NEUROPATHOLOGY

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Introduction

At the dawn of Neurosurgery and Neurosciences in India, keeping in tradition in the West, the neurosurgeons made the diagnosis of brain tumor and tumor like mass lesions in the brain. In the early period spanning from 1960 to 1980, Prof. D.K. Dastur, Dr. C.G.S. Iyer, Prof. D.H. Deshpande, laid foundation for neuropathology, giving a place as a subspeciality in the broad field of pathology as practiced till then. They concentrated on histological diagnosis of brain tumors. In addition, in view of high prevalence and clinical need, neuro-tuberculosis and neural leprosy remained in the centre stage. Prof. D.K. Dastur stands out as an internationally renowned neuropathologist, having contributed to neuro-oncology, neuro tuberculosis, neural leprosy and many other topics. Subsequently, Prof. A.P. Desai and Dr. V.S. Lalitha in Mumbai, Prof. Sarala Das, NIMHANS, Bangalore, Prof. Subimal Roy at AIIMS, New Delhi, Prof. A.K. Banerjee at PGI Chandigarh, Prof. Sarasa Bharati at Chennai, continued the tradition of diagnostic neuropathology. Dr. V.S. Lalitha, while working at Cancer Research Institute, Mumbai has carried out investigative studies in neuro-oncology using animal models and teratology. Prof. Subimal Roy concentrated on in-depth Ultrastructural studies on brain tumors, while Prof. A.K. Banerjee studied cerebro-vascular diseases and neuroinfections in addition to other aspects. Dr. S. Sriramachary, after a short stint at All India Institute of Mental Health (now NIMHANS), Bangalore moved to Indian Registry of Pathology at Department of Pathology, Safdarjung Hospital, New Delhi. Dr. Sarala Das received her Ph.D degree working on biophysical and enzyme histochemical aspects of brain tumours and Dr.Balani, a veterinary pathologist worked on evolution of cerebral oedema, using a private model, at Indian Registry of Pathology. Later Dr. Sriramachari a trained neuropathologist concentrated on developing teaching material, documenting various pathological lesions and popularize color photography to prepare kodachrome slides. Whenever sought, he offered expert opinion in diagnostic interpretation.

A quantum jump in diagnostic and investigative neuropathology has been achieved during the past two decades (from 1989 to 2008), with enthusiastic, relatively young neuropathologists actively collaborating with basic scientists. This has significantly blurred the boundaries between the clinical and basic sciences and widened the scope of neuropathology. Even the basic scientists content to be in their ivory towers have realized the need of pathomorphological studies to validate their observations in tissue, to translate their observations on the bench to the bed side. This has significantly transformed the face of neuropathology bringing the basic pathogenetic studies to the forefront from the conventional “binocular microscope centred”, detailed morphological descriptions of various entities. With time neuropathologists have realized the limitations of just morphological studies.

Now the application of immunohistochemistry, various molecular biological techniques applicable to biopsies, electron microscopy, analytic biochemistry, neuro-imaging (MRI in various forms), MR Spectroscopy, Mass Spectroscopy, elemental analysis in tissues and body fluids have become necessary modalities of investigations integrated with neuropathology. Now the diagnosis offered is an amalgamation of these various modalities to arrive at a mechanistic answer. Virtual-digital imaging technology, advances in telecommunication, electronics and computer science has entered the field of histopathology facilitating digitization, transmission of images and teleconferencing to share information and knowledge. Advances in tandom mass spectroscopy, the genomics and proteomics have opened new vistas in the study of normal and abnormal human physiology and pathology, with a prospect of identifying biomarkers for minimally invasive diagnosis. Establishment of National Brain research Centre at Manesar, close to Delhi and Human Brain Tissue Repository at National Institute of Mental Health & Neurosciences has brought the basic scientist close to human nervous tissue for detailed studies. Possibly because of human reasons, the interaction between the basic scientist and the pathologist has not been optimum. Similarly the veterinary neuropathology has not evolved well in comparison to the developed countries, as it remained essentially agro and veterinary economy centred. Comparative neuroanatomy and neuropathology also has not developed in the country, thus hampering the progress of the field by crossbreeding of the thoughts and philosophy.

Depending on the local needs and personal interest of the neuropathologists at each centre, the neuropathology has grown in fragments of excellence, but not a holistic growth. Though neurological and neurosurgical centres have grown well in India, due to faulty policy and lack of job opportunities, the field of neuropathology had a stunted growth. The department of Neuropathology at AIIMS has made a mark in neuro-oncology and molecular neuro-oncology while NIMHANS has made an earnest beginnng. At PGI Chandigarh, Nizam Institute of Medical Sciences, Hyderabad, Christian Medical College Vellore, Sri Chitra Tirunal Institute of Medical Sciences and Technology, Trivandrum, diagnostic neuropathology flourished, with occasional investigative studies. National Institute of Mental Health and Neurosciences, Bangalore, has made a mark in diagnostic neuropathology with special reference to muscle and nerve pathology, neuro degenerative diseases and neuroinfections (CJD, HIV/AIDS) and has entered into molecular neuro-oncology. In Mumbai, the general pathologists with special interest in neuro-oncology have been assisting the clinician and assisting the research workers. Unfortunately in many institutes in various parts of India, neuropathology as a speciality has not taken roots, thus forced to depend on the few developed centres. Waning of autopsy service for diagnosis and understanding pathological basis of disease has slowed down the progress of the field. Even in centres where the autopsied are performed, consciously the cases of Creutzfeldt–Jakob disease (CJD) and HIV are avoided, thus losing an opportunity to study and learn the pathology.

An attempt is made to present the progress made in the field of neuropathology in the country, at times transgressing the boundaries with the basic sciences. There could be a bit of bias, but is only to high light the fields we felt are important in the country, but by no means to side line other scientific studies. The presentation is not meant to be a review, but a 'status paper' in the field of neuropathology in India, during the past two decades, subsequent to the initial presentation published in 1989 by neurological society of India and CSIR, Govt. of India.

Neuroinfections

Infections of the nervous system are assuming greater importance in neurological practice worldwide with frequent epidemics of meningitides and encephalitides, including emerging and reemerging infections that are occurring with alarming frequency worldwide posing a heavy burden on health care resources of many nations.

In Asia particularly, central nervous system infections are of interest and importance, because of endemicity of many infections such as Japanese encephalitis and tuberculosis. Yet there is a dearth of epidemiological data from these countries. More epidemiological studies to generate prevalence data, determine epidemiological trends, facilitate disease surveillance, characterize pathogen transmission are urgently needed to formulate clinical management strategies and disease prevention and control.

In the first half of the twentient century, research had focussed on hard core neuropathology of bacterial and mycobacterial infections, leprosy and viral infections like poliomyelitis, rabies and subacute sclerosing panenecephalitis, while there has been a paradigm shift towards opportunistic fungal and viral infections parallelling the changing face of infections with advent of HIV/AIDS in the 1989 in India. Attention has also shifted towards diagnostic, pathogenetic and molecular biologic aspects of infectious diseases.

Neurotuberculosis

Indian literature was initially devoted to pathological aspects of neurotuberculosis and its complications, but interest has shifted to developing more sensitive and specific diagnostic methods and at the same time simple, rapid, and suitable for use in laboratories with limited resources as culture confirmation is notoriously time consuming and carries low sensitivity.

Concerted attention in this direction has come from Prof Radhakrishnan and co-workers from the Sree Chitra Tirunal Institute of Medical Science and Technology, Trivandrum who have evaluated various serological tests for detection of different mycobacterial antigens (Radhakrishnan & Mathai, 1990; Mathai et al., 2001) antibodies (Mathai et al., 1990) and immune complexes (Mathai et al.,

1991a). A simple dot enzyme immunoassay to detect mycobacterial antigen and antibodies was developed to facilitate rapid diagnosis (Mathai et al., 1991b). The test was modified to detect heat stable mycobacterial antigens (Mathai et al., 2003) sensitive enough to detect antigen as low as 1ng/ml in CSF, more sensitive than PCR (Sumi et al., 2002a). Direct detection of mycobacterial antigen by immunochemistry on CSF cytopsin smears has been attempted to facilitate early diagnosis of tuberculous meningitis(Sumi et al., 2002b). At National Institute of Mental Health & Neurosciences, Bangalore the efficacy of an in-house developed IS6110 uniplex PCR (uPCR) in the diagnosis of tuberculous meningitis was evaluated by Prof Chandramuki and co-workers (Rafi et al., 2007) in a large prospective, blinded study of 677 cerebrospinal fluid samples. It had an observed sensitivity of 76.37% and a specificity of 89.18%. Harinath and his team from Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra evaluated the efficacy of detection of excretory/secretory antigens of Mycobacterium tuberculosis in CSF (Bera et al., 2006). This study showed the usefulness of mycobacterial serine protease antigen and its antibody in detecting neurotuberculosis. Usefulness of adenosine deaminase activity in CSF has been studied from Central India Institute of Medical Sciences, Nagpur (Kashyap et al., 2006).

Studies from Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, evaluated usefulness of neuroimaging modalities such as conventional and diffusion MR imaging and proton MR spectroscopy to aid in differentiation from fungal, and pyogenic abscess that can mimic tubercular lesions in the brain (Luthra et al., 2007) Phosphorous MR Spectroscope studies showed cytosolic amino acids, acetate and succinate in the pyogenic abscesses, whereas lipid/ lactate was seen in the tubercular abscesses. The fungal abscesses showed lipid lactate, amino acids and multiple peaks between 3.6 and 3.8 ppm assigned to trehalose. Kumar and co-workers investigated the factors responsible for paradoxical response to chemotherapy in neurotuberculosis in children (Kumar et al., 2006a). New abscesses/granulomas were noted along with hydrocephalus despite regular therapy. An interesting observation was made that immature faintly enhancing granulomas were more likely than well formed large sized granulomas to resolve with chemotherapy. Large sized granulomas had a greater risk of paradoxical enlargement. The same authors also reported the clinical presentation, pathophysiology and treatment response of tuberculous abscesses in children using contrast CT, MRI and MR spectroscopy although confirmation required demonstration of acid fast bacilli in the pus by staining or by culture (Kumar et al., 2002).

Interest in pathogenetic aspects of neurotuberculosis still remains the purview of the early years with Dastur and coworkers from Mumbai, who presented a review on pathology and pathogenesis of various forms of neurotuberculosis, meningitis, granuloma formation, myeloradiculopathy and the immune mediated allergic “encephalopathy” (Dastur et al., 1995). It has been observed that with the

extended programme of BCG vaccination in India did not prevent natural tuberculous infection of the lungs and its local complications, although it reduced the haematogenous complications of primary infection. Malnourished children, inspite of BCG vaccination, can develop serious, and often fatal types of tuberculosis such as miliary, meningitic and disseminated tuberculosis in contrast to BCG vaccinated, well-nourished children who manifest modified patterns of tuberculous disease, following with a tendency for isolated organ involvement and localised involvement of the brain and meninges. Localisation of the disease by T cell immunity following BCG vaccination is considered responsible for this modified pattern of disease. It is important to relearn the new patterns of tuberculosis disease seen in vaccinated, healthy and malnourished children, who may require tailoring of antituberculous therapy (Udani, 1994).

In the same vein, with the advent of the HIV pandemic, incidence of neurotuberculous is once again on the rise and interest has focused now on the changing patterns of presentation, manifestation and complications that co-infection with HIV can induce. The few studies in this respect have come from Mumbai. Dr.Katrak, a neurologist and colleagues have in an elegant study compared the clinical, pathological as well as radiological profile of tuberculosis between HIV positive and negative patients (Katrak et al., 2000) and the profile of tuberculous meningitis in pediatric AIDS (Karande et al 2005). An interesting study from Chandigarh documented elevated nitric oxide production among patients with HIV infection, especially so among HIV/TB co-infected patients, that declined significantly following 4 weeks of antitubercular therapy (Wanchu et al., 2002). More detailed studies into complex interplay between HIV and *M tuberculosis* that will dictate clinical, pathophysiological and therapeutic responses is the need of the hour, to determine neurologic sequelae in long term survivors.

Fungal infections

With the rising numbers of immunosuppressed individuals in the society thanks to widespread use immunosuppressive regimens as cancer therapy, transplantation as well as the advent of the HIV pandemic, there has been an upsurgence of fungal infections both globally and in India.

Studies at various Institutions have focussed on pathological and microbiological aspects. Most of the publications in this field have come from Nizam's Institute of Medical Sciences, Hyderabad and Postgraduate Institute of Medical Education & Research, Chandigarh where active transplantation work is in progress. Interestingly from both centers, reports of fungal infections in the HIV positive individuals are not reported.

Sakhuja and colleagues report on spectrum of CNS complications in renal transplant recipients (Sakhuja et al., 2001). Fungal infections were common etiological agents (cryptococcal meningitis, mucormycosis and aspergillosis) with high mortality (70%). Chakrabarti and colleagues from the National Mycology Referal

Centre at PGI, Chandigarh reported on epidemiology of fungal infections in the country and the spectrum of opportunistic infections (Chakrabarti, 2007; Chakrabarti, et al., 2008). Increasing incidence of invasive candidiasis, aspergillosis, and zygomycosis are common amongst the opportunistic mycoses. The emergence of fungal rhinosinusitis, penicilliosis marneffei and zygomycosis due to Apophycomyces elegans is unique in the Indian scenario. The global change in spectrum of Candida species is also observed in India. High prevalence of aspergillosis is expected in Indian hospitals where construction activities continue in the hospital vicinity without a proper impervious barrier. Invasive zygomycosis is an important concern as the world's highest number of cases of this disease is reported from India.

A recent inter-institutional collaborative effort elegantly documented varied spectrum of fungal infections in CNS in different Institutions across the country (Shankar et al., 2007a).

Fungal infections have been focus of interest at Nizam Institute of Medical Sciences, Hyderabad addressing various issues including clinical, histopathological, microbiological and prognostic factors. Pathology of full spectrum of fungal infections encountered over 17 years' experience is reported (Sundaram et al., 2006). Sinocranial aspergillosis, a form of aspergillosis unique to South India has been the focus of study in several publications (Murthy et al., 2000; Murthy et al., 2001; Nadkarni & Goel, 2005). Rare presentation including true mycotic aneurysm due to Aspergillus is recorded.

A clinical study looked at identifying early diagnostic and prognostic features to improve outcome of patients with rhinocerebral mucromycosis (Jayalakshmi et al., 2007). Similar findings were also reported by Dhiwakar (Dhiwakar et al., 2003) from New Delhi. From National Institute of Mental Health & Neurosciences, a large series of clinicopathologic aspects of cladosporiosis was documented (Garg et al., 2007). Reports of phaeohyphomycosis from other parts of the country seems rare with sporadic reports that document rare forms of Nodulosporium species isolated from a case of cerebral phaeohypomycosis.

With advent of HIV/AIDS, most reports of fungal infections are devoted to cryptococcal meningitis. An analysis of predisposing factors, laboratory findings and outcome in patients from South India with special reference to HIV infection as well as clinical and therapeutic aspects has been reported from NIMHANS, Bangalore (Garg et al., 2007; Khanna et al., 2000). Similar study has also been published from Deaprtment of Microbiology, IHBAS, New Delhi (Thakur et al., 2008). Increasing incidence of cryptococcosis has also been reported from Chandigarh(Das & Sawhney, 1998; Chakrabarti et al., 2000). A recent study from Maulana Azad Medical College has focussed on correlation of CD4 counts with cryptococcal meningitis. The authors observed that occurrence of crytptococcal meningitis is an indicator of progression of HIV infection and in fact suggest that it could be

used as a reference to start antiretroviral therapy in settings where facilities for CD4 estimation is not available (Wadhwa et al., 2008).

Uma Banerjee and co-workers from the Department of Microbiology, All India Institute of Medical Sciences, New Delhi (Banerjee at al., 2001) presented an overview of status of cryptococcosis in India from its first description to present times in light of its increasing incidence with pandemic of AIDS. C neoformans var neoformans was the most common serotype in clinical samples although C neoformans var gatti has also been reported. Both immunocompetent and immunocompromised were found to be affected. An interesting observation by the group is the first report of phenotype switching in Cryptococcus neoformans var gatti strain from its parent mcuoid colony to a smooth morphology (Jain et al., 2006a). The switch was associated with changes in the polysaccharide capsule and therefore its virulence, as demonstrrated in murine models. Interestingly the thin polysaccharide capsule associated with smooth strain permitted more eficient crossing of the blood brain barrier therby promoting dissemination to the central nervous system. These obervations have important implications in pathogenesis of cryptococcosis and gave an insight into host-pathogen interactions in local milieu of nervous system.

Other fungal infections are rare in India and are limited to sporadic case reports of cerebral blastomycosis, eumycetoma of cerebellopontine angle and Rhodotorula glutinis as a rare cause of meningitis and meningoencephalitis in a patients with SLE (Chander et al., 2007; SaiKiran et al., 2007). Nocardiosis, an uncommon infection of the past, is being increasingly reported in recent years with rise in immunosuppressed patients (Shivaprakash et al., 2007). A large series of 12 cases was reported from Chandigarh of which 3 involved the brain.

Viral Infections

Earlier research in field of viral infections focused on mostly autopsy pathology of poliomyelitis, rabies, Japanese encephalitis and subacute sclerosing panenecephalitis.

Attention now has turned to diagnostic and pathogenetic mechanisms operative in these infections. The National institute of Communicable Diseases, New Delhi has concentrated on evaluating sensitivity of tests for diagnosis of fatal neurotropic viral infection rabies. The sensitivity and reliability of *in vitro* isolation of rabies virus using mouse neuroblastoma cells (MNA) was compared with mouse inoculation test (MIT), direct fluorescent antibody test (FAT), Sellers staining and rapid tissue culture infection test (RTCIT. The latter appears to be a fast and reliable alternative to MIT, that holds promise in antemortem diagnosis of rabies (Chhabra et al., 2007; Chhabra et al., 2005).

Radotra and Banerjee from Chandigarh, have evaluated the utility of using immunohistochemistry in diagnosis (Jogai et al., 2000) and detection of rabies

viral antigen in extraneural organs including adrenal glands, heart, gastrointestinal tract and pancreas, confirming the centrifugal spread of the virus (Jogai et al., 2002). The authors suggest that detection of rabies viral antigen in the extracranial sites may serve as a useful tool in the ante-mortem diagnosis by subjecting the extracranial tissue to biopsy and subsequent immunohistochemistry. Use of MR imaging in differentiating between paralytic (radiculomyelitis) rabies and acute disseminated encephalomyelitis (Desai et al., 2002) is also reported.

Extensive pathological studies on Japanese encephalitis (JE) with topographic distribution of viral antigen in different neuroanatomical areas of the brain were reported by Desai et al from NIMHANS (Shankar et al., 1983; Desai et al., 1995). Desai and colleagues from Department of Neurovirology, NIMHANS studied determinants of prognosis in CSF like cytokines and neural antigens (Desai et al., 1994). An interesting observation from NIMHANS was co-existence of neurocysticercosis with JE that enhanced morbidity. This finding has been further corroborated on MR imaging from Lucknow (Singh et al., 2001). The authors suggest that co-occurrence is not a coincidence but neurocysticercosis acts as a positive modulator of the encephalitic process.

Much of the studies on Japanese encephalitis from SGPGI, Lucknow are focussed on pathogenesis. Role of cytokines-tumor necrosis factor-alpha (TNF-alpha) and interlukin-2(IL-2), in the pathogenesis of JE has been evaluated (Babu et al., 2006). A marked increase in the levels of TNF-alpha in the serum and CSF was found, while IL-2 levels were unaffected suggesting involvement of TNF-alpha pathway in neuroinflammation. Sequel of pathological changes and its correlation with inducible nitric oxide synthase (iNOS) mRNA, proinflammatory (IFN-gamma, TNF-alpha) and anti-inflammatory (IL-4, IL-10) cytokine expression, and viral load has been analysed in mice (Saxena et al., 2008). Progressive decrease in IL-4 and IL-10 level following viral infection inversely correlated with increased level of proinflammatory cytokines and histopathological changes. The authors suggest that insufficient anti-inflammatory cytokine response indicated by IL-4 and IL-10 in the brain is associated with increased tissue pathology and viral load. The same group also demonstrated protective role of induction of nitric oxide synthase during infection (Saxena et al., 2001).

A significant effort towards understanding molecular pathogensis of Japanese encephalitis came from experimental mice models inoculated with JE virus from Rangarajan and co-workers at Department of Biochemistry, Indian Institute of Science, Bangalore. They identified nine different genes whose expression is upregulated in the central nervous system of mice during Japanese encephalitis virus (JEV) infection (Saha et al., 2006). Interestingly it was demonstrated that all the CNS genes activated by JEV were also upregulated during rabies virus infection, and Sindbis virus, an alphavirus (Saha & Rangarajan, 2003). This supports the proposal that common host cell pathways are activated in the CNS by different neurotropic viruses.

An exciting report from National Institute of Virology demonstrates intracerebral injection of DNAzymes inhibit JE virus replication in brain of mice, resulting in a dose-dependent extended lifespan or complete recovery of the infected animals.

Other viral infections that have received attention are subacute sclerosing panencephalitis (SSPE) and dengue viral infection. Early detection of white matter damage by diffusion tensor imaging in SSPE, when conventional imaging studies are normal may have therapeutic implications (Trivedi et al., 2006). Taly and co-workers reviewed the clinical aspects of adult onset SSPE (Prashanth et al., 2006).

The clinical, radiological and neurophysiological changes in 17 dengue patients with neurological manifestations, the largest study from India is reported by Mishra and colleagues from SGPGI, Lucknow (Misra et al., 2006). Encephalopathy and acute pure motor quadriplegia due to myositis were the common presentations (Kalita et al., 2005). Those with encephalopathy had more severe illness and poor outcome. Isolated report of dengue viral infection involving the CNS presenting as mild encephalopathy is reported from All India Institute of Medical Sciences, that was characterized as dengue – 3 virus by RT-PCR from CSF.

Experimental work in bonnet monkeys investigated the distribution of virus and the pathology in the spinal cords by inoculating poliovirus type 1 (Mahoney) into the right ulnar nerve. Comparative study of wild-type and attenuated poliovirus invasiveness using bonnet monkey model has shown interesting results.

Recent interest has focussed on molecular pathogenesis of virus induced apoptosis in herpes simplex encephalitis.

HIV/AIDS

Most studies on pathology and pathogenesis of neuroAIDS has come from Lanjewar and group from Grant Medical College & JJ Hospital, Mumbai and Shankar and Satichchandra and their team from NIMHANS as well as few studies from Armed Forces. These are the only centres where active autopsy services on patients dying of neuroAIDS is being conducted.

From Mumbai, Lanjewar and co-workers published on the profile of central nervous system pathology in AIDS (Lanjewar et al., 1998a) and study of individual opportunistic infections including toxoplasmosis (Lanjewar et al., 1998b) and tuberculoisis (Karande et al., 2005). Clinical, pathological as well as radiological profile of tuberculosis has been compared between HIV positive and negative patients (Katrak et al., 2000). Clinical spectrum of neurological complications including both opportunistic and non-opportunistic complications in children and adults are recorded (Wadia et al., 2001; Udgirkar et al., 2003; Shah et al., 2005).

Pathogenesis of host resistance to toxoplasmosis has been studied in experimental mice in a collaborative study (Flores et al., 2008).

Studies from NIMHANS have focused on clinical (Satishchandra et al 2000) and pathological aspects (Satishchandra et al., 2000; Shankar et al., 2005).

Opportunistic infections remain the most common complications of NeuroAIDS. Cryptococcal infections are observed to be more common from NIMHANS, Bangalore unlike Lanjewar and co-workers who found neurotuberculosis to be more common. This may be a reflection of geographic differences in disease prevalence. Similar reports have appeared from AIIMS (Sharma et al., 2004a) and PGI Chandigarh and a few other centres. From AIIMS, Maheshwari and co-workers collated spectrum of neurological disorders in patients with HIV/AIDS (Sharma et al., 2004a). Reports of progressive multifocal encephalopathy although rare have been documented with biopsy/autopsy confirmation from NIMHANS (Shankar et al., 2003).

From Vellore, only clinical studies have been published with the first report of pediatric AIDS in India (Renuka et al., 1993). In addition, important molecular epidemiology and subtyping studies of HIV have come from Sridharan and co-workers from Department of Virology with reports of HIV 2 and HTLV-1 but no pathologic correlates have been studied (Nerurkar et al., 1993; Kannangai et al., 1999; Kannangai et al., 2003; Ramalingam et al., 2008). Interesting observations by this group have shown low circulating CD4 levels in Indians.

Pioneering work in establishing HIV- 1 virus circulating in India to be predominantly subtype C unlike subtype B prevalent in the West has come from Uday Ranga and co-workers (Siddappa et al., 2004). In an elegant study, Ranga and co-workers demonstrated that the mutation in dicystein motif consistently seen in subtype C results in defective chemoattaraction for macrophages. This could be responsible for the low prevalence of HIV associated dementia in India (Ranga et al., 2004). Clade specific differences in neurotoxicity have also been demonstrated (Mishra et al., 2008). With tat protein of subtype C being less neurotoxic than tat-B. Biological effects of subtype C virus in contrast to subtype B on hypothalamopituitaryadrenal axis is a subject of study by Satishchandra and co-workers from NIMHANS (Chittiprol et al., 2008).

Pathological studies initiated at NIMHANS have demonstrated presence of HIV infected cells in the inflammatory infiltrates associated with various opportunistic infiltrates (Mahadevan et al., 2007). Although the subtype of HIV virus prevalent in India is less neurotoxic and therefore less likely to cause dementia, if patients with neuro AIDS survive and are successfully treated for OI, the presence of these HIV infected cells that have gained entry into the brain within macrophages may lead to dementia in later stages. Other findings noted by the same group is the presence of significant axonal damage in optic nerves of patients dying of AIDS

even in the absence of visual symptoms implying significant subclinical damage (Mahadevan et al., 2006).

Parasitic/ Protozoal Diseases

Following earlier studies from Madras and New Delhi (AIIMS), recent studies on neurocysticercosis (NCC) have mostly come from SGPGI, Lucknow and NIMHANS, Bangalore. In Lucknow, studies have concentrated on radiological methods of discrimination of cysticercus from close mimcs such as tuberculois, fungal granulomas and neoplastic conditions. Garg proposed diagnostic criteria more suitable for Indian patients modifying criteria given by del Brutto (Garg et al., 2008). In vivo proton MR spectroscopy studies suggest that higher succinate rather than acetate levels could be of help in differentiating degenerating cysticerci from anaerobic abscesses (Agarwal et al., 2004). Gupta et al studied naturally infected swine to determine clinical signs of porcine neurocysticercosis confirmed by ex vivo MRI and autopsy and suggested that naturally infected swine as useful animal models for further research in NCC (Prasad et al., 2006). Prof Nuzhath Hussain and Dr. Lily Pal contributed the neuropathological aspects. Workers from Chandigarh and Vellore have focused on serodiagnosis of neurocysticercosis.

From NIMHANS, Shankar et al have worked extensively on several pathogenetic aspects of neurocysticercosis, including structure of the larva, its neural innervation and commonalities with host protein that enables successful parasitism (Vasantha et al., 1992; Shankar et al., 1994; Shankar et al., 1995). Hydatidosis, visceral larva migrans and sparaganosis of nervous system are also reported (Rumana et al., 2006).

Many workers have focused on diagnostic aspects of cerebral toxoplasmosis, assessing antigen detection and comparing the MR imaging features in HIV infected and immunocompetent individuals. Very few neuropathological studies are available (Malla et al., 2005; Chandramukhi, 2004; Vastava et al., 2002). Prof R.K.Visista from PGI Chandigarh described the neuropathology of soil amoeba related encephalitis and the neuroimaging features.

Cerebral Malaria

Experimental studies on cerebral malaria from the School of Life Sciences, Hyderabad reported altered glycoprotein profiles leading to cytoarchitectural changes in RBC membrane to establish contact with the host endothelial cells (Kumar et al., 2006b). These observations may be central to the microvascular sequestration and pathology of cerebral malaria. Another study on experimental model of fatal murine cerebral malaria showed calpain activation and spectrin breakdown after Plasmodium berghei infection providing strong evidence for the role of calpains during the cell death (Shukla et al., 2006). Given the role of calpains in neurodegeneration and cell death, the authors suggest that calpains are important mediators of cell injury and neurological sequelae associated with falciparum

cerebral malaria. NIMHANS has recorded unusual manifestations of Cerebral Malaria. From Rajasthan Prof Kochar et al carried out clinical studies on Cerebral Malaria.

Pyogenic infections

Research in this field is mostly limited to radiological studies in an effort to prognosticate complications. An interesting study at AIIMS looked at blood flow velocities in large basal vessels of the anterior circle of Willis and correlated with CSF pleocytosis and CSF sugar values (Kalra et al., 1997). Mean blood flow velocities were found to be directly proportional to the CSF white blood cell (WBC) count and were inversely proportional to the CSF sugar values. Another study evaluated acute phase CT abnormalities with respect to post inflammatory hydrocephalus and ventriculomegaly in cases of pyogenic meningitis (Kalra et al., 1997). Feasibility of cerebral perfusion pressure-targeted therapy in children with raised intracranial pressure caused by meningitis or meningoencephalitis was evaluated from Chandigarh (Shetty et al., 2008).

From Hyderabad, Sundaram et al reviewed pathology and pathogenesis of brain abscesses (Sundaram & Lakshmi, 2006) as well as microbiological aspects of brain abscesses and ventriculoperitoneal shunt infections (Lakshmi et al., 1993). Rare causes including actinomycosis, Entameba histiolytica, nocardiosis and parasites like sparaganosis and Angiostrongylus cantonensis were recorded. Diagnostic utility of squash smears in diagnosis of inflammatory lesions was assessed (Sundaram, 2003).

Case reports of uncommon infections like Naegleria meningitis is reported. It was diagnosed by wet mount cytology of cerebrospinal fluid (CSF) and successfully treated (Jain et al., 2002). Othe reports of amebic infections of CNS have come from Hyderabad. Systemic brucellosis presenting with meningitis, salmonella meningitis and increasing incidence of cranial meliodosis are on record.

Creutzfeldt-Jakob Disease (CJD)

A Registry for Creutzfeldt-Jakob disease established in 1989 at NIMHANS has been collecting cases from all over India (Satishchandra & Shankar, 1991). With greater awareness, more cases are coming to light from various centers, especially from the state of Kerala and Karnataka, though it may not reflect true increase in prevalence. Occasional familial cases of CJD and a probable case of Familial Fatal Insomnia are recorded (unpublished). Inspite of awareness, molecular genetic studies to characterize the mutations in prion protein has not been established in India till date. Two centers in Delhi, one at NBRC and other at Delhi University, basic scientists are initiating molecular biological studies to facilitate enzyme solubility of fibrillar, pathological prion protein, thus reduce the tissue load in the brain and its replication potential in mouse neural stem cells. Not a single case of nCJD or Bovine spongiform encephalopathy have been recorded from India.

Realising the economic catastrophy if BSA is found in India, Ministry of Agriculture and Animal Husbandry, Govt of India has established laboratories in different parts of India to screen for BSA related lesions in the brainstem, in the slaughtered cattle. Till date no case has been detected by the veterinary pathologists, to the relief of all. Largest series of human brain biopsies from cases of CJD, (cases both from NIMHANS and those referred) were studied demonstrating the temporal evolution of prion protein deposition in the brain leading to clinical disease (Mahadevan et al., 2002).

New emerging infections

A large outbreak of acute encephalitis of unknown origin with high case fatality (183 of 329 cases) was reported in children from Andhra Pradesh state in southern India during 2003. The causative agent was identified as Chandipura virus by the National Institute of Virology, Pune (Rao et al., 2004) by viral isolation, sequencing, electron microscopy, complement fixation, and neutralisation tests. Sequencing of five of these RNA samples showed 96.7-97.5% identity with the reference strain of 1965. Chandipura viral antigen and RNA were detected in brain tissue of a deceased child by immunofluorescent antibody test and PCR. Autopsy and neuroimaging findings of the emerging viral infection, chickungunya encephalomyeloradiculitis is reported from Mumbai (Ganesan et al., 2008).

A national network is needed to characterize the infections of nervous system intergrating different diagnostic modalities and establish the pathology and pathogenesis. This can lead to evolving management strategies.

Neuro Oncology

Tumor marker, which is defined as 'substance that makes possible either a qualitative diagnosis of neoplasia or a quantitative estimate of tumor burden' has become the order of the day in most of the centres providing diagnosis in neuro-oncology. The tumor markers used for the prognostic evaluation include cell differentiation markers, cell cycle proteins and proliferation markers, oncogene/ tumor suppressor gene proteins, growth factors/ receptors, hormone receptors, cell adhesion molecules and angiogenic factors. Molecular biology and molecular genetics related to brain tumors have emerged as a tool for clinical stratification and to plan therapy. Most of the molecular profiling is carried out using immunohistochemistry as the primary tool in various centres. The expression of p53, c-myc, EGFR and Rb gene have been evaluated. Detailed studies on the molecular signatures of primary and secondary glioblastoma have been carried out, both at AIIMS (Jain et al., 2007a; 2007b; Sarkar et al., 2004) and NIMHANS (Dr.Vani Santosh) (Britto et al., 2007; Somasundaram et al., 2005).

The immunohistochemical and molecular studies have been carried out highlighting the utility of proliferative and apoptotic markers, oncogene and tumor supprosor gene products on the clinical out come in adult and paediatric tumors

(Sarkar et al., 2005; Anvinder et al., 2006; Ganigi et al., 2005). Intra operative cytology (squash smears) for rapid diagnosis is being used extensively in neurosurgical practice (Goel et al., 2007) in most of the centres in India, even in places where neuropathology is not practiced as a superspeciality. Stereiotactic brain biopsy to diagnose deeply situated lesions is practiced and the neuropathologists have acquired the needed expertise (Jain et al., 2006b). Many common and new variants of brain tumors are described as series and case studies from different centres, thus developing a data base of brain tumor phenotypes (Arivazhagan et al., 2008; Rumana et al., 2007; Atri et al., 2007; Malik et al., 2006; Sharma et al., 2006; Gupta et al., 2006; Sharma et al., 2004b; Devaprasanth et al., 2003; Pal et al., 2008).

Some of the noteworthy studies in glioma biology are the identification of subsets of Glioblastoma based on clinical and molecular status and characterizing the utility of tumor markers in prognosticating paediatric glioblastoma. Studies utilizing molecular techniques have demonstrated intratumor heterogeneity in low-grade gliomas, which has implication on clinical and biological behavior, though routine histology may not reveal the same (Srivatsa et al., 2007). Large part of these studies have been carried out at Dept. of Pathology, AIIMS in collaboration with Dept. of biochemistry, followed by Dept. of Neuropathology, NIMHANS. A new genetic marker for astrocytic tumors located at 17p13.3 region, harbouring HIC-1 has been shown (Sarkar et al., 2003). The correlation of this marker with tumor grade, proliferation and apoptosis has been extensively evaluated. Anjali Shiras and her team from National Centre for Cell Science, Pune have isolated a 'tumor stem cell' from human gliomas and have demonstrated aberrantly overactivated and defective 'DNA damage response pathway' facilitating self renewal (Shiras et al., 2003). More detailed studies on this subject have been carried out at NBRC by Ellora Sen and these studies have suggested that development of therapies that could target the DNA damage checkpoint response in 'cancer stem cell' may provide a therapeutic window for malignant brain tumors.

The advent of high through put complementary DNA (cDNA) and oligonucleolide micro array technology has allowed comprehensive gene expression analysis of the brain tumors. Several differentially expressed genes and proteins in different grades of gliomas and primitive neuroectodermal tumors have been studied by cDNA microarray-gene expression profiles at NIMHANS, Bangalore and ACTREC at Mumbai. The differentially regulated gene profiles have been validated by RTP PCR and immunohistochemistry. Dr.Vani Santosh from NIMHANS, in collaboration with Professor MRS Rao from Jawaharlal Nehru center for advanced scientific research (JNCASR), Bangalore, Professors Kumaravel Somasundaram and P.Kondaiah from Indian Institute of Science, Bangalore, while probing for molecular genetic alterations in glioblastoma using the cDNA microarray technology, found novel glioblastoma gene products (Reddy et al., 2008a). The group has identified a novel serum biomarker *P*re-*B*-cell colony *e*nhancing *f*actor *1* (PBEF-1) which is of diagnostic and prognostic significance for malignant glial tumors (Reddy

et al., 2008b). The protein profiles of gliomas have been studied by using a two-dimensional gel electrophoresis-mass spectroscopy approach. By this method, several differentially expressed proteins are found to be potential molecular indicators in understsnding gliomagenesis (Chembulkar et al., 2005). The process of identifying immunodiagnostic markers and designing a microarray chip for prognostication and characterizing therapeutic target is in progress. Scientists from University of Hyderabad and Prof Sundaram from Nizam Institute of Medical Sciences, Hyderabad, have studied extra-cellular signal regulated kinase (ERK) in gliomas, which has a critical role in tumor cell proliferation, thus a possible therapeutic role (Bhaskara et al., 2005). Evolution of brain tumour is probably modulated by interacting multigenetic mutation pathways. It may be useful to look for gene networks than individual mutated genes to identify biomarkers and evolve therapeutic strategies. Most of the work in India at present is directed to probing and following single or a small set of genetic mutations. The effort can be optimized by forming research consortia and sharing the analytical work, analyzing multiple pathways and analyzing the results by bioinformatic tools. This scientific philosophy is yet to take root in India.

Molecular cytogenetic studies on identification and quantification of 1p and 19q chromosomal deletions in anaplastic oligodendrogliomas by interphase fluorescence in-situ hybridization (FISH) technique has facilitated delineating a cohort of patients responding well to chemotherapeutic regiment with longer survival. The FISH technique for 1p – 19q deletion is practiced, though to a limited extent at NIMHANS - Bangalore, AIIMS – New Delhi and CMC – Vellore and a few other centres.

The molecular biologic and genetic studies have made possible to tailor chemotherapy for brain tumors. With an international collaboration a 'Glioma Tissue Bank' is likely to be established soon, with inter-institutional net working in India. Neuro-oncology has progressed well in India during the present decade and the face of diagnosis and therapy would change.

Pituitary adenomas attracted great attention in neuropathological studies. Professor Subimal Roy and Professor Chitra Sarkar from AIIMS and Professor Geeta Chacko from CMC, Vellore have carried out in depth studies using immunohistochemistry and electron microscopy to characterize the cells and their hormonal secreting potential (Chacko et al., 2003; Lath et al., 2001; Sarkar et al., 1990). In collaboration with endocrinologists, both groups offered clinical correlation to the evolution of pituitary adenomas. Similar neuro endocrine tumors are described from their centers as well. Prof Nuzhath Hussain from K.G.Medical College and Dr.Lily Pal from SGPGI concentrated on diagnostic neuropathology and attempted to elucidte the biology of some of the CNS tumours. Dr.Neelima Dhar, Dr.Shashi Singhavi and Dr.Kusum Mathur, General Pathologists, after brief training at NIMHANS have been providing diagnosis services in neuro-oncology at Jaipur.

One of the major biological problems in the clinical management of brain tumors is the evolution of cerebral edema and its management. Dr. Radotra and his Ph.D student at PGI Chandigarh, have carried out immunohistochemical and stereological studies on microvessels in malignant gliomas and characterized a 'putative stem cell' for the tumor vessels. Many centers are studying the vascular endothelial growth factors, the molecular basis of their expression, in an attempt to modulate therapy of brain tumors. Study of tumor vasculature and therapeutic modification is a field to be addressed in India, to synergize brain tumor treatment.

Chemotherapy-modifiers

Photodynamic and hyperthermic sensitization of brain tumour to chemotherapeutic drugs have been tried as a therapeutic modality by Prof V.K.Jain and Dwarakanath from NIMHANS and later at Institute of Nuclear Medicine and Allied Sciences, New Delhi (Mohanty et al., 1996; Kalia et al., 2007). Subsequently 2-Deoxy-D-glucose and other glycolytic inhibitors are being tried at different centers. Modulating the therapy of cerebral gliomas with 2-Deoxy-D-glucose has passed through phase I and II multicentric clinical trials, the neuropathologists and neurosurgeons actively participating in it. Feasiblity of administering this treatment (2DG+5GY) is demonstrated by the excellent tolerence observed in the patients. The clinicopathological and radiological studies also showed the absence of adjacent brain parenchymal damage. Temozolomide is a second generation alkylating agent undergoing clinical evaluation for patients with newly diagnosed and recurrent gliomas, alone or in combination with radiotherapy, in various centers in India. In view of associated haematological toxicities and evoloving drug resistance to Temozolonide and radiation combination, another adjuvant Lonidamine is under *invitro* and *invivo* trials. Prabhakara and Kalia have shown that a combined Lonidamine and Temozolomide administration is efficacious in inhibiting cancer cell proliferation (Prabhakara & Kalia, 2008). Similar studies are being evaluated at Advanced Centre for Treatment, Research and Education in Cancer (ACTREC). Navi Mumbai. Investigators from Radiation Biology and Health Sciences Division, BARC, Mumbai have been evaluating potential of traditional aurvedic formulation, Triphala, as a novel anti cancer drug, essentially on haematological cancers and yet to initiate similar study in neuro-oncology (Sandhya et al., 2005). Neuropathologists have an active role in validating these observations.

Epilepsy, Geriatric Pathology, Degenerative Diseases, Metabolic Disorders

Epilepsy

In the field of epilepsy and its pathological basis, the basic scientists have become interested and collaborative studies are carried out. Epilepsy surgery has become common in different centers, various surgical procedures being followed. Sri Chitra Thirunal Institute of Medical Sciences and Technology at Thiruvananthapuram (Radhakrishnan et al., 1999), All India Institute of Medical Sciences, New Delhi (Sarkar et al., 2006) and National Intitute of Mental Health

and Neurosciences, Bangalore have emerged as major centers carrying out surgical treatment for epilepsy and large series of pathological studies are reported highlighting the spectrum of lesions. Recently, from NIMHANS, the role of dual pathology (lesional pathology in medial temporal lobe along with hippocampal sclerosis) on the evolution, stabilization and prognosis of mesial temporal sclerosis, correlating with pathological studies, is reported (Basu et al., 2008). Larger series of studies are needed from different centers in India, to advance the understanding of pathophysiology.

Rapid strides have been made in understanding the pathological basis of reflex epilepsy. A team lead by Prof Satish Chandra, Professor of Neurology, NIMHANS and Prof Gautam Ullal, Department of Physiology, Ramaiah Medical College, Bangalore, a well characterized rat model for 'Hot water Epilepsy' was developed (Ullal et al., 1996a). Reduced threshold to hot water stimulation, progressive lowering of latency for initiation of seizure activity, neuroanatomical localization to hippocampus and hypothalamus and the pathological basis of kindling for further propagation in the brain, have been described in the animal model (Ullal et al., 1996b; Ullal et al., 1998; Ullal et al., 2006; Satishchandra et al., 1998). Due to non-availability of pathological material from well-characterized cases of hot water epilepsy similar understanding in human system could not be achieved. Pathology of Rassmusen's encephalitis has been reported from AIIMS, New Delhi. Though immunohistochemistry has been in vogue in India for long time' it has been used only to a limited extent in the study of pathology of epilepsy (Deb et al., 2006). Recently studies are initiated by Dr.Lily Pal at Sanjay Gandhi Post Graduate Institute, Lucknow, to characterize the antigenic profile of neuronal proteins at the epileptic focus, including the stem cell potential. Good correlative studies on *invitro* electrophysiological recording of human hippocampal slices and the associated pathology have not been initiated till date in India, though technology of recording electrical activity in hippocampal slices is available at Department of Physiology NIMHANS and a few other centers. With the advent of proteomics and bioinformatics, Department of Neuropathology, NIMHANS has initiated microarray analysis of well characterized lesional and adjacent control brain tissue resected at surgery for genomic and proteomic profiling, in collaboration with Institute of Bioinformatics, Bangalore.

Dr.Anuranjan Anand, a geneticist from Jawaharlal Nehru Centre for Advanced Scientific Research, Jakkur, Bangalore, in collaboration with clinical scientists at NIMHANS has described novel epilepsy gene focus on chromosome 3q 13.1-q21 following genetic linkage analysis of members of three generations with family history of epilepsy. A novel, patient specific genetic mutation in G.protein coupled receptor family (Calcium Sensing Receptor family CASR) has been reported recently in 2008 (Kapoor et al., 2008). Calcium Sensing Receptor is known to be physiologically important in regulating systemic extracellular calcium concentration in various tissues including brain. While human brain specific functional role of CASR remains to be probed, the observations from the group indicate important

role for this receptor mediated genetic mechanism in pathophysiology of epilepsy. Similarly the group is at the threshold of identifying the genetic locus for 'hot water epilepsy'.

Another dimension to the clinical spectrum of epilepsy studied from India is progressive myoclonic epilepsy (PME). PME is a syndrome complex characterized by the development of myoclonic epilepsy, ataxia, neurological defecits and dementia with a genetic basis to the evolution. Many of these conditions like Lafora body disease, neuronal ceroid lipofuscinosis are recognized all over from India and more from the South. IMHANS has been providing the diagnostic support in characteristing and discriminating different clinical phenotypes to the practicing neurologists. Large number of cases of Lafora body disease and ceroid lipofuscinosis are identified from South India (Acharya et al., 1993; Sinha et al., 2007). Dr. Ganesh, Associate Professor Biological Sciences and Bio engineering at Indian Institute of Technology, Kanpur, in collaboration with Department of Neurology and Neuropathology has described mutations in genes EPM2A, encoding 'laforin phosphatase' and NHLRCI encoding 'malin ubiquitin ligase' and proposed that altered subcellular localization of the mutant proteins could be the molecular basis of LD phenotype (Mittal et al., 2007; Singh et al., 2008). Scientists at NBRC, Manesar are also carrying out genetic and molecular biological studies in these groups of disorders.

Geriatric Pathology, Degenerative diseases, Metabolic Disorders

Geriatric Pathology and various genetically determined degenerative diseases received limited attention in India. Geriatric Society of India and Alzheimers Society of India have been doing yomen service, with lot of effort to encourage clinical and social research. Similarly the Advanced Center on Ageing Research at Hyderabad under the guidance of Prof K.Subba Rao have been carrying out studies on biochemical aspects and molecular geriatrics. In an experimental study Dilip Murty and Desi Raju (Singh et al., 2008) utilizing the EM facility at NIMHANS have shown differential effect on the ontogeny of synapses in limbic cortical regions, following malnutrition and rehabilitatory nutrition, where the cingulate cortex synaptic density could be restituted, but not hippocampal zone. This has relevance to the interplay of malnutrition and cognitive impairment in human aging in India and its response to therapeutic intervention. Lack of active interest among the pathologists, dwindling number of clinical autopsies and taxing and capricious neuroanatomical and histological techniques needed to study, are the major causes for lack of progress in this field, though Indian geriatric population is increasing fast. A study from NIMHANS and PGI Chandigarh has described the cellular pathology in normal ageing in comparison to Alzheimer's disease (Yasha et al., 1997). Both familial and sporadic cases of Alzheimer's disease are reported (Mohanty et al., 2004; Satishchandra et al., 1997) from different centers and referred to NIMHANS for further characterization. Pathologists at BYL Nair Hospital, Mumbai in Collaboration with MayoClinic, USA have initiated studies on age related changes in the brain

and compared it with the West. Now immunohistochemistry has become a routine tool for studying various cytosolic and cytoskeletal protein changes and aggregation in cases of neurodegenerative diseases with ready availability of monoclonal and polyclonal antibodies commercially. Scientists from NBRC and Delhi University have initiated molecular and biochemical studies to disaggregate the tissue deposited amyloid b protein in the brain, in a attempt to reduce the protein burden and thereby the disease evolution in animal models. Efforts are made to evolve immunotherapeutic strategies to develop potential vaccines for Alzheimer's disease and restrict development of immune mediated meningoencephalitis following vaccination by enhancing Th2 type of immune response (Subramanian & Divya-Shree, 2008). Inspite of platitudes, the close interaction between basic scientists on one side and the clinicians and pathologists has not been achieved and this has remained an impediment to progress in the field of geriatric biology. In an international collaborative study, Shankarnarayana Rao from Department of Physiology, NIMHANS has shown loss of presenilin, a synaptic and nuclear protein that leads to impaired memory and synaptic plasticity followed by age dependent neuro degeneration (Carlos et al., 2004). This finding has an implication in the evolution of familial Alzheimer's disease in humans.

The establishment of Human Brain Tissue Repository for Neurobiological studies (Human Brain Bank) at NIMHANS in 1995 has eased the situation (Shankar & Mahadevan, 1999), though a lot needs to be achieved. Improper clinical records without proper psychological assessment, imaging studies, indifferent attitude of pathologists to conduct timely autopsies to retrieve the brain, lack of appropriate infrastructure and transport facility by air are the major impediments, though few centers are making active effort to facilitate research.

A few cases of Alzheimer's disease, frontotemporal dementia, multi system atrophy, Pick's disease, Diffuse Lewy Body disease, Parkinson's disease etc are studied and limited frozen tissue samples are stored at Human Brain Bank, NIMHANS. Prof AK Banergee from PGI Chandigarh, Prof Sundaram from Nizam Institute of Medical Sciences, Hyderabad and Prof Geeta Chacko from CMC Vellore have studied a few cases of Alzheimer's disease and frontotemporal dementia and further attempts are being made to develop geriatric pathology. Voluntary consent for postmortem examination and facility for rapid autopsy are the issues to be addressed for the progress. Pathological studies on cases of Parkinson's disease (Lalitha et al., 1995a), Motor neuron disease (Lalitha et al., 1995b), are reported from India. The first pathologically confirmed case of unique Madras type of Motor Neuron Disease has been published (Shankar et al., 2000) and further cases are collected. In close collaboration with neurologists and International Brain Banks, the relationship of melanised neuronal cell members in substantia nigra to Parkinson's disease are studied at NIMHANS (Muthane et al., 1998; Muthane et al., 2006). The interesting observations made by Dr.Phalguni Anand, Department of Neurophysiology in collaboration with Department of Neuropathology, NIMHANS includes (a) absence of age related nigral dopaminergic neuronal loss and relatively

preserved nigral function in Asian Indians (b) unlike in West, a-synuclein levels in neurons in India brains do not rise linearly with age (c) the soluble a-synuclein expression is low in the foetal substantia nigra and it increases in levels till 20 years and then stabilizes. Probably this age related changes account for late occurrence of protein misfolding diseases in melanised neurons manifesting clinically as Parkinson's disease and Parkinsonism.

Investigators from Kolkata, Hyderabad and other centers are studying the altered mitochondrial pathway in the evolution and progression of Parkinson's disease in animal models and invitro studies. Some of the centers are involved in identifying therapeutically relevant molecules in herbal medicines and validating the effect on animal studies (Dr.Mohan Kumar, Calcutta, Dr. Srinivas Bharath, NIMHANS).

Similarly the Departments of Neurophysiology and Biophysics, NIMHANS have been studying the pathobiology of Amyotrophic Lateral sclerosis and had suggested that presence of a neurotoxic neurotransmitter in patient's CSF and resultant ionic perturbations in CNS lead to the evolution of motor neuron disease in animal models (Raju et al., 1999; Shobha et al., 2007). This needs to be further substantiated on human autopsied specimens and correlate with clinical evolution. A synthesis with human biology needs to be achieved by active collaboration, than remaining in islands of excellence but devoid of scientific exchange of ideas and progress.

One significant contribution of Electron microscopic facility of NIMHANS is ultrastructural characterization of lysosomal, peroxisomal inclusions in brain, peripheral nerve, liver and skin biopsies and assist in diagnosis of neurological conditions like neuronal ceroid lipofuschirsis, metachromatic leucodystrophy, adrenoleuco dystrophy, Lafora body disease, various forms of neurolipidosis etc. This has assisted in identification and genetic counseling. At NIMHANS more than 150 brain biopsies are studied for diagnosis and assist the clinician.

With the advances in molecular biochemistry and analytical chemistry, inborn errors of metabolism in the unborn child, the neonate and in paediatric age are recognized. Phenotypic variants in lipid storage disease, Neiman Pick's diseases are recognized, though no neuropathological studies are carried out due to lack of autopsies. Neuroimaging partially filled the void in the study. Wilson's Disease, a disorder of copper metabolism is found to be common in India, especially South India, with distinct genetic basis. The neuropathological features are reported from NIMHANS and molecular genetic basis is studied at CMC, Vellore and a few other centers.

It is recognized that majority of the neurodegenerative disorders have complex and multifactorial aetiologies. Various cellular processes contribute synergistically to neurodegeneration, which include oxidative stress, mitochondrial dysfunction, proteosomal dysfunction, protein aggregation, apoptosis and neuroinflammation.

As it is almost impossible to study these multifactorial interactions at organ and tissue level, 'computation in silico' approach using systems biology is initiated, validating the results in tissues. Cell Works Research India Pvt. Ltd., Bangalore lead by Shireen Vali is pursuing the studies in collaboration with Dr.Srinivas Bharat of Neurochemistry Department, NIMHANS. There could be other groups of scientists carrying out similar studies at other basic science centers. Similarly Subhash et al from NIMHANS showed lowering of ionisable calcium and phosphorous in human CSF with ageing, more so in cases of dementia (Subhash et al., 1991). Some of these studies are validating the hypothesis that protein aggregation is triggered by oxidative stress and is further enhanced by presomal synaptic dysfunction and mutation in the genes involved in Parkinson's disease, Alzheimer's disease and other neurodegenerative disorders. Team lead by Dr. Jagannatha Rao from Central Food Technological Research Institute (CFTRI) Mysore in collaboration with ICMR Center for Research on Aging and Brain (CRAB) Hyderabad and Department of Neuropathology, NIMHANS have studied the DNA topology and stability in brain regions in cases of Parkinson's disease (Hegde et al., 2006). The groups showed that DNA from midbrain in PD accumulates significantly higher number of DNA strand breaks followed by striatum and thalamus and least in the cortex. Circular dichroism studies have shown that DNA conformation is altered with imprecise base stacking in different neuroanatomical areas in PD. It remains to be established whether these topological changes in DNA is the cause or effect of neurodegenerative change, probably mediated by depleted energy (mitochondrial) and / or ionic imbalance in the cell. The same group of scientists utilizing the human material have studied the role of tracemetals and aluminium in the evolution of Alzheimer's diseases (Jagannatha Rao et al., 1999; Gupta et al., 2005).

At Guru Nanak University, Amritsar Prof Gurucharan Kaur et al have been studying structural remodeling of neurons, expression of neuronal cell adhesion molecules and glial cell cytoskeletal protein expression in rat model, to understand neuronal-glial plasticity during normal aging and its probable relation to neuro degeneration.

Under the leadership of Prof K.Subba Rao a team from Centre for Research and Education in Ageing, School of Life Sciences, University of Hyderabad have shown that the DNA repair mechanism can be enhanced in the cortical neurons by dietary caloric restriction. This is an interphase study to integrate pathobiology of ageing brain and enhance the repair mechanism by dietary calorific modulation.

Very few studies are being carried out to characterize the pathological basis of psychiatric disorders, due to paucity of postmortem studies on psychiatric cases. This has necessitated dependence on animal models and extrapolation to human disorder. Neuroimaging studies in humans with depression revealed stress induced volume reduction in hippocampus and prefrontal cortex. Bhagya et al. from Department of Neurophysiology (Bhagya et al., 2008), NIMHANS, following neonatal

clomipramine administration, established a rodent model for depression similar to human endogenous depression. To account for the behavioral and cognitive deficits, they demonstrated cholinergic dysfunction and early disruption of serotoenergic function with deleterious effect on cognition and hippocampal synaptic plasticity. The brains of the few cases of schizophrenia and psychosis autopsied at NIMHANS are stored at the Human Brain Bank for biochemical and morphological studies.

Multiple sclerosis/Demyelinating Diseases

Except for reporting a few pathologically confirmed cases of multiple sclerosis (Nandini et al., 1993), no serious studies are carried out to evaluate the changing trend in the pathomorphological features and distinguishing this entity from other demyelinating disorders. Multiple demyelinating lesions presenting as brain tumours are recognized from different centers in India by pathological studies (Jain et al., 2006c). As they respond well with relatively good prognosis, it is essential to descriminate these from brain neoplasms. Allergic encephalomyelitis as a sequel to administration of 'Semple's sheep brain antirabies vaccine (Kumar et al., 1997) has almost disappeared with discontinuation of production of this vaccine as a Governmental policy. Post infectious demyelinating encephalomyelitis appears to have increased during the past decade with the recognition and increased awareness of various viral infections. This is found to manifest as monophasic acute disseminated, haemorrhagic or non-haemorrhagic encephalomyelitis, causing diagnostic dilemma to the neurologist at the initial presentation. Various neuropathological studies have established the association of demyelination and varied clinical manifestations in relation to endemic infections like Japanese encephalitis, neuroleptospirosis, neurotuberculosis and chikunguniya viral infection.

No meaningful attempts are made to gain in sight into immunopathogenesis of MS and translate it to therapeutic strategies.

Recently Neurologists at NIMHANS have observed a changing trend in the clinical manifestations of multiple sclerosis during the present decade. The pathological substrate needs to be elucidated yet.

Neuropathology of Trauma (Head Injury./ Peripheral nerve injury) Spinal cord Ischemia

Prof Sarala Das, at NIMHANS has lead a group to study neuropathology of head-injury. Her team described the pathology and evolution of non-messile blunt head injury and its biological variability in response at different ages (Kudesia, 1997). They described the neuropathology of diffuse axonal injury. From Defense Services clinicians have described the biology of head injury, more of clinical and imaging characters than neuropathology and biology. Detailed neuropathology of hypothalamic and pituitary damage following blunt head injury has been reported from NIMHANS (Sukla et al., 2007) and AIIMS (Praasad et al., 1990).

Peripheral nerve injury and surgical repair has been practiced for many years in various neurosurgical, orthopaedic and plastic surgery clinics with variable success rates. However, the cell and molecular biology of peripheral nerve injuries is an open field not yet explored in India. This is important in view of genetic and ethnic polymorphism, the innate immune mechanisms and endemic infections modulating the host tissue response to injury. Dr.Vani Santosh and Dr.Yasha Muthane in collaboration with Prof B.Indira Devi, Neurosurgeon initiated a feasibility study of preserving nerve grafts for bridging the gaps caused by injury and resection of traumatized and scarred ends. There is an urgent need of developing a Human Cadaver Nerve, Dura and Bone Tissue Bank Facility, with quality control for the Nation, (where the material is available and yet wasted).

In the West a close genetic association of ApoE-ª4 allele with head injury, cerebral stroke, evolution of cranial haematoma, leading to worse prognosis has been reported. A pilot study by Department of Neurosurgery and Neuropathology in collaboration with Department of Human Genetics, Delhi university, has revealed that there is no such association of ApoE ª4 alles with worse biological progression of traumatic brain injury and is probably associated with ApoE ª3 unlike West. These observations need further validation on a larger sample and it provides the influence of genetic polymorphism in the population at risk to traumatic injury and innate repair mechanisms.

Spinal Cord Ischemia

Post traumatic and post infective spinal cord ischemia is a major problem in neurological and neurosurgical practice, especially in military service and in society following strife. Due to labour intensive and time consuming process in retrieving the spinal cord at post mortem, neuropathological studied remained elementary in India. However realizing the clinical importance of the condition, studies on animal models were conducted at Department of Neurosurgery, NIMHANS by Prof K.V.R.Sastry and his team of young neurosurgeons in collaboration with NBRC and investigators from Department of Neurophysiology, NIMHANS. They studied the role of excitotoxicity and apoptosis in the progression of neuronal death following ischemia and its modulation by therapeutic agents abrogating the neurotoxicity of excitatory neurotransmitters. The same mechanism could be operating following traumatic brain injury during initial stages of 'ionic storm' and calcium influx. Variable glial response in the repair of traumatized brain at different ages has not been systematically studied, though age dependent post traumatic changes are known. The study of cytokines and chemokines, expression of early genes and stress proteins in the traumatized human brain and its reflexion in CSF are useful fields for studies. Details of studies carried out at Armed Forces Institutes are not accessible to the civilians, thus remain a restricted knowledge, delaying the translation of knowledge to therapy to alleviate the suffering.

Department of Neurophysiology, Neurosurgery and Neurology, AIIMS, New Delhi have initiated studies on the effect of pulsed electromagnetic field on the axonal growth and accelerated functional recovery following spinal cord injury in rat model 2-8 weeks post injury.

Cerebrovascular Diseases

Cerebrovascular disease leading to stroke was estimated to be 5.8 million deaths in 2005, two thirds of them occurring in developing countries. Demographic changes, urbanization and related life style changes and exposure to major stroke risk factors for stroke are responsible for this shift in trend. Because the criteria for stroke are based on clinical definition, it is one of the few clinical diseases that are amenable to surveillance. Currently most of the data on cerebral stroke are from high-income countries, where the surveillance and management are relatively better and the prevalence is low, in contrast to higher prevalence in developing and under developed countries. The disparity between the stroke and coronary heart disease incidence rates in Indians and Asians is attributed to high prevalence of hypertension, low serum lipids due to low levels of animal fat in the diet. Parsis in Mumbai, because of ethnic difference are found to have higher prevalence than the others in India. The data on stroke related mortality is sparce in India. Stroke represented about 1.2% of total deaths in the country (Kiran et al., 1998; Ravikumar et al., 1999).

The mortality among the cases of cerebral stroke in India is found to be an average of 25% among the cases (BURNS Study NIMHANS)

The neuropathological data from India is scarce due to limited autopsy studies. From PGI, Chandigarh, Prof A.K.Banerjee in a series of consecutive 2023 autopsies has reported 2.12% of cerebral vessel aneurysms, 36.8% of cases of stroke in young (below the age of 40 years of the patient) 10% of these cases constituted cortical venous thrombosis, majority of them presenting in the post postum period (Banerjee et al., 1989; Banerjee, 2000). At NIMHANS, Bangalore among 1496 autopsies conducted from 1994 to 2008, 160 cases had cerebral stroke-cerebral infarction with thrombosis 56 cases; cortical venous thrombosis 80 cases, aneurysms –10 cases, venous malformation –1: stroke with subarachnoid haemorrhage due to various causes –13 cases. Majority of cases of cortical venous thrombosis in females occurred during post partum period. Among the males cortical venous thrombosis was found to be more common following alcohol binge or infection. The incidence of aneurysms has increased, with the availability of neuroimaging and interventional radiology to treat these cases. In view of it, the recognition of aneurysm at autopsy has decreased and clipping, surgical resection and endovasecular coiling has increased in many centers in India, both North and South. Even the mortality and morbidity pattern also has changed with the establishment of “stroke units with intensive care facilities”. In addition to diabetes, hypertension and smoking, hyperhomocysteinemia and nutritional folate and B12

deficiency have been identified as important risk factors (Nagaraja et al., 2008; Wadia, 2007). Nagaraja et al from NIMHANS have observed that though mutation in factor V Leiden is highly prevalent in the population in Karnataka, it was not associated as a risk factor for cortical venous thrombosis (Nagaraja et al., 2007). He also highlighted the fact that there are racial differences in the risk factors for thrombosis. Whether these genetic and biochemical differences translate into varied patterns of pathological lesions needs to be studied. In Mumbai large number of medicolegal autopsied are performed due to the Coroner's law. The prevalence study of cerebrovascular diseases in this cohort will be valuable, though the clinical and imaging features may not available, thus forming a limitation in the data generated. Sri Chitra Tirunal Institute of Medical Sciences and Technology has surgical samples representing cerebrovascular diseases, because of active group of neurologists and interventional radiologists. In North India, except for PGI, Chandigarh, autopsy service is very limited and hence no meaningful data is forthcoming.

Among the neuroinfections manifesting, as stroke, tuberculosis and fungal infections are important followed by viral infections like Varicella zoster and HIV. At NIMHANS, in a cohort of 1041, cases of HIV examined during the past 16 years (1989 to 2006), 35 cases (2.9%) presented as stroke. From Mumbai, Dalal et al reported 8% of tuberculous vasculitis presenting as stroke while 19% of cases of tuberculous meningitis from Chandigarh, both based on clinical studies. In a stark contrast, from NIMHANS, just above 1% of cases of stroke in young were secondary to tuberculous vasculitis (5/455 autopsied cases) (Shankar et al., 2007b). An unusual case of HIV associated dolichoecrtasia of vertebrobasilar system was reported from NIMHANS (Mahadevan et al., 2008). From the initial pure morphological studies, now biochemical, molecular biological and genetic studies are being carried out from various centers with clinical and neuroimaging correlation. With the emergence of AIDS and associated opportunistic infections, study of cerebro vascular pathology assumes greater importance, especially because of subtype variation of HIV virus and associated newly emerging viral, bacterial and fungal infections in India.

Peripheral Neuropathies and Muscle Diseases

Peripheral Neuropathies

During this decade as well as in previous years, Hansen's neuropathy continued to be a public health problem, with morbidity and social stigma and center of study. Effective chemotherapeutic regimens at best reduced the burden, but unusual forms have emerged masquerading as inflammatory, demyelinating neuropathies, hereditary neuropathies, thus foxing the treating neurologist. With treatment the cutaneous manifestations have come down, the bacilli finding the Schwann cells in the peripheral nerves a safe sanctuary to persist. The initial work carried out by Prof DK Dastur, Dr Ganapathy, Prof CK Job gave a sound base for

the next generation to dwell into the evolution and basic pathogenetic mechanisms. Foundation for Medical Research (FMR), Mumbai, St Thomas Hospital and Leprosy Centre, Chettupattu, Tamil Naduand JALMA Institute in Agra have contributed to the epidemiological and pathogenetic issues. Investigations in various centers have studied the route of entry of the bacillus (Job et al., 1994a) Schwann cell infectivity and propogation (Singh et al., 1998a), role of host immune status (D'Souza et al., 1990), the macrophage mediated cellular (Shetty, 1993) and humoral immunity (Choudhury et al., 1989; Job et al., 1990), modifying effect of cytokines, the mechanism of axonal injury and the possible causes for recurrence.

A semi quantitative study of the bacterial load in plastic embedded semi thin sections showed involvement of different cell types in the nerve, with maximal involvement of schwann cells around unmyelinated fibers (Shetty & Antia, 1996). Further ultrastructural studies have revealed *M.leprae* in the endothelial cells, thus forming a route of entry and hematogenous propogation of the infection (Kumar & Sengupta, 2003). The investigators from FMR have described the time course of the infection in immunocompetent and immunodeficient rodent model (Shetty & Antia, 2002). Save and Shetty et al. in collaboration with NIMHANS, have shown that defective phosphorylation of H and M peptides of neurofilaments in the axon following Hansen's disease could be the cause for axonopathy and axonal atrophy which is reversed following regenerative response (Save et al., 2004). In spite of national effort, Hansen's disease is continuing to be a cause for morbidity following neuropathy. Probably the attention needs to be shifted to elucidate the immunopathogenetic role of host response, with special reference to immunogenetics, the biochemical basis of tissue response, the pharmacogenetics, the ethnic and environmental factors responsible for the persistence and spread of the disease, and discovery of newer drugs. Immunohistochemical evidence of persistence of mycobacterial antigens in pauci- and multibacillary disease supports the notion that the nerve damage could be secondary to bacterial antigen than viable bacilli (Shetty et al., 1994).

A major problem that still needs to be addressed is the reactive state or the recurrence of symptoms. Ebenezer et al studied the persistence or absence of bacilli following chemotherapy (Ebenezer et al., 2004). The efficacy of the 12-month course of multi drug therapy (MDT) was confirmed by light and electron microscopic studies, which showed almost, complete absence of viable bacilli (Job et al., 2005). However, another study from FMR showed that an extended treatment regimen led to a longer disease free period, but may not be a total elimination of the bacilli (Shetty et al., 2005). By histology and molecular diagnostic testing, PCR for Lepra bacilli (Job et al, 1997; 2008) have demonstated lepra bacilli both in the superficial keratin layers of skin and nasal epithelium in multibacillary cases. A proportion of clinically unaffected household contacts (4-17%) also tested positive which could contribute to persistence and spread of the disease. Emphasis on early diagnosis of Hansen'd disease by routine histology complemented by immunolabelling staining for *M leprae*, S-100 for Schwann cells

in cutaneous nerves and PCR is highlighted (Singh et al., 1998a; Job et al., 1997; Job, 2007). Fine needle aspiration of neural lesions has also been attempted (Jayaseelan et al., 1999; Siddaraju & Yaranal, 2007) with limited success.

To understand the host response to the infection at different stages of the disease following therapy and states of reaction, team led by Dr Dharmalingam from Madurai Kamaraj University has initiated serum proteomic study of patients with ENL reaction (Gupta et al., 2007). The group showed increased expression of one of the isoforms of haptoglobin in the serum as a marker protein. In addition, they noted antileprosy drug induced anhaptoglobinemia reverting back to normal state following termination of treatment. This is the first attempt at serum proteomic study for any infective condition in India and no similar study has been carried out using neural tissue.

In India, nerve biopsy for diagnosis of neurological disorders is carried out routinely at NIMHANS (Bangalore), and less frequently at AIIMS (Delhi), PGIMER (Chandigarh), CMC (Vellore) and NIMS (Hyderabad). Thus NIMHANS is serving as a referral center. Nerve biopsies are studied at NIMHANS for the diagnosis of vasculitic neuropathy (Mahadevan et al., 2001), various forms of demyelinating neuropathies, hereditary neuropathies (Mahadevan et al., 2000) and genetically determined metabolic neuropathies like metachromatic leukodystrophy (Bindu et al., 2005), Tangier's disease, etc (Sinha et al., 2004). Asymptomatic and symptomatic neuropathies associated with HIV/AIDS are described, in one of the cases demonstrating retrovirus (Mahadevan et al., 2001). Additionally, cases of giant axonal neuropathy, infantile neuroaxonal neuropathy (Mahadevan et al., 2000), amyloid neuropathy (Sarkar et al., 2005), metabolic neuropathy and a rare form of dysmyelinating neuropathy associated with a benign form of megalencephalopathy with subcortical cysts (Panicker et al., 2007) and similar unusual forms are recorded. Electron microscopy and immunohistochemistry formed part of the diagnostic procedures.

The studies on peripheral nerves have essentially centered around diagnosis, but systematic research activity is lacking in India. It is worth considering the establishment of a comprehensive center for the study of peripheral neuropathy as a referral center for the whole country, with advanced analytic facilities and trained manpower.

Disorders of muscle

Pathological studies of skeletal muscle disorders have been undertaken in a few centers in India (NIMHANS, Bangalore; AIIMS, New-Delhi; CMC, Vellore; JJ Hospital, Mumbai; NIMS, Hyderabad; SCTIMST, Trivandrum, IHBAS, New Delhi; GB Pant Hospital, New-Delhi; SGPGIMS, Lucknow and PGI, Chandigarh. In most institutions the diagnosis is by routine histological and histochemical techniques. Electron microscope as a tool for diagnosis/ research is used only in a few centers.

In the recent years, techniques such as immunohistochemistry and molecular genetics have been utilized for diagnosis in some centers.

The published literature on the pathology of muscle diseases reflects the gamut of disorders encountered in Indian population. An overview on recent developments in the diagnosis of muscular dystrophies is enumerated by Sarala Das (Das, 1998). Reports on muscular dystrophies demonstrate lack of dystrophin by immunohistochemistry in Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) (Jain et al., 1993). Similarly reports on congenital muscular dystrophy (CMD) (Das et al., 1997) were followed by reports on immuno histochemically diagnosed cases of merosin deficient CMD (Ralte et al., 2003) and emerin deficiency in Emery - Dreifuss muscular dystrophy (EDMD) (Gayathri et al., 2006). Autosomal recessive limb girdle muscular dystrophies with primary of alpha, beta, and gamma sarcoglycans deficiency have been recognized (Sharma et al., 2004c; Kapoor et al., 2005; Meena et al., 2007; Khadilkar et al., 2002).

A retrospective mutational study and prevalence of DMD /BMD in different 'caste group' in Uttar Pradesh by Mishra et al (Mishra et al., 2004) has shown higher prevalence of the disease in Brahmins and Vaishyas as compared to other castes groups in that region.probably related to consanguineous marriage. It was found that 80% of the mutations were clustered at the central hot spot region between exon 43 and 52. However mutational pattern was not different in various caste groups. Anand et al., 1999, studied genetic polymorphism in muscular dystrophy to explore its potential in discriminating the two allelic forms (DMD and BMD) of the disease. The results revealed presence of three transcripts: 598bp, 849bp and 1583bp long which are selectively expressed in the muscles afflicted with muscular dystrophy as compared to the normal muscle. While 1583bp gene transcript was conspicuously present in the muscle tissues of both DMD and BMD patients, 598bp and 849bp long transcripts were exclusively present in DMD but not in BMD patients or normal human subjects. Thus, based on the selective expression of these three gene transcripts, one could not only differentiate between DMD and BMD diseases at the molecular level, but also between normal and dystrophic muscle. Further, these findings also reveal that apart from dystrophin gene, these gene transcripts may also be responsible for the differential progression of DMD/BMD phenotype. Molecular genetic diagnosis are carried out at JJ Hospital Mumbai, PGI Chandigarh, AIIMS New-Delhi; NIMS, Hyderabad. Commercially this facility is regularly available at Department of Genetic Medicine, Ganga Ram Hospital, New Delhi. With the availability of molecular genetic diagnosis for Duchenne muscular dystrophy, some of the centers have stopped the invasive muscle biopsy and the family is screened for the carrier state using peripheral blood and counseled. However the muscle biopsy studies are carried out for other musculo-skeletal disorders.

In a clinicopathological study on 73 cases of idiopathic inflammatory myopathy, Prasad et al. (Prasad et al., 1992) found higher incidence of vasculitis

in dermatomyositis and systemic connective tissue disease. Hereditary and sporadic forms of inclusion body myositis with characteristic immunohistochemical profiles and ultrastructural features has been reported by Gayathri et al., 2000a. Diagnostic utility of screening for major histocompatibility complex (MHC) class I and II in idiopathic inflammatory myopathies has been reported (Jain et al., 2007c).

Among the infantile neuromuscular disorders, a study on etiological diagnosis in 35 floppy infants revealed spinal muscular atrophy was the most common condition followed by congenital muscular disorders, congenital myopathies, metabolic myopathies and congenital myasthenia (Vasanth et al., 1997). A series of reports on congenital myopathies have highlighted the importance of enzyme histochemistry in recognizing the various forms (Gayathri et al., 2000b; Sharma et al., 2004d) and an analysis of 100 cases of congenital myopathies have found centronuclear myopathy to be the commonest. Case reports on nemaline rod myopathy (Deepti et al., 2007; Sharma et al., 2007a), core disease (Sharma et al., 2007b) and protein aggregate myopathies particularly desmin related myopathy have been documented (Sridhar et al., 2005).

Case series on metabolic disorders include mitochondrial myopathies have been described by Mehndiratta (Mehndiratta et al., 2002) from New Delhi, Challa et al. (Challa et al., 2004) from Hyderabad and Medha Tatke (Tatke, 2007) from New Delhi. In a clinicopathological study of 60 cases of mitochondrial disorders reported by Challa et al., were diagnosed by the presence of ragged red fibers. Clinically, 38/60 cases presented with progressive external ophthalmoplegia. The other clinical spectrum of cases described were encephalomyopathy (5), Kearns –Sayre syndrome (4) and MERRF (4). Diagnostic modalities of mitochondrial myopathies are discussed by Tatke. Atypical Kearns –Sayre syndrome, MNGIE (Santoshkumar et al., 1997), MERRF (Seth et al., 2000), adult onset Leigh's syndrome (Lekha et al., 2007), lipid storage disorder (Mannan et al., 2004) and metabolic disorders presenting as vacuolar myopathies (Gayathri et al., 1999) are some of the other reports.

Case reports on clinical and genetic study of spinal muscular atrophies (Mishra et al., 2004) and atrophic changes in the skeletal muscle secondary to nerve pathology in skeletal fluorosis (Sesikeran et al., 2000) are documented.

Dr. Thangaraj at CCMB, Hyderabed, Dr. Mohan Kumar, Kolkata and another group in Pune are actively involved in characterizing mitochondrial pathology causing myopathy and encephalopathies. Dr Thangaraj has identified many unique mitochondrial mutations in South Indian population presenting with musculo-skeletal disorders.

Dr. Jyostna Dhawan at CCMB, Hyderabad has been studying the stem cell component in the skeletal muscle and its differentiation into mature cell. Satellite cells are the primary stem cells in adult skeletal muscle and are responsible for postnatal muscle growth, hypertrophy and regeneration. Dr. Jyostna Dhawan

(Schidananda et al., 2002) have also been studying this stem cell component and its differentiation potential in *in-vitro* system. They suggested that in myoblast, the Rho pathway and regulation of acto-myosin contractility may define a control point for conditional uncoupling of differentiation and cell cycle. The satellite cells in addition to generating new cells are sources for signaling molecules involved in tissue remodeling during regeneration. In addition, the muscle cell differentiation is accompanied by regulated rearrangement of the lamins, the structural proteins (Muralikrishna et al., 2001).

A close interaction with pathologists and neurologists may bring out new avenues for understating the basis of muscle diseases. From the initial morphological studies, the present decade has seen the evolution of molecular genetic tests for the characterization of the disorders. The attempts of stem cell therapy for the neuromuscular disorders have not been randomized, are very few and not encouraging.

Neurotoxicology

A significant contribution to this field of neurotoxicology is biochemical detection, isolation and characterization of xenobotic enzymes like cytochrome P450 and flavinmono-oxigenases and their induction in human brain by phenobarbitone (antiepileptic), chronic alcoholism, environmental aromatic carcinogenic substances by Dr.Vijayalakshmi Ravindranath in collaboration with Department of Neuropathology NIMHANS (Ravindranath et al., 1989; Anandatheerthavarada et al., 1993; Bhamre et al., 1995). The genetic polymorphism in relation to gender and differential neuroanatomical distribution of these enzyme systems in the neurons has been elucidated. In future, the role of these xenobiotics in the metabolism and degradation of addiction forming psychotropic substances, chemotherapeutic drugs, antibiotics, the environmental toxins, industrial polutants, explosives, toxins of bioterrorism etc need to be studied by an integrated team of biochemist, molecular biologist, systems biologist, clinical neurologist and neuropathologist. Establishing and maintaining a Brain Bank as a National Research Facility has contributed to it. It is apt to place on record the vision and untiring efforts of Prof P.N.Tandon, a neurosurgeon, Emeritous Professor and a neuroscientist from AIIMS to facilitate the establishment of first Human Brain Tissue Repository for the Neurobiological studies at NIMHANS, Bangalore as a National Research Facility. The Bhopal industrial toxic gas accident was the largest human tragedy, the consequences spanning to next generation. Though enormous amount of human material has been collected at autopsy, unfortunately neuropathological studies on nervous system of the victims had been tardy, suboptimal and a lost opportunity for neuroscience in India. Though peripheral neuropathy as a clinical manifestation is a common symptom in routine neurological practice, studies on toxic neuropathies relevant to Indian population has been limited. A few cases of neuropathies and encephalopathies following TOCP toxicity, neem oil toxicity (Srinivasan & Shankar, 1993) are studied at NIMHANS. Though adulterated liquor

and spurious congeners are added to indigenously manufactured alcohols and thus related human tragedy is common to India, no systematic neuropathological studies are carried out in close collaboration with forensic pathologist, biochemist and toxicologist. Similar is the case with toxic food adulterants and colouring agents. Understanding mechanism and the response of human brain to the toxins will form the scientific backbone to understand and counter these slowly acting man made toxic tragedies. In one of the recent episodes of liquor tragedy, putaminal infarct was recorded secondary to methanol toxicity (used as an adulterant) as described in older literature. Department of Neurophysiology, NIMHANS under the guidance of Prof T.Desiraju and Prof T.R.Raju and Mazumdar et al. from West Bengal have described neurotransmitter perturbations in the brain following chronic consumption of arsenic, mercury and aluminium compounds (Mazumdar et al., 1988; Nagaraja & Desiraju, 1994; Lakshmana & Raju, 1996). An unusual neurological complication of cortical myoclonus with biochemical and pathological evaluation in a young lady following injection of mercury (in an attempt at suicide) was reported from NIMHANS (Raghothaman et al., 2007). Prof Venkatesh established an internationally accredited Biochemistry Referral Laboratory to study lead toxicity at St.John's Medical College, Bangalore and carried out a few studies on human foetuses collected at autopsies.

Organophosphorous toxicity following agricultural use and following suicidal consumption is common in rural India. Though many clinical reviews are available, studies on neuropathological basis are scarce, probably because the toxicity is mediated through neurotransmitters. Exposure to organophosphorous components and 2-4 dichlorophenoxy acetic acid (organic herbicide used as difoliant under the code name 'Agent orange' in Vietnam by US military) can be handy in bioterrorism, causing longterm neuropathological changes. Studies to elucidate the pathobiological basis could be under way at ITRC, Lucknow and Defence Research Laboratory, not accessible for civilian scientists. Most of the studies centred around biochemical and some electrophysiological basis were carried out at NIMHANS. Unfortunately, no serious neuropathlogical studies were carried out either in animal system or humans following accidental exposure. These studies are the need of the hour to understand the acute and chronic features.

Field of neurotoxicological pathology and study of environmental pathology has remained relatively primitive in India, though work could be happening in a few centers in isolation (see chapter on Neurotoxicology). With industrialization, advances in science and technology, environmental influences on human development have acquired greater importance. There are suggestions to implicate the environmental pollution and toxicity in various neurological disorders, especially in the neonatal period and paediatric age with behavioral disorders (Shailesh-Kumar & Desiruju, 1990). This field assumes greater importance with the emergence of bio-terrorism and psychological warfare spreading into generations. Altered biosafety practices (as in mad cow disease-BSA and new variant of CJD) genetically modified agricultural and animal food products are likely to have effect in the evolution of yet

unknown neurological and neuropsychiatric disorders. Scientific community, especially neuroscientists need to bestow attention to this field urgently. Various phenotypic forms of mitochondrial disorders and metabolic disorders could be secondary to the environmental toxicity.

Stress related pathology – an interphase between Physiology and Pathology

Significant contributions have been made by physiologists in India on high altitude pathophysiology, because of paramount importance to the armed forces. Chronic stress induced structural plasticity of neurons in amygdala has been described by a team from Department of Neurophysiology, NIMHANS and National Centre for Biological Sciences, (TIFR) Bangalore. This could form a candidate cellular substrate for affective psychiatric disorders triggered by stress (Vyas et al., 2002; Bennu et al., 2007). The aviation pathology and neurophysiological and cognitive changes in deep sea and in confined space under extreme stress remains a classified knowledge within uniformed services. Forensic pathology as a specialty has not well developed in India. All these fields of study, as applicable to neuroscience have to develop to meet the challenges associated with supersonic aviation, space journey, expeditions to deep sea, uninhabitable Northern and Southern Poles of earth and bioterrorism.

Though it does not constitute classical pathology, the investigators at Department of Neurophysiology at NIMHANS and AIIMS, have shown increased and aberrant synaptic density, vulnerability to stress related glutaminergic toxicity and altered neurotransmittor physiology in specific neuroanatomical areas (Ramesh & Kumar, 1998; Srikumar et al., 2006; Titus et al., 2007). These changes escape the eyes of conventional pathologist because of limited technology that is routinely used. A close amalgamation of conventional pathology with modern day molecular biology will bring the changes to light.

On the other hand, the role of transcription and translation of stress related proteins in animal and human systems are evaluated by scientists at various academic institutes. Dr.Utpal Tatu at Indian Institute of Science has elucidated the interesting stress response of malarial parasite as a defence reaction to the host immunity. Team from IISC lead by Prof G Padmanabhan have described the metabolic pathway adopted by malarial parasite mimicking the human system for its survival. The finding has immense clinical implication, especially in cerebral malaria, bridging the gap between the research at the bench to bed side. Similar phenomenon could be taking place in relation to other infections, trauma and neoplasia, providing phenomenological insights.

Developmental Neuropathology

This field has expanded with the availability of ultrasonography during the antenatal period and the experience gained by the ultrasonologist. The MRI facility and phasing out of CT scan has added greatly in delineating the normal and

anomalous nervous system. Pathologists and anatomists have started collecting the aborted fetuses to study the abnormal development and correlate it with imaging. Unfortunately, only gross brain pathology is examined to concur or differ with the imagologist, but no detailed pathological studies have been carried out. Availability of molecular genetics has given an impetus to undertake these studies at K.G.Medical College and SGPGI, Lucknow though no publications on neuropathology have come out. However no concerted studies on developmental neuropathology have been in progress except for a few case reports. This is a fertile field to study in India correlating with inborn errors of metabolism, the biochemical alterations leading to anamolous growth, MRI, MR Spectroscopy, Tandem Mass Spectroscopy and advanced imaging techniques will contribute significantly, probably minimizing the conventional structural studies. It is essential to study the abortuses to understand the role of environmental factors (Thorium sands in Kerala) the teratological effect of large-scale industrial accidents, genetically transmitted metabolic disorders (genetic peroxidase deficiency and thyroid disorders) in the evolution of development neuropathology both in humans and in veterinary practice.

Stem Cell Biology

Organ and stem cell transplantation has become popular with advances in immunohaematology and transplantation technology and establishment of necessary infrastructure in many centers. Professor Gomathy Gopinath and Prof P.N.Tandon at AIIMS have heralded the studies on foetal neural grafts, their viability and structural integration in rodent and primate models. They also attempted to train and develop manpower to carry out the studies in different centers. The groups has succeeded in grafting the embryonic ventral mesencephalon into the rodent brain and showed the viability of the graft (Gopinath et al., 1996). However, they noted delay or absence in establishing appropriate connections and expression of adhesion and growth promoting molecules in the grafted neurons, reflecting delay in maturation of the neurons. These technical hurdles and failures have retarded further growth of the field in animal models. Similar attempts at a few other centers also did not yield results. The desperate need in the clinical field has prompted some to initiate human studies with a fond hope of success. LV Prasad Eye Institute had some success in establishing ocular limbal stem cells and uses it for the treatment of corneal dysplasias. This line of study is pursued proactively. Many institutions have been attempting autologous bone marrow and mesenchymal stromal cell transplantation for spinal cord injury, cerebral stroke with limited success. There are reports of foetal brain transplantation for Parkinson's disease and a few cases of movement disorders, at times in violation of scientific and human right – ethical guidelines. A few animal studies are being carried out at the Department of Neurophysiology, NIMHANS, in collaboration with basic scientist from National Centre for Biological Sciences, Bangalore to localize the transplanted cells and their migration along neuroanatomical pathways. Many commercial ventures have been started in India to harvest and bank placentral and bone marrow

stem cells and provide for therapeutic purposes. Scientific centers in Mumbai, Bangalore, National Centre for Cell Sciences Pune and National Brain Research Centre, Manesar have evolved technology to promote differentiation of stem cells into neurons, especially of dopaminergic lineage, temping to start human clinical trails for Parkinson's disease and other neurodegenerative diseases. The concept of CD34 and nestin expressing tumour stem cells has emerged with targeted therapeutic implications. The neuropathology of stem biology is rather in primitive stage in India, inspite of enthusiastic clinicians and basic scientists. To facilitate this bridging between clinician, stem cell biologist, molecular biologist and biochemist, Institute for Stem Cell Science and Regenerative Medicine has been established in Bangalore by Department of Biotechnology, Govt of India. The rigidity with which the stemcell and transplantation technology has been advancing can be a ray of hope for individuals with neurodegenerative diseases and traumatic injuries. The boundaries between neuropathologist and basic science are blurring now with advance of technology. It is essential to monitor and direct this field with stringent ethical guidelines. Neuropathologists should take active part in the studies, which is not happening at present (see chapter on Neural Transplantation).

Training in Neuropathology

Training in Neuropathology in India is restricted to a few centers in India. There is acute paucity of trained neuropathologists, never keeping pace with growth of Neurology, Neurosurgery and Psychiatry. In most of the centers neuropathology remained synonymous to neuro-oncology, and obvious neuroinfections, leaving metabolic and neuro-degenerative diseases to a few specialized centers. Lack of job opportunities has discouraged the newly trained pathologists to venture into the field. All India Institute of Medical Sciences, New Delhi, National Institute of Mental Health and Neurosciences, Bangalore, Christian Medical Collage, Vellore, Nizam Institute of Medical Sciences, Hyderabad, Sanjay Gandhi Post graduate Institute and KG Medical College, Lucknow, Postgraduate Institute of Medical Education and Research Chandigarh, Srichitra Tirunal Institute of Medical Sciences and Technology have been offering various levels of neuropathology training. In other centers general pathologists with special interest in neuro-oncology are assisting the neurosurgeons. A few of the neurologists trained in myology have been interpreting the muscle pathology for the management of the patients. Prof Sarala Das has initiated concerted effort to start a Post Doctoral Fellowship in neuropathology at NIMHANS, in view of rich surgical material available, round the clock autopsy service and functioning Human Brain Bank for the past 10 years, to train man power in diagnostic neuropathology. NIMHANS has been offering Post Doctoral Fellowship in neuropathology and trained seven batches from the year 2001 (1-2 Post Doctoral Fellows per year offering salary equivalent to Senior Resident). Prof Geeta Chacko at CMC Vellore has started 2-year course of Neuropathology Diploma. Departments of Pathology, at PGI Chandigarh, JJ Hospital Mumbai, AIIMS, New Delhi are recognized by Indian College of Pathologists to offer specialized training in Neuropathology. In addition, from time to time senior

pathologists from various oncology centers, corporate hospitals and Armed Forces undergo short-term training in neuropathology to assist in diagnosis, and work for Ph.D in Neuropathology.

Various neuroscientists in the country, though use animal models for their research, rarely have a neuropathologists or a pathologist in the team, thus very valuable material remains incompletely analysed (ignoring the tissue response to various forms of injury and repair mechanism), probably because of conflict of interest and 'ego clash. This malady has to be rectified, learning from the West, to progress in the broad field of neurosciences. The neuropathologists also need to have basic training in biochemistry, molecular biology, systems biology, bioinformatics and instrumentation, to facilitate their interaction with basic scientists in level playing ground. Tele pathology and teleconsultation extending to neuropathology has been in practice to a limited extent, but it needs to be optimized for wider application for manpower development and promote neurosciences.

Conclusion

With rapid advances in neuroscience and technology, the field of neuropathology has emerged and progressed to encompass various branches and evolved into an amalgamated branch of science to provide insight into the pathological basis for the deviation from health to sickness to death. Basic scientists and the morphologists (anatomist and pathologists) have realized the need to share the platform of knowledge. India has made a beginning and it is still long way to go. Policy makers with vision can see the potential in this field of study and promote it. It is essential to develop trained manpower in a sustained fashion, show career opportunities to the younger generation and teach the art of crossing the boundaries between various specialities for the ultimate goal of understanding the basis of disease. India can do it.

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As this presentation is a 'status paper' in the eyes of neuropathologists, there could be omissions by ignorance and oversight. For the sake of brevity all the references are not cited, but they can be sourced through the references included). This does not mean to diminish the importance of the work going on various centers and fields and we apologize for the lapse from our group compiling it.

We thank Indian Academy of Sciences for giving this opportunity to compile the information, for the second time, thus covering nearly three decades of neuropathology in India and a peep into the near future.

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