and newer studies on physiological approach to study Tumours have been developed [36], [37]. Estimation of proliferative index (PI) by flow cytometry and labelling index (LI) of human brain Tumours, determined by immunohistochemical techniques using monoclonal antibodies to Bromodeoxyuridine (BrdU) has gained widespread acceptance as accurate reflectors of proliferative potential of these tumours in vivo [36], [38]. The cell cycle associated proteins, KI67 and PCNA have been extensively associated with cellular proliferation. Recent studies have shown that cell adhesion molecules (CAM) such as very late antigen (VLA-4) vascular cell adhesion molecules (VCAM), intercellular adhesion molecule (ICAM), neural adhesion molecule (NCAM) and others play an important role in tumor cell invasion and metastasis [36]. Some adhesion molecules promote while others inhibit the vascular basement membrane invasion in various gliomas [39], [40]. Further, cytokines such as tumour necrosis factor alpha can induce changes in surface antigen expression of certain adhesion molecules such as ICAM-I and this results in differences in the growth potential of certain astrocytomas.

The patch clamp technique is one of the good means to investigate functional properties of cells. This method was first used in cultures and freshly dissociated cells. Now it has been adopted to slices. Using this technique, Stephan Patt et al [41]. have speculated that there are two possible cellular origin for tumour cells,

(a) precursor cells which do not differentiate

(b) mature cells which de-differentiate.

Their physiological investigations have demonstrated that ion channels and receptors are expressed in distinct patterns in different types of brain tumours. This could be the initial tool for further studies which will have an impact on therapy. In fact, the blockade of K^+ channels appears to be a promising approach for the modulation of growing astrocytoma cells. Blockade of Na+ channels could modulate the growth of oligodendroglioma. Lee et al [42]. have demonstrated that tumor cell growth can be inhibited by blockade of ion channels. Hence extensive studies on physiological approach are necessary for the modulation of growth of CNS tumours.

Gene amplification and loss of function of tumour suppressor genes by chromosomal loss, deletion or mutation have been demonstrated in the CNS tumours. The chromosomal regions which are lost and the genes which are amplified, however are distinct to individual, tumour types. Using restriction length polymorphisms, cytogenetic and molecular genetic analysis, it is shown that malignant gliomas frequently have gains of chromosome 7 and losses of chromosomes 9p, 10, 17p and 22. Loss of 17p is associated with point mutations of the p53 gene which resides on this chromosome, suggesting that loss of suppressor activity of this gene is important in this tumour type. Mutations of the p53 gene are among the earliest changes observed in Tumours to initiate the process of malignant transformation. There is an association between p53 expression and the increasing histological grades of malignancy. Homozygous and heterozygous loss of p16 as well as CDK4, gene amplification are associated with transition of low grad e astrocytoma to anaplastic astrocytoma and glioblastoma multiforme [37].

Gene transfer experiments designed to generate animal models of human diseases are of particular interest to neuropathologists. Retro-virus mediated gene transfer and neural transplantation have been

combined to introduce activated oncogenes into the brain [43], [44]. Now, gene transfer therapy has opened new doors for the treatment of brain tumours. This new approach seems very attractive especially for glioblastomas, since treatment of these brain tumours has failed using conventional therapy regimens. Many different modes of gene therapy have been tested in culture and in vivo. Many of these approaches are based on previously established antineoplastic principles, like prodrug activating enzymes, inhibition of tumour neovascularisatrion and enhancement of the normally weak anti-tumour immune response. Delivery of genes to tumour cells have been mediated by a number of viral and synthetic vectors. For example HSV-tk (HSV combined with thymidine Kinase) is genetically transferred to the malignant cells in the brain. Subsequently when gancyclovir is administered it will destroy HSK-tk positive malignant cells [45], [46]. This has proved to be a potent therapy with minimal side effects in several rodent brain tumor models and has proceeded to phase I clinical trials [46].

Recent advances in understanding injury to the brain and spinal cord

Head injury resulting in brain damage which in turn causes death or persistent disability is a major health problem in most countries. The economic and social consequences of injury to the central nervous system (CNS) have stimulated much research in many countries into its incidence and causes, the nature of the injury sustained and prevention of morbidity and mortality by improved methods of clinical management. Therefore, the pathologist should be aware of the problems of the interpretation of injury [47]. The identification and interpretation of brain damage resulting from non-missile head injury is often not easy. The situation is clear if there is a large hematoma or a Contusion. However, not infrequently, more subtle forms of pathology are present and these can be identified only microscopically. A systematic and pragmatic approach through the autopsy is therefore required and the tissues should be retained in ways that are appropriate for cellular and molecular studies [48].

From a neuropathologist's point of view there are two stages in the development of brain damage; primary damage which occurs at the moment of injury resulting in laceration of scalp, fractures, contusions and lacerations of brain, diffuse axonal injury and intracranial haemorrhage and secondary damage which are porduced by complications much after sustaining the injury such as brain damage due to infection, raised intracranial pressure and others.

Recently, it has been shown that axonal damage is not the immediate consequence of traumatic tissue tearing. Rather, it is a delayed consequence of complex axolemmal and / or cytoskeletal changes evoked by the traumatic episode which then lead to cytoskeletal collapse and impairment of axoplasmic transport, ultimately progressing to axonal swelling and disconnection. Secondly, the traumatized brain has an increased neuronal sensitivity to secondary ischemic insult. This has been speculated by demonstrating that even after a mild traumatic injury, the damage of CA1 neuronal cell population can be precipitated by the induction of sublethal ischemic insult within 24 hours of the injury. Further, it is evidenced that this increased sensitivity to secondary insult is triggered by the 'neurotransmitter storm' evoked by traumatic brain injury, allowing sub-lethal neuroexcitation. This prolonged post traumatic brain hyper sensitivity offers a potential window for therapeutic intervention. The use of competitive muscarinic (scopolamine) and NMDA (phencyclidine) antagonists have been shown to provide substantial protection against secondary ischemic insults [49]. Therefore, there is now a hope for the better care and management of traumatically brain-injured humans.

Recently, the possibility for achieving repair after brain trauma has been suggested by the use of grafts using different cell lines. For example, 0-2A progenitor cells type 2 show a greater ability to fill glial free areas within damaged tissues. These glial cells fills up the defective area even though axons have not been induced to regenerate till now. Hence modern neuroscience provides an insight which may ultimately limit the amount of damage and improve the outcome particularly in young individuals where trauma has resulted in severe disability [50].

Molecular biology of muscular dystrophies

During the last decade, the discovery of the dystrophin gene and its protein product has resulted in the recognition of dystrophinopathies and related disorders. This was the first time that the reverse genetic approach was used for identification of a defective gene in a genetic disease. The mutation in this dystrophin gene which is localised to position 21 on the short arm of the x-chromosome i.e., the xp21 position has been shown to be the cause of Duchenne muscular dystrophy (DMD) and some of its allelic variant, Beckers muscular dystrophy (BMD). This has facilitated diagnosis (to some extent prognosis) prenatal detection, genetic counselling and has provided a stimulus for the development of gene therapy strategies [51].

In addition, the discovery of dystrophin has allowed identification of important dystrophin isoforms and dystrophin associated molecules that form an inter related complex at the muscle fibre surface. These include dystroglycans, sarcoglycans, (including adhalin), syntrophins and merosin or α -2-laminin. The study of these molecules have helped to further understand the structural and functional organisation of the surface membrane associated with the cytoskeletal system. Deficiency of some of these molecules which in turn is due to a mutation in the respective gene has recently been recognised as the cause of certain autosomal recessive muscular dystrophies including limb girdle dystrophy and congenital muscular dystrophy [52], [53].

These dystrophin associated molecules are not only involved in providing structural and functional integration to the cell membranes of muscle fibres including neuromuscular and myotendinous junction but also for non-muscle tissue including the brain which is involved in Duchenne and Congenital muscular dystrophy [51], [53]. Given the central role of neocortical and hippocampal function in cognition and memory, a localisation of the DMD gene product to these anatomical structures is a reasonable basis for a genetic defect producing mental retardation. Conversely the paucity of dystrophin in basal ganglia, thalamus, hypothalamus and brain stem is consistent with absence of extrapyamidal deficits, sleep cycle abnormalities and homeostatic dysfunction in the usual clinical picture of DMD. However, an issue that needs to be resolved is the relative contribution of various dystrophin isoforms on cognitive function and more important the exact role of dystrophin in neuronal physiology.

In spite of this progress in understanding the molecular biology of the various dystrophies, the exact mechanism by which the deficiency of these molecules triggers muscle fibre damage and death is not clear [51]. It is now known that all patients with DMD/BMD have a mutation of the D/BMD gene. Three types of mutations have been described. These include deletions, duplications and point mutations. However the exact type of mutations in dystroglycans, sarcoglycans and in syntrophins responsible to cause human muscle disease is not known. Now, animal models for dystrophin and

merosin deficiencies are available and further research may clarify many of these doubts. Additionally, a close autosomal analogue of dystrophin, i.e. utrophin has been recognised. Since utrophin and dystrophin are similar in sequence, utrophin may be able to replace dystrophin in dystrophin deficient muscle. Hence, the possible upregulation of utrophin holds therapeutic promise in DMD [54].

What we have seen in only a birds eve view of some aspects of Pathology, its contribution to understanding the disease. At this juncture, it is worth noting the prophetic words of Theodor Meynert, teacher of Sigmund Freud, pioneer in biological psychiatry and neuroanatomy, as summarised by Schnaper and Meyer [55] - "Pathology can not profitably limit itself to the laboratory work : it is not as its best in mere autopsy work or in neuropsychology or neurochemistry. It must aim to reduce the cases to terms of experiments of nature, in terms of cause and effect and to put the emphasis on a search for the factors which can be modified for the experimental understanding of the abnormal conditions and for the benefit of the patient". This is possible only by breaking the artifical barriers of scientific compartmentalisation and sharing the thought, ideas and knowledge for the ultimate goal - 'furthering the neuroscience in the interests of humanity'.

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