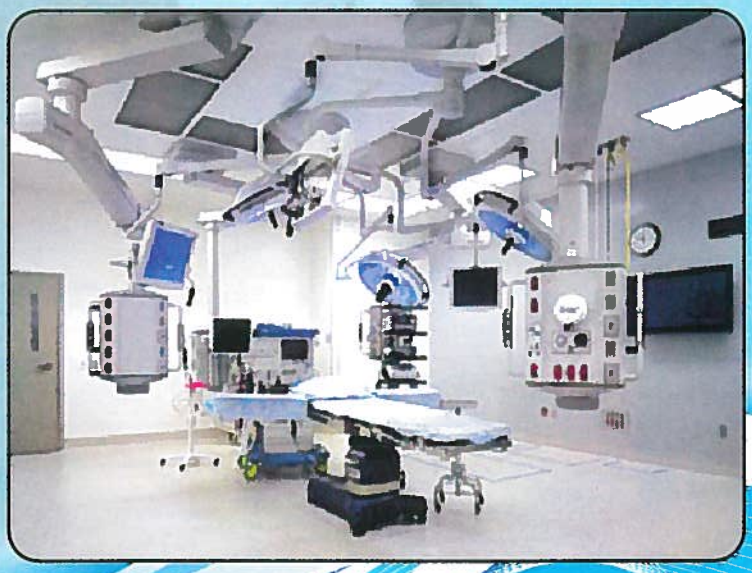
My Tryst with Bio-Medical Research

(the motivation, the environment, the result)

MONOGRAPH

by

Professor P N Tandon



The National Academy of Sciences, India (NASI)

5, Lajpatrai Road, Allahabad - 211002

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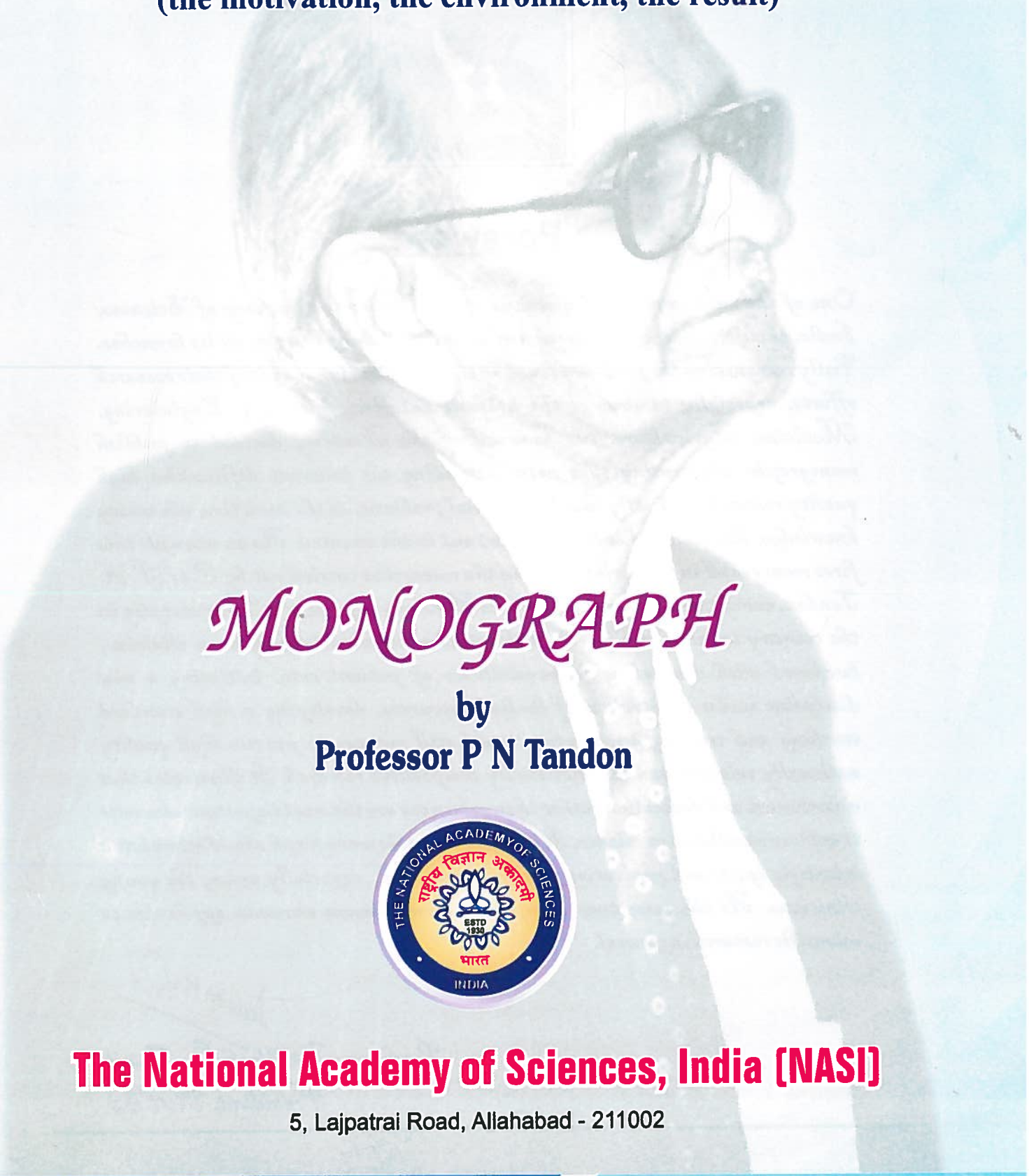

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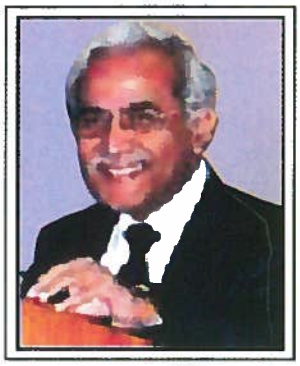

Foreword

One of the most important objectives of the National Academy of Sciences, India, is cultivation and promotion of science and technology in all its branches. Fully recognizing the problems faced by the scientists in pursuit of their research efforts, especially in some of the professional disciplines e.g. Engineering, Medicine, Agriculture, the Council of the Academy decided to publish monographs illustrating that notwithstanding the inherent difficulties high quality research, specially to solve national problems, at the same time advancing knowledge, has been and is being carried out in the country. As an example this first monograph in the series based on the researches carried out by Prof. P.N. Tandon, one of the past Presidents of the Academy, a pioneer in Neurosurgery in the country is being published. It illustrates how an extremely busy clinician, burdened with demanding responsibilities of patient care, initiating a new discipline under constraints of limited resources, developing a high standard teaching and training programme, could still manage to pursue high quality nationally relevant and internationally competitive research. It illustrates that commitment and dedication rather than resources are the most important elements to achieve excellence in science. It is hoped that this monograph would stimulate a scientific spirit and motivation to pursue research especially among the young clinicians. At the same time it refers to some common elements applicable to scientific research in general.

Professor Akhilesh K. Tyagi
President, NASI

Preface

A number of scientometric studies have established that bio-medical research in India is by and large a neglected subject in most of our medical colleges. At the same time there is a great need and immense opportunities for it. Unlike basic science, knowledge gained elsewhere cannot be directly applied to our health problems. Diseases often have varied manifestations, course and therapeutic response in different geographical and socio-economic environment. These are best studied locally.

While pre-occupied with looking after the immediate needs of patients, caring clinician, with an enquiring mind, is confronted with many doubts and unanswered questions which call for systematic investigations. These critical questions asked in the (hospital) ward provide an invaluable opportunity for clinical research with or without the help of field, laboratory or experimental studies. It is obvious that for many of these questions only carefully-conducted clinical studies can provide the answer.

Excessive burden of patient care, lack of research training, paucity of research facilities, inadequate recognition of scientists, inadequacy of funds, are some of the common alibis held responsible for the poor status of bio-medical research in the country. While all these factors are true to varying extent, none of these in itself is truly the culprit. To illustrate that fruitful research can be carried out notwithstanding such limitations, attempt has been made to draw upon personal experience from a busy professional life of a clinician. It would be observed that many of these studies were based on questions/doubts raised during the day to day care of our patients, most of them did not require sophisticated facilities or large funds, but were the result of critical observations and careful documentation of our findings.

On the face of it these studies may not always match the scientific sophistication of basic research, yet in terms of their practical utility for reducing human misery they helped us to improve our patient care, challenged the prevailing hypothesis and beliefs and practices, established new therapeutic strategies and in general added to new knowledge.

No doubt majority of these studies required help and cooperation of other colleagues, mostly colleagues and students from our department, but many others from within the institute and even the country. It would not be possible to thank all of them individually since without their participation most of these studies would not have been possible.

This monograph is not meant to seek any approbation but to encourage the younger generation of present day clinicians to spare some of their time to contribute to and raise the standard of biomedical research in the country.

I wish to thank profusely Dr. V.P. Sharma*, former President, NASI who personally helped in giving a final shape to this monograph. At the same time I would like to thank President and the Council of the National Academy of Sciences, India to publish it.

P.N. Tandon

(P.N. Tandon)

P.S.

*It is a matter of great personal loss that just a few days after helping me to give final touch to this monograph, Dr V.P. Sharma had a sudden brain hemorrhage from which we could not save him. I take this opportunity to pay my heartfelt tributes to this great soul for his exemplary commitment and contributions to bio-medical research.

Prologue

In order to objectively evaluate the significance of any scientific research it is important to be aware of the general status of research during the concerned time period, the overall intellectual milieu, the opportunities and challenges confronting the investigators, the facilities and resources available. It was, therefore, decided to add a bird's eye view of the evolution of scientific temper in the country preceding and during the period covered by the contributions of the author.

The purpose of this presentation is not to look for cudoes or acclaim but to illustrate that medical research is not only necessary but also possible and rewarding even under circumstances not conducive to it. It is not only a cultural necessity, not for national pride but unlike some other branches of science, say mathematics or physics, the knowledge gained elsewhere cannot always be applicable in a different geographical, socio-cultural, economic environment, which have unique influence on the health and diseases afflicting a society. Socrates admonished, "To live on the ideas of others is a sickness".

Jawaharlal Nehru, the patron saint of Indian Science, pointed out, "It is inherent obligation of a great country like India with its traditions of scholarship and original thinking and its great cultural heritage, to participate fully in the march of science, which is probably mankind's greatest enterprise today". It is a well known fact that India continues to lag behind in biomedical research. Often it is attributed to poor resources, lack of sophisticated facilities and the 'overburdened' clinicians. One of the important purposes of this presentation is to disprove these myths. Leave aside creation of new knowledge, research is needed to guide, adapt and accelerate the application of existing knowledge and technologies in diverse setting of our country. India has persisting scourges, of little interest to others, emerging threats different from others, our own limitations and strengths. Notwithstanding these we should be able to meet these challenges if we have the will to do so.

The 'Western' system of medicine was introduced in the country with the arrival of Europeans as missionaries, commercial organizations (East India Company initially by the Dutch in early sixteen hundred and later the British between 1612 and 1757) later to be superseded by the colonial governments. As a matter of fact the first European Hospital was established by the Portuguese as early as 1510 in Goa. Medical training was initiated here in 1702-03 and it was upgraded to Goa Medical College in 1842. The French started their first Medical College in Pondicherry in 1823. The British East India Company established the first hospital to look after its employees at Fort St. George, Madras in 1664, which later was shifted to another site and became the Government General Hospital in 1772 further elevated to the status of a medical college in 1835. The first such hospital in Calcutta (Kolkata) –the Presidency Hospital - was

established at Old Fort Williams in 1707, ultimately converted into the Medical College Calcutta in 1835, the fore runner of the present day Institute of Postgraduate Medicine and Research.

A medical school- the Thompson Medical School – was established at Agra in 1854 which was upgraded to Sarojini Naidu Medical College in 1939. The Grant Medical College in Bombay (Mumbai) was established in 1845 and the Lahore Medical School (1860) was later upgraded to the King Edward Medical College (Now in Pakistan). The King George's Medical College Lucknow came into being in 1911, (is now the KG Medical University). Lady Hardinge Medical College for women was established at New Delhi in 1916. Other medical colleges came up at Amritsar (1920/1943), Vishakhapatnam (1923), Mysore (1924), Patna (1874), Vellore (1900/1942), Orissa (1875/1944), Guntur, Ahmedabad, Gwalior (1946) and Dibrugarh, Nagpur, Jaipur (1947). There were a few others.

Thus in 1947 at the time of our Independence there were less than 20 medical colleges in the post-partition India. In addition after 1857, there were nearly a dozen health research institutes e.g. Imperial Bacteriological Laboratory, Izzatnagar (1889), King Institute of Preventive Medicine, Madras (1903), Pasteur Institute, Kassauli (1904); Pasteur Institute, Coonor (1908) later morphosed into the National Institute of Nutrition and moved to Hyderabad; Haffkine Institute, Mumbai (1899/ 1926); Indian Research Fund Association (1911) later upgraded to Indian Council of Medical Research (1949); School of Tropical Medicine Calcutta (1910) and Institute of Hygiene and Public Health, Calcutta (1932), Malaria Research Institute in Delhi (1938).

I joined the KG Medical College, Lucknow in 1945. It was recognized as one of the best medical colleges in the country. The World War II (1939-45) had just ended. The hectic political activity for attaining Independence dominated the nation's consciousness. Surprisingly around the same time the colonial government appointed The Health Survey and Development Committee (1943-1946) popularly known as the Bhore Committee, (named after its Chairman Sir Joseph Bhore). Among its many valuable recommendations to restructure the Indian Health System, there were also some regarding the climate for medical research and measure to strengthen it, the following quotation from the report is very revealing:

"Broadly speaking medical research receives little or no attention in the medical colleges in India"____ "The authorities responsible for staffing and financing medical colleges are usually ignorant of the importance of research in relation to the achievement of a high standard of teaching and the development of a correct attitude of mind in the students" ____ " Speaking generally, medical students in this country complete their studies without coming in contact with planned scientific investigations. The serious deficiency in their training is, in our view, of even greater importance than failure to advance knowledge of the subject".

This truly reflected the milieu in which our medical colleges functioned at the time of our Independence. Thus I started and completed my under graduate medical education totally deprived of exposure to research methodology leave aside participation in research. As stated elsewhere the statutory requirement of a research thesis for the PG degree MD/MS was to say the least a farce. Unfortunately nearly fifty years later the situation is not much better. Reddy et al (1991) in a bibliometric survey of research publications of 128 medical institutions between 1981-1988 found that only 6 (4.7%) institutions had over 50 articles, 43(38%) had 1 to 5 articles and 41 (32%) had less than one. Among the top 6 were All India Institute of Medical Sciences, New Delhi; The Postgraduate Institute of Medical Science, Chandigarh, The Institute of Medical Sciences, Varanasi; Tata Memorial Hospital and Cancer Research Centre, Bombay; and the Christian Medical College, Vellore. These observations were confirmed in another study by Arunachalam (1997) and yet another by ICMR & DBT a few years later.

Without dismissing all medical research carried out in India as trivial, outstanding research was and is being carried out during the period covered here. Some outstanding examples are listed below. There are no doubt others which do not find mention due to my ignorance and not their significance.

Prior to 1947

- Kala-azar first reported from Bengal in early 1800s, hundred years later its etiological agent was discovered by William.
- WB Leishman in 1901 and Charles Donovan in 1903 independently discovered the causative agent of Kala-azar. Its vector, the sand-fly was recognized by Swaminathan in 1942. UN Brahmachari discovered Urea Stibamine for the cure of the disease in 1929.
- Robert Koch discovered the causative organism of Cholera in Calcutta in 1884.
- Waldemar Haffkine carried out an extensive trial of the first Cholera Vaccine in India in 1893 and a vaccine against plague in Bombay in 1899.
- Lewis discovered microfilariae in peripheral blood in 1872 in Calcutta.
- Ronald Ross – born in India, carried out a large part of researches working in Ooty, Hyderabad and Calcutta, described the complete life cycle of malarial parasite in mosquitoes in 1898. He received Nobel Prize for it in 1902.

The reason to mention these is to illustrate that outstanding biomedical research could be carried out against all odds by individuals who were motivated to do so. It may be mentioned that same was true for other disciplines. Just to mention a few of these Indian pioneers, who contributed to internationally recognized research include J.C. Bose, S.N.Bose, C.V.Raman, Meghnad Saha, P.C. Ray.

After Independence

Similarly some path breaking research could be carried out in Independent India under extremely difficult circumstances. Mention may be made of contributions to basic medical sciences, clinical medicine and health sciences including development of drugs and vaccines. The identification of cholera exotoxin by S.N. De (1959); the systematic study of visceral receptors including the J-receptors by A.S. Paintal (1950s and 1960s); the identification of feeding and satiety centres by B.K. Anand and his colleagues (1960s); demonstration of enzymatic disorders in the brain (Bachhawat and Colleagues 1960s and 1970s); high altitude, physiology, the exposition of nutritional pathology (V. Ramalingaswami and colleagues (1950s and 1960s), iodine deficiency disorders (Ramalingaswami and colleagues 1950s and 1960s), the detailed studies on pathology of neurotuberculosis by Darab Dastur (1966) are some examples of research in basic medical sciences. The evidence for rheumatic fever and rheumatic heart disease occurring in tropics by K.L. Wig (1940s); The elaboration of the diverse clinical manifestations of neurotuberculosis, the variations in clinical manifestations and course of a host of diseases in India compared to the same illness in the West, description of unique diseases seen in India – Indian childhood cirrhosis, non-cirrhotic portal hypertension, lathyrism, Madras motor neuron disease, the Kyasanur forest disease, Chandipura virus infection, are such examples of clinical research.

The large scale epidemiological studies on iodine deficiency disorders, their diagnosis and control, the BCG trial, the rotavirus diarrhoea, studies leading to establishment of short-term chemotherapy for tuberculosis, the failure of three dose oral polio vaccine prophylaxis, bio-environmental control of malaria in India illustrate example of health research.

Beginning with the work of Col. R.N. Chopra (1882 – 1973) on herbal drugs, Indian scientists made significant contributions in the field of natural products chemistry and introduction of a few new drugs. In more recent years utilizing researchers in chemical technology India has acquired a leadership role in the field of generic drug development. Utilizing advances in molecular biology Indian scientists and pharmaceutical industry have entered in the field of vaccine development.

The example above are illustrative of atleast some noteworthy contributions (Names of those still with us whose researches have been included in the list are not mentioned).

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My Tryst with Bio-Medical Research

(the motivation, the environment, the result)

The seed for creating a desire to peruse scientific research was no doubt sown by some vague familiarity with Papaji's* involvement with it. During the two years I spent at Allahabad studying for Inter Science (+12) I was exposed to his interest in research, occasional reference to a paper he was working on or the one which was recently published. I recall his work on wheat rust due to *Alternaria tenuis* or the studies he carried out for his Ph.D. in London on fungal diseases of tomatoes. An occasional visit home by his research scholars for advice regarding their thesis added to the trickling of such information. What impressed me most was that some fungi he had isolated and studied were named after him. Living in a 'university town' like Allahabad, having a large number of academicians and outstanding scientists in the neighbourhood must have further strengthened an instinct to follow such a path. I vividly remember the excitement generated by a talk in our college by Sir C.V. Raman – undoubtedly one of the heroes of the country. These subliminal impingements on my consciousness, no doubt, must have generated some interest in scientific research. But my childhood cherished desire to peruse a medical career overwhelmed the attraction of a purely research oriented academic pursuit. Obviously if I had failed to get admitted to a medical college I would have chosen the latter path.

Entering the medical college with its very demanding curricular activities and the mere instinct for survival coupled with a general lack of research environment, even at the faculty level, proved to be uninviting (unconducive) to nurture any desire for scientific activity. The prevailing system of education, borrowed from the British, which as a rule was against encouraging original thought or independent enquiry among the 'natives', proved to be an added dampener for such efforts. Notwithstanding the renaissance of Indian basic science in the early decades of nineteen hundreds of the outstanding, internationally competitive research by the likes of Ramanujam, CV Raman, JC Bose, Satyen Bose, Meghnad Saha, etc. this spirit of scientific activity had not percolated to professional institutions, be it medical or engineering. It is not surprising then that there were hardly any original contributions in these fields at that time.

Not only was the environment not conducive to do research, there was, to a certain extent, an active resistance to it. Those days the real stamp of one's academic excellence was to obtain FRCS or MRCP from England. The local MD or MS, which required at least some token research in the form of a thesis, was considered an inferior qualification. It may surprise the votaries of research in higher education that during a course prior to the final FRCS examination, in one of the most prestigious medical colleges in London, one was advised not to read any professional and scientific journal of last 10 years. Only the established, old traditional knowledge was acceptable.

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*Papaji refers to my father Prof. R.N. Tandon, who retired as a Professor of Botany, University of Allahabad. He was a Fellow of the three science academies and the Agriculture Academy. He was President of NASI.

I did work for a thesis as a part of my M.S. course. Unlike others who chose a retrospective clinical study to fulfil this requirement I thought of doing some lab-based prospective investigation on a subject on which there was no prior Indian publication and few authentic large scale reports from abroad (Potassium Deficiency in Surgical Patients). I must admit that I have never been proud of this slip-shod investigation for which I had little training nor the required mentorship. It is not surprising that I have never published a paper based on it. I may add this was a classical example of how research should not be done. Before describing my involvement in biomedical research, an interesting episode in my life is briefly described below.

Meningitis

While doing the evening round of patients in surgical ward 1, as house surgeon my attention was diverted to a new patient being wheeled on a trolley. Even though it was not my emergency duty I, being the only doctor in the ward could not help rushing to attend to the patient who had a very noisy laboured respiration (like loud snoring). I discovered that the patient's neck was swollen due to cellulitis (inflammation of the soft tissue), the tongue was protruding, he could hardly breathe and was already turning blue. I asked the sister to call the doctor on the emergency duty since in my assessment the patient needed a tracheotomy (making a hole in the air pipe). By chance Dr. M.K. Goel, a young lecturer in the surgery arrived and I promptly told him about my concern. He appeared hesitant to consider doing a tracheostomy and remarked, "the basic principle of surgery is never to touch cellulitis, always drain an abscess". While this dialogue was on, the patient suddenly collapsed, this stopped to breathe and lost consciousness. The nurse quickly produced a surgical knife and with the Goel's permission I stabbed the patient's neck to open the trachea and as a fool without taking any precaution started to provide mouth-to-tracheostomy breathing. As should have been obvious if I had a moment to think that I was exposing myself to infective secretions from the patient's trachea. This being my first emergency procedure I was only concerned with somehow saving the life of this patient. In spite of our valiant efforts we failed to revive the patient. Only then I realised that I had badly contaminated my mouth and throat. I immediately gargled and as a prophylaxis took an injection of Penicilline and forgot the whole incidence.

Few days later, which happened to be Holi (festival of colours), I woke up with fever and sore throat. Yet I decided to go for the morning round lest the Chief presumes that I was playing hooky. During the round I was hardly able to keep pace with the Chief. At the end I told him that I was not feeling well and would like to take the day off. He then looked at me and with his shrewd clinical sense recognized that I was really sick. He then remonstrated and said " who allowed you to come on duty" and asked an orderly to take me to my quarter in a wheel chair. By this time all my other friends with whom I shared the accommodation had gone to play Holi. I just hit the bed and by the time my friends returned I was in stupor having very high temperature. I was admitted to the hospital in an unconscious state. Next morning when I woke up I realized that I was in a private ward in the hospital, and by now I had developed a swelling of one side of my neck-something like our patient had. With penicillin and sulfa drugs I started to improve. The fever subsided as also the neck swelling. However a single gland (lymph node) remained swollen and then developed into an abscess. This had to be drained surgically.

The day after the surgery my fever recurred and even though the abscess was healing the fever increased to 103°-104° F along with severe headache. This failed to respond to then available drugs-crystalline penicillin, streptomycin and sulphonamide. My headache became worse and persistent, and I developed frequent vomiting. Our Professor of Medicine- Dr. B.B. Bhatia was requested to examine me. He thought all these symptoms could be drug induced and ordered all medicines to be stopped. My parents were called and since there was no improvement in my condition a feeling of impending death pervaded, of course without my knowledge. A new antibiotic Achromycine had recently been introduced. It was obtained from Bombay (now Mumbai) but there was reluctance to use it since it has not been used before.

Nearly a week passed by with temperature not coming below 103° F at any time, headache and vomiting unrelenting. There was hardly any oral intake. Various tests- blood, urine, x-ray chest done were unhelpful. I suggested to my friend looking after me that since nothing is found, why not do a lumber puncture to examine the CSF. At this stage a family friend Dr. R.N. Tandon, Chief of Tuberculosis in the college learnt about my illness, so came to visit my parents in the hospital. At the same time he examined me thoroughly. He repeated clinical tests for meningitis, but these were equivocal. He went to Prof. Bhatia's residence and ultimately was able to persuade him to do the lumber puncture that very evening. The spinal fluid was personally taken by Dr. Tandon to the private labs of Prof. Manglik and Prof. Gupta. Both independently reported definite evidence of Meningitis, and suspected it to be Tubercular. The treatment was accordingly started with 8 hourly streptomycine injection and an intrathecal (spinal route) dose daily besides 3 hourly crystalline penicillin and injectable sulphonamide. This also proved futile, all hopes were lost and ultimately, with consent of my parents, achromycine oral was started. My mother told me later that on that day I once again became unconscious but momentarily woke up, finding her obviously anxious and told her, "Mummy don't bother, I will soon be well. Race has just begun; I have still a long way to go". I lapsed into unconsciousness soon after. Some 36 hours later I woke up, for the first time in days, feeling well. I told the nurse looking after me, when she took my temperature, "Today you won't have to tell a lie my temperature has come down". And really it had. Over the next few days, I made progressive recovery. In retrospect it is obvious that I suffered from septic (bacterial) meningitis modified by all the penicillin and streptomycine I had received maskraiding as TBM. I was left as a skin and bone skeleton weighing less than 70 lbs.- unable to walk unsupported. But I had survived to join as a PG student after recuperating at Mussoorie for two months.

Introduction to Scientific Research

Before, embarking upon the enumeration of various research projects / programmes I pursued during my professional career and post retirement it is necessary to record that in most, if not all, there were others who participated in these efforts to a varying extent. While for the majority the idea was initiated by me, in most the efforts to involve others was mine and I was generally responsible for the plan of studies. In case the actual collection of the data was carried out by my associates / collaborators, I was personally involved in scrutinizing and/or analysing it.

The manuscript for publication, if not drafted by me, in every case I participated in editing it. Having said this, it must be reiterated that this does not minimise the contributions of others which in some cases was much greater than mine. As will be observed the origin of the study was often prompted by some observations made on the bed-side, in some others by unexplained features of some disorder. There were others where development/availability of new techniques/technologies, or knowledge provided an opportunity to explore the unanswered questions faced during day to day care of the patients. It was, no doubt, often times motivated by a desire to enhance knowledge and to demonstrate ones involvement in intellectual exercise, an essential attribute of an academic position one occupied. One of the most rewarding elements of all these efforts, was the joy how some of the results could directly benefit our patients, even if it did not add to ones "citation index". I have often felt that it was more important to find the impact of our research on improving patient care than its reflection in the "Impact factor" or h-index. It may be mentioned in this regard that we were often prompted to publish our observations in Indian journals so that our colleagues in the country can benefit from it. This was specially so for researches related to disease conditions common in our country and not of much interest to others. It may be observed that in contrast to our colleagues in natural sciences, our investigations were more often than not guided to find a solution for a real-life problem, than being purely driven by curiosity. Nevertheless, the efforts required were no less scientific or intellectually demanding (Tandon, 2015)[1].

My first attempt at writing a research paper had to wait till I joined the WHO team, led by Dr. L.E. Volodarsky, at the SJTB Hospital, Delhi in 1954. I was asked by Dr. Volodarsky to analyse the results of our cases of Semb's thoracoplasty for pulmonary tuberculosis (TB). While routine thoracoplasty was already a well established procedure in India, its improved modification, proposed by Carl Semb of Oslo, was not practised in India. I had assisted or independently performed nearly one hundred such operations. A monograph on the subject published on the basis of work done in Prof. Semb's Department provided an inspiration to critically appraise our results. Though Dr. Volodarsky was supposed to present it during the Annual Conference of the Tuberculosis Workers of India at Amritsar, he deputed me to do so. I vividly recall the spirited questioning and unexpectedly long discussion that followed my presentation in which the 'giants' of Chest Surgery of that era – S.K. Sen (Delhi), A.K. Basu (Calcutta), Santokh Singh Anand (Amritsar) – participated. I overheard someone comment "poor Dr. Tandon". I, of course, not only withstood the barrage but really enjoyed it. The paper was later published in Indian Journal of Tuberculosis[2]. It is interesting that A.K. Basu, on his way back to Calcutta, stopped over at Delhi and came to our centre, probably hoping to watch Dr. Volodarsky operate. But he found me operating yet he stood through the whole operation. What a boost for my morale!.

My next venture in scientific writing was after I joined Dr. Kristiansen at the Ulleval Hospital, Oslo (February 1957). Assisting him during, what was probably my first major brain tumour operation, a lateral ventricular epidermoid was excised*. On being informed that it was a rare tumour at this location I embarked on a search of literature, and found that there were only ten well documented cases of epidermoids in the lateral ventricle in the world literature. I not only briefly described this

*Lateral ventricle- A cavity filled with cerebrospinal fluid in the cerebral hemisphere.
Epidermoid- A benign developmental tumour of ectodermal origin.

patient and summarised the other ten but extensively reviewed the literature. With the help of Dr. Volodarsky I even had a large series of epidermoids (112 cases) by W. Mahoney from Germany[3] and another by Lepoire & Pertuiset from France (100 cases)[4] searched for such cases. I dared to briefly present this case to the Norwegian Medical Association at least partly in Norwegian. It was later published as a rather lengthy paper: Epidermoid of the Lateral Ventricle[5]. This was followed by another case report of a rare condition – Spontaneous Ventriculocisternostomy with relief of obstructive hydrocephalus[6].

Cranio-Cerebral Trauma: The Monograph

However, my more serious involvement with research at Oslo was prompted by a request from Dr. Kristiansen to survey the records of a consecutive series of head injury patients treated in the department during the years 1950-1957 so as to help him prepare an invited talk on sequelae of severe head injury to be presented during the Annual Conference of the Scandinavian Neurological Society. Little did I realise the magnitude of the task I had accepted to undertake (Fig. 1 shows a patient of head injury).

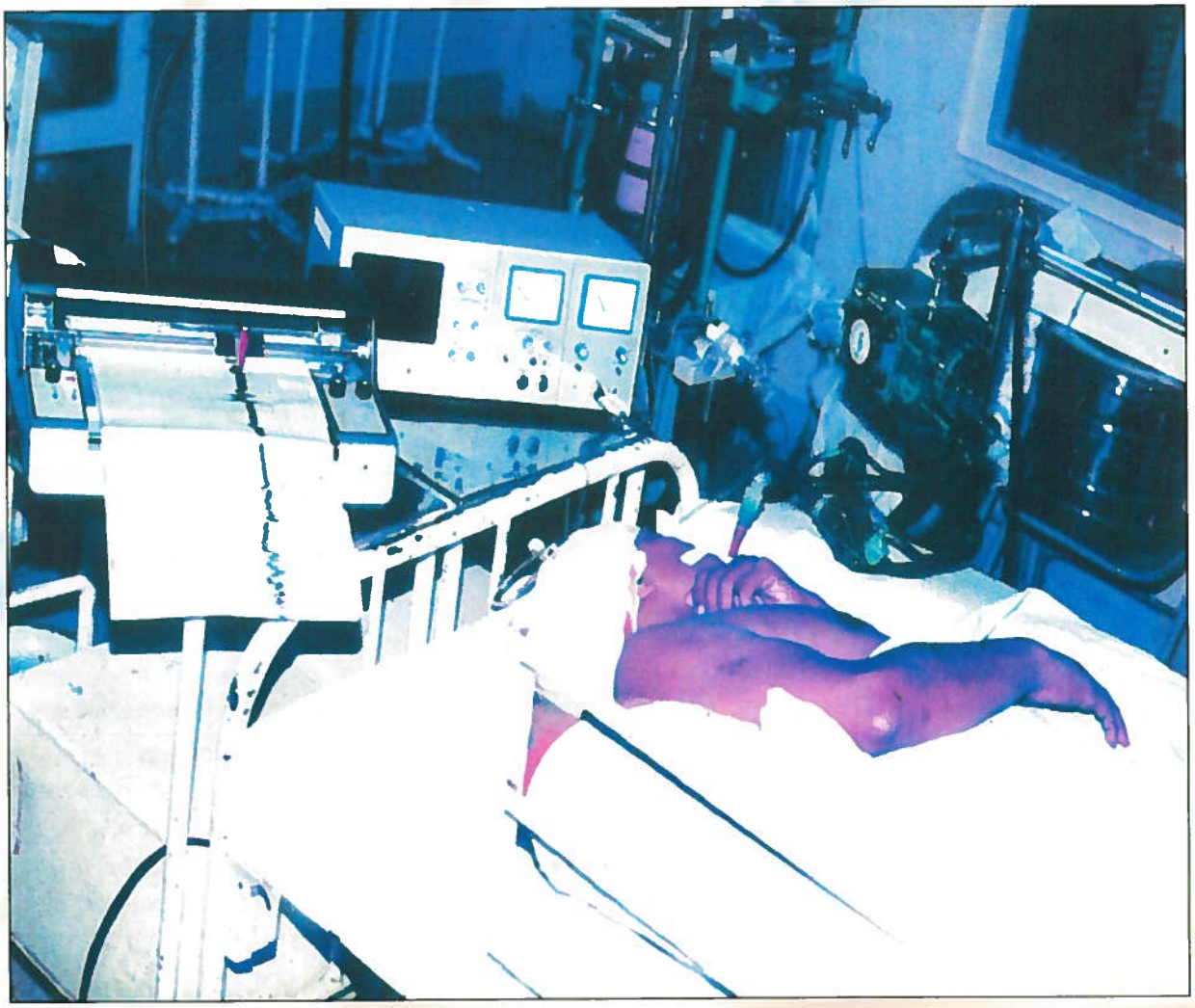

Fig. 1: Patient of severe head injury in I.C.U.

I surveyed the case records of nearly 3000 patients, most of them in Norwegian, and not surprisingly, according to the Scandinavian tradition meticulously maintained full of details including follow-up (and post mortem observations on fatal cases). Besides collecting data for his talk, I utilised the opportunity to fulfil another cherished desire of mine to produce a monograph in the Scandinavian tradition to which I was exposed by the monograph on Semb's Thoracoplasty mentioned earlier and several others I found later in Dr. Kristiansen's library. I quietly worked towards that goal, specially analysed 265 cases of severe head injury, 164 of whom had either been operated upon or succumbed to death prior to surgery and were autopsied. This was not the era of computers and hence each case was summarised on an index card in long hand, then entered in big master charts, grouped and regrouped according to various criteria. Only when I was convinced that it could be published as a monograph, I approached Dr. Kristiansen to seek his advice about the future course.

My friend in Indian Embassy G.S. Mehta volunteered to type the hand-written manuscript for me (and did a remarkable job of it!). It had taken me nearly a year of hard work and time was running out for me since I was to leave for Montreal at the end of the year. Dr. Kristiansen was very pleased to see the draft and advised me to leave it with him for editing and giving it a final shape. It was decided to publish the monograph as a special issue of J. Oslo City Hospital[7]. The significant new observations of this study were:

I) *A need for better clinico-pathological classification of head injury*

II) *Pathogenesis of acute subdural and intracerebral haematomas being a consequence of cerebral contusion*

III) *The incidence and significance of primary and secondary brainstem dysfunction and haemorrhage —the two being clinically indistinguishable and not to be considered invariably fatal*

IV) *The incidence and significance of cerebral contusion in modifying the clinical picture and determining the prognosis*

V) *Difficulty in differentiating between intracerebral haematoma and cerebral contusion / laceration and associated oedema acting as a mass lesion*

VI) *Inadequacy of simple burr-hole evacuation of acute subdural haematoma without attending to the associated parenchymatous lesion*

VII) *Value of early angiography for diagnosis owing to the impossibility of differentiating various types of intracranial pathologies on clinical ground*

VIII) *Irrationality of elevating most of the closed depressed fractures of the skull*

IX) *Undesirability of delaying investigations and surgery in a case of suspected intracranial haematoma till clinical deterioration and focal signs appeared as was the current recommendation*

X) *Satisfactory outcome of patients with chronic subdural haematomas evacuated through one or two burr-holes without attempting to excise the membrane or need for manoeuvres to artificially expand the brain then being generally advocated.*

XI) *The need for surgery for intracerebral haematoma and parenchymatous lesions mimicking it Generalised hypothermia was found to be useful in selected cases but no clear cut indications could be established.*

One of the reasons to publish it as a supplement of this journal was to follow the tradition of preparing scientific monographs in Norway. There was also the need to quickly build up my list of publications for seeking a job on return to India. It is, however, interesting that notwithstanding its

publication in this not well known journal, the prestigious British Journal – Lancet published an annotation on it highlighting its significant contributions. It commented, "The treatment of severe head injury is clearly becoming less the province of inactive masters that it has been hitherto". This study taught me many lessons – paved the way for continued involvement with the subject of head injury, a search of answers for various unresolved questions and to provide a proof of several conjectures/beliefs arising out of it, but above all generated an unquenched thirst for research (more of this later). An interesting side story was the comment I received from my friend Dick Rovit, a colleague at MNI, to whom I had given a copy of the monograph. A few days later when we met he in his usual flamboyant style remarked, "Prakash, I always admired your intellectual abilities, but failed to recognise your traits of stupidity". Taken aback by this comment I enquired the reason for this 'insult'. He promptly said, "That monograph of yours". I could not help rebutting, "I am sure you could not produce one like it". The 'wisdom' behind the comment proved to be revealing. He, of course, found the monograph to be excellent, but told me, "If I were you, I would have first published each chapter as a separate paper in different journals and then combined them as a monograph. I would then have 8-9 publications to my credit and you have wasted all this labour and will get only one addition to your list of publications". He added, "This is how we worked in America"!

Over the years in a series of investigations along with my colleagues at AIIMS, I attempted to find answers to some of the questions raised by this initial study. This not only helped our understanding of the pathophysiology of brain injury but also resulted in providing scientific basis for improved management of these patients, resulting in a distinct reduction in their mortality. These studies led to challenging the prevailing, often misconceived, management strategies for lesions like acute subdural haematoma, traumatic lesions of temporal lobe, depressed fracture skull, cranio-cerebral erosion and brainstem injury. A critical, independent comparison of treatment outcome of our patients managed under resource limited circumstance to those from a high-tech, input-"maximalist" therapy centre in US testified to the rationale of our approach.

These investigations over the years resulted in over two-dozen publications in several prestigious journals like Acta Neurol Scandinav, Acta Neurochirurgica, Surgical Neurology, Journal of Neurosurgery and of course our own Neurology, India. {Please see later}

While in Montreal, the routine service workload was overwhelming, hardly permitting any worthwhile research. My request for posting me to the experimental lab for six months was turned down by Dr. Rasmussen. He said, "we would like to equip you to be a competent neurosurgeon to serve your people since there are so few of them in the country. I will happily accept your nominee for training in basic research once you establish your clinical service back home". However, on my persistent request he permitted me to study the records of patients who had undergone focal resections in the sensory-motor cortex for treatment of epilepsy. It turned out that he himself had once planned to do such a study but for a variety of reasons did not peruse it. After a time consuming effort I prepared drafts of two papers and submitted these to Dr. Rasmussen. He could hardly find time to review these. Some days prior to my departure from Montreal he invited me to stay with him for a weekend when we could finalise the papers. He took me home with him and we

spent sometime giving final shape to these papers. These were left behind with him and ever so often, over the years, in his letter to me he would inform me that he plans to send these for publications "soon". Nevertheless, atleast one of these, in a modified version, saw the light of the day in 1994[8]. So much for my effort! The second paper was never published.

During my stay in Montreal I collected the material for a case report on Subarachnoid Ependymal Cyst, but only published it much later when we had another such case at AIIMS[9]. A detailed review on EEG localization of brain tumours prepared by me for a journal club while I was posted in EEG lab during the last six months of my stay at MNI, was later published in Neurology India[10]. It may be mentioned that at that time except for EEG there was no other non-invasive diagnostic procedure available for diagnosis of brain disease. Isotope encephalometry, though utilized in some advanced centres abroad, was not yet available in India. By no stretch of imagination these could be considered great research contributions but these are only indicative of a persistent desire to contribute to scientific literature.

Keeping Research Interest Kindled in Environment not Conducive to it

On return to India, to start with as a Pool Officer at my Alma Mater, my primary concern was to face the trials and tribulations of establishing a safe, dependable, neurosurgical service – no mean task at the best of time but worse so in absence of even the basic facilities, supportive diagnostic services and staff. No trained surgical assistant, anaesthetist, neuroradiologist or intensive care facilities. Most patients coming for treatment were in advanced stage of disease, yet the expectations were to deliver miracles. One had to be head cook and bottle washer – be your neurologist, neuroradiologist, guide the anaesthetist, the OT staff, train the uninitiated, reluctant resident (assistant) posted with you, often against his wish, in an environment where hard work was not in fashion. However I must record that I enjoyed immense support and good-will from all quarters probably because I was the product of the same institution. Special mention may be made of Prof. S.C. Misra HOD Surgery, Prof. R.V. Singh, Prof. of Surgery and later Principal, and Prof. B.N. Lall, HOD Radiology for their immense support.

Notwithstanding all these difficulties the desire to find ways and means to gather material for publication was constantly with me. Talking to colleagues and friends, who were my contemporaries during the student days, I was repeatedly warned that any research in the prevailing environment was a dream destined to failure. None of them had published a paper and except for some isolated examples like those in the departments of pharmacology or pathology, few "indulged" in such "frivolous" activities. I soon realised that the remarkable wealth of clinical material – unique in many respects, untapped by others, could be the treasure I was in search of to satisfy my needs for enquiry and the possibility of contributing to knowledge at a later date. I thus personally started maintaining records of all my patients. In the meanwhile I tried to explore the material collected at Oslo and Montreal for possible publications so as to keep me intellectually engaged. But I had to wait for three years after joining KGMC to publish any paper. But in 1964, I was able to publish 5

papers – one on brainstem haemorrhage* in craniocerebral trauma in Acta Neurol Scandinav and another on Pupillary Signs in intracranial haematoma in Ind. J. Surgery based on the material collected for Head Injury Monograph[7]. Both challenged some of the existing views on the subject. The time honoured belief that intracranial hematoma manifest as Hutchison's pupils was found to be incorrect and it certainly was not always a reliable sign of enlarging haematoma. Whilst the ominous import of bilateral fixed dilated pupils was confirmed, the pinpoint pupils believed to indicate pontine haemorrhage was not found to be so.

In the meanwhile I along with my friend R.N. Misra, (Ravindra) and one of his students collected retrospective data on 266 consecutive admissions for paraplegia (paralysis of both legs) in the Departments of Medicine and the Neurosurgery Unit in our hospital and compared this series with three other such series published from India. It revealed the variations in etiology of non-traumatic paraplegia in our population compared to the experience in the West. Thus a variety of tubercular pathologies dominated the pictures, while syphilitic lesions involving spinal cord were still seen though much less frequently than earlier (24 cases). Primary lateral sclerosis (25 cases) and acute transverse myelopathy (35 cases) were the common degenerative lesions[11]. This study highlighted the relatively lower incidence of multiple sclerosis in India as compared to the West.

Based on this material a paper was published next year on 35 cases of Acute Transverse Myelopathy which seemed to be more frequent compared to the West. The response to corticosteroids administered early in the course of illness was dramatic in a number of cases. This was first such report from India and one establishing a therapeutic strategy[12].

On the request of Prof. Kristiansen a paper on Brainstem Dysfunction in Cranio-Cerebral Injuries was prepared for presentation at the IIIrd International Congress of Neurological Surgery to be held at Copenhagen. This provided so far unreported evidence that clinical signs like decerebrate rigidity or coma do not necessarily imply irreversible damage to the brain stem, even transitory respiratory arrest did not exclude full functional recovery if adequate treatment is promptly instituted[13]. This challenged the prevailing attitude of therapeutic nihilism for management of such patients generally prevalent. As will be seen later clinico-pathological correlation of brain stem lesions continued to be a subject of interest over the years resulting in several publications confirming our initial observations utilizing more sophisticated diagnostic techniques like electrographic studies of sleep, vestibulo-ocular reflex, brainstem evoked potentials and ultimately CT Scan[14-16].

Infantile Tremor Syndrome

My old class fellow and friend, a paediatrician Dr. P.C. Bajpai introduced me to a bizarre syndrome in infants and young children with tremors associated with characteristics facies, hyperpigmentation of skin, sensorial regression without any focal neurological deficit. These represented an unique

*Brain stem is the part of the brain that connects it to the spinal cord. It contains the neural centres for vital functions like the respiration, heart beat and other autonomic functions. It is intimately responsible for consciousness.

syndrome labelled by us as Infantile Tremor Syndrome not described in the neurological literature, but similar cases were reported from a couple of other centres in India under different titles. I got involved in this prospective study to explore its etiology, pathophysiology, pathology, prognosis etc. In the process we did EEG, Pneumoencephalography and even brain biopsy in selected cases besides some haematological investigations including serum B 12 studies. Tremors and the associated clinical features regressed spontaneously over a period of 6-8 weeks but left behind residual deficits specially mental retardation. When we submitted a paper based on a series of 79 cases studied at Lucknow to Neurology (Minneap) it was rejected. The referees comments were not only unhelpful but some of these outright illogical. Sometime later Prof. Refsum, then President of World Federation of Neurological Societies, was visiting Delhi. As a matter of fact I had known him from my days in Oslo and he was my house guest. I showed him a couple of such patients in our hospital and he asked me why you have not published it. I gave him the manuscript alongwith referees comments and editors communication. After going through these documents he found the referees comments 'ridiculous' and rejection uncalled for. He said he would write to the editor accordingly but wanted to take the manuscript with him for publication in Acta Neurologica Scandinavica which promptly published it[17]. The comprehensive data on the subject was later presented by me at the joint conference of the International Federation of Neurology and World Congress of Neurological Surgeon held at New York, 1969[18]. Even though by this time I had moved to Delhi, my interest in the subject continued and jointly with Bajpai and Misra we published 4 more papers on different facets of the disease. It remains a mystery why this syndrome reported from Lucknow, Vellore, Indore and Delhi in 1950s and 60s virtually disappeared over the years and we don't seem to see any such patients now.

My efforts in persuing research interests, howsoever tentative created some interest in our other colleagues in the college at Lucknow. While Bajpai was most enthusiastic others were motivated. P.C. Dubey a brilliant student, a competent surgeon wanted me to arrange for his exposure to research with Prof. Semb at Oslo. I succeeded in this with the help of Dr. Kristiansen. Unfortunately his stint for a year there, where he collected some useful data on partial nephrectomy (resection of kidney)only resulted in unfinished papers (much to Prof. Semb's dismay). These were never completed on his return to India. R.P. Sahi, whom I tried to entice to neurosurgery, however got interested in publishing papers. During the next couple of years he published a number of papers, some even in international journals. However, on the whole my enthusiasm could not 'infect' others.

During my stay at Lucknow, there was an epidemic of Lathyrism in and around Hardoi – P.C. Bajpai's home town. I saw couple of these patients at Lucknow. So with the help of PCB we arranged a visit to Hardoi and the adjoining villages. In our short visit we could examine a sizeable number of these patients – all male, rapidly developing spastic paraplegia, spasticity being out of proportion to

weakness, no sensory signs except painful cramps in calf muscles as initial symptoms. I was impressed by the spastic element of the disorder. This reminded me of Tarlov's experimental studies on spinal paraplegia where in he found that involvement of interneurons was responsible for disproportionate spasticity observed in some of his animals. However, since I soon moved to Delhi I could not pursue this subject any further but the idea of establishing an animal model persisted. Besides these completed studies a couple of other case reports were published during my stay at Lucknow from August 1961 to February 1965. I had collected some other clinical material like a variety of cases of meningo-encephalocele, the like of which I had not seen during my four years of training abroad, which was published after leaving Lucknow. However, two clinical observations and a preliminary experimental study initiated there became subjects of later detailed investigations. (Please see later).

Pulmonary Oedema* in Raised Intracranial Pressure

Besides clinical studies I was keen to initiate some experimental work. One of the best animal experimental lab in our college at Lucknow was in the Department of Pharmacology where my friend Dr. K.P. Bhargava (KP to us)was the Chief. Based on an observation of a patient of a bilateral chronic subdural haematoma# under my care at Montreal Neurological Institute (MNI) I had an impression that acute rise in intracranial pressure (ICP) can produce fulminating pulmonary oedema. This 69 year old lady waiting for investigations for symptoms and signs of raised ICP without focal neurological deficits, whom I had examined a short while earlier, suddenly lapsed into coma soon afterwards while I was still around. The ward nurse literally howled for me. Besides being unconscious with dilating pupils I heard the noisy respiration and froth bubbling out of her mouth. She had obviously herniated resulting in pressure on the brain stem. Time appeared to be crucial, I promptly made two twist drills holes in her skull in the ward itself with a view to drain cerebro spinal fluid (CSF) from the ventricles to relieve the raised pressure. As I introduced the brain needles I was greeted with the chronic subdural blood gushing out. Within minutes the patient regained consciousness and her bubbling lungs made as dramatic a recovery as it had developed. But for this somewhat unconventional approach the patient would expire in a matter of minutes.

I discussed this with K.P., who was already working on cardio-vascular responses from the brainstem. He made all arrangements for me to initiate experiments on dogs using extradurally transplanted balloon to raise ICP. While inflating the balloon in a conscious dog inadvertently a rather larger amount of fluid was injected. I suddenly heard a loud cry as the dog slumped on the table and immediately large quantities of frothy fluid gushed out from its mouth virtually flowing over to the OT floor. As I released the fluid from the balloon, equally dramatically the dog regained consciousness and the pulmonary oedema subsided. I could not carry on this study further as I was to leave for AIIMS soon after. However, the idea to pursue this matter persisted. Initially I could not find anyone to collaborate with me for such a study at AIIMS. I did not need a proof that raised ICP produces pulmonary oedema. Though not as dramatic, but wet lungs were common in number of

*Pulmonary oedema-accumulation of fluid in the lungs

Subdural haematoma- blood clot inside the skull overlying the brain.

patients with raised ICP. The need was to explore the pathophysiology of this phenomenon. Many years later I could convince our colleagues at the AIIMS in the Pharmacology Department, Dr. S.D. Seth and Dr. Y.K. Gupta to carry out such a study in collaboration with me. A Ph.D. student A. Chugh took this as the subject for her Ph.D. thesis. Inspite of some excellent work done, she left the Department soon after submitting her thesis without publishing the results (Chugh A: Pharmacological intervention in Neurogenic Pulmonary Oedema: A Haemodynamic Study, Ph.D. Thesis, AIIMS, 1993). After a great deal of persuasion YKG could get only a couple of minor papers published[19,20].

The Years at AIIMS

After joining AIIMS, in March 1965, I was once again faced with the task of creating a new department from a scratch. As described elsewhere the existing facilities were worse than those at Lucknow when I started. The positive elements were the unstinted support by Dr. Baldev Singh who joined the Institute at the same time as Professor of Neurology, a helping hand of Dr. A.K. Banerji who joined me as an Assistant Professor, a couple of months later and S.K. Ghosh whom I had initiated in Neuroradiology at Lucknow having preceded me at AIIMS as an Assistant Professor in Neuroradiology. Besides the daunting task of establishing a safe, reliable clinical service in the absence of basic facilities –not even a full set of routine neurosurgical instruments, a neurosurgical operation table, suction or cautery, leave aside the other ancillary support services, and not even a resident (assistant). At the sometime the prevailing culture in the Institute, unlike at KGMC, was of very high expectations for research. After all, even though in its infancy the Institute was regarded as an apex national organization already having internationally recognised medical scientists like V. Ramalingaswami, B.K. Anand, N.H. Keshwani, Col. Kalra, G.P. Talwar and renowned clinical researchers like K.L. Wig, S.B. Roy, N. Gopinath, Baldev Singh, among others. One was expected to attain their standards if not more and that too in as short a time as possible. On the professional front there were well established national figures like Jacob Chandy, B. Ramamurthy, Ram Ginde, R.N. Chatterji, Ashoke Bagchi to compete with. Early during my stay at AIIMS, one day Dr. B.K. Anand reminded me, "Here it is not how many patients you treat or operations you do that counts but how much research you do and what you publish that matters". In addition to all these challenges I had the added concern of having up-rooted my wife from a promising professional career and a one and a half year old son to care for in a rather daunting environment.

Amidst these challenging demands, in absence of any supporting staff, not having been trained in laboratory work, I had to quickly initiate research. It was here that my two chance clinical observations at Lucknow came in handy.

Auditory Functions In Raised Intracranial Pressure

A ten-year old boy with evidence of raised intracranial pressure (ICP), already becoming blind due to it, was found to be hard of hearing also. One could easily pass it off as a co-incidental finding. But this reminded me that just as extension of CSF pathways along the optic nerve was responsible for papilloedema and ultimately blindness in patients with raised ICP, could a similar mechanism not be responsible for hearing impairment since anatomically similar communication exists between CSF

pathways and the internal ear. A search of the English literature revealed very little information. However, an Italian report in 1951 had recorded that variations in cerebrospinal fluid pressure could be transmitted to the fluid system of the labyrinth through the cochlear aqueduct. There were a few stray reports in German and Russian literature but there was no systematic planned study. I, therefore, approached my friend A. Sinha – the Chief of ENT Department, for help in conducting this study. He immediately requested his Assistant Professor Dr. S.K. Kacker and a postgraduate student R.K. Saxena to help me undertake the study. It may be mentioned that Dr. Kacker had already studied a couple of my patients with raised ICP while still at Lucknow. Moreover this initial collaboration in our study, followed by several other neuro-otological investigations, prompted Dr. Kacker to specialise in neurootology. The ENT Department at AIIMS soon came to be recognised nationally as one of the few centres for this speciality in the country.

Coming back to our initial study, it established beyond doubt that a high percentage (88% in our series) of cases of severe raised ICP, due to a variety of supratentorial lesions, were associated with a significant degree of hearing impairment – on an average of 30dB. Furthermore, this deficit was reversible following relief of the ICP. These observations were confirmed in a much larger series and later with the help of Békésy Audiometery[21a,b & 22]. [*Comments: A casual bed side observation in the background of knowledge of neuroanatomy, provided a hypothesis which could then be thoroughly investigated with the help of willing colleagues from the Department of ENT, utilizing contemporary technologies. It resulted in three students writing their MS Thesis. It did not require any financial inputs.*]

Vestibulo-Ocular Reflex – Brain Stem Functions – Consciousness

Vestibulo-ocular reflex or the cold caloric test had been primarily used by the ENT surgeons to evaluate vestibular functions*. I had read a couple of case reports, published in late 1950s, about the possible use of this test in detecting ocular nerve deficits in unconscious patients and diagnosis of tentorial herniation. Being fully aware of the anatomical and physiological studies on the brainstem reticular formation and its role in consciousness (a hot subject of study at that time by Alf Brodal, Magoun and Morruzi, Rossi, Jasper, Szentagothai among others#) aroused my earlier interest in brainstem disorders and the possibility of utilizing this reflex for evaluating unconscious patients. This appealed to me as a subject for research. It required no sophisticated equipment – only a syringe and a bowl of ice cold water – nor any manpower or financial resources – just careful clinical observations and their meticulous recording.

There were hardly any detailed studies on the subject available in the literature. It may be mentioned that we had only one resident on the service already overburdened with clinical service responsibilities. I once again approached my friend Dr. A. Sinha, H. O. D., E.N.T. Department.

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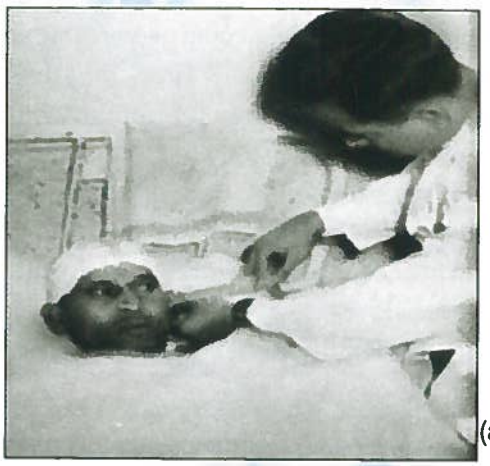
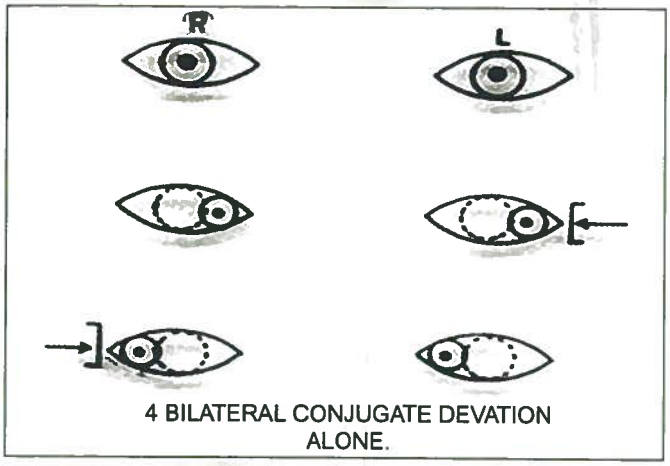
*Vestibular system located in the inner ear and connected to the brain stem through vestibular nerve is primarily concerned with musculo-skeletal equilibrium.

#While at Oslo and Montreal where at both places there was keen interest in this subject I had extensively read the literature on the subject. At the same time the investigations for the Monograph on Head injury had already aroused my interest in brain stem pathophysiology.

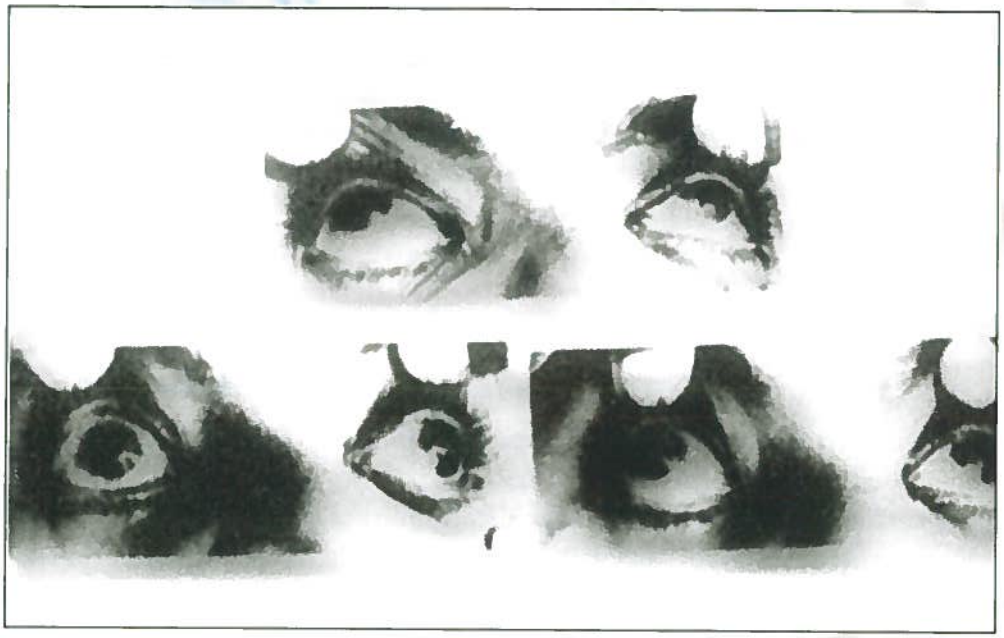


(a)



(b)

Fig. 2 (a): Vestibulo ocular reflex being tested; Fig. 2(b): Vestibulo-ocular reflex (i) normal position of eyes (ii) cold water injection in LT ear (iii) cold water injection in RT ear.



(c)

2 (c): Abnormal response to cold-caloric test due to injury to brain stem

He enthusiastically welcomed my proposal to initiate a well-planned prospective study. He deputed one of his students, Dr. W.R. Jadhav for this purpose. It took Dr. Banerji and myself to first lay down guidelines for precisely grading the state of consciousness. We adopted the criteria recommended by Marrubini (1965) with some modifications, classifying consciousness in 7 grades. This was before the now well known Glasgow Coma Scale was developed. The conscious state was recorded by one of us personally, simultaneously we standardised the cold caloric test as well as oculocephalic reflexes and classified these into 17 types. It was no mean task to train and motivate Dr. Jadhav to carry out the tests (of no interest to him as a postgraduate student wanting to be an ENT Surgeon). Ultimately we succeeded in collecting reliable information on 75 patients with altered state of consciousness between November 1966 and August 1967. It may be pointed out this very detailed

study was initiated shortly after joining AIIMS and was completed within a couple of years. We spent a lot of time correlating the observations (Fig. 2) to the various grades of impaired consciousness[23]. The study was based on a total of 371 observations made at regular intervals on these 75 patients. It revealed very valuable information for purposes of objectively grading consciousness, following its progress at different intervals, evaluating brainstem integrity and determining prognosis. As a matter of fact this became a routine clinical test for all patients with impaired consciousness in our service and later adopted by many others[24]. It is a pity that owing to the circumstances of the study it was published in an ENT journal and not in a reputed neurological journal. Hence it was hardly citied even though such detailed correlation of various types of this reflex to different grades of impaired consciousness is not yet available. This inspite of the fact that there is general recognition of the diagnostic and prognostic value of this reflex. its absence constitutes as one of the essential criteria of brain death. We published another paper on the subject a couple of years later which further elaborated those observations[25]. Several years later we had an opportunity to compare the prognostic value of this test to results of brainstem evoked responses, an electrophysiological investigation requiring sophisticated equipment[26]. {*Comment: Once again it may be noted that scientifically an important study, based on an original hypothesis requiring no sophisticated facilities or any budget, could provide a valuable tool to study the integrity of brainstem function at the bed-side. This was prior to the availability of modern neuro-imaging techniques like CT and MRI. The cold-caloric test was known for a long time only for study of vestibular functions but its use for evaluating the level of consciousness, unmasking occult neurological deficits and determining prognosis was an original concept.*}

Besides the specific projects mentioned above, these activities created interest in Neuro-Otology as a distinct sub-discipline among the students and faculty of the ENT Department. We had a monthly joint seminar between ENT & Neurosurgery on selected topics of mutual interest. Dr. S.K. Kacker, Assistant Professor decided to go to UK on a Commonwealth Fellowship to work with Dr. Hinchcliffe to specialise in this field. On his return he further strengthened activities in this area – adding a Békésy Audiometer and later equipment for Electronystagmography and a temporal bone laboratory. The Department came to be recognised nationally as a centre for neuro-otology and catalysed the initiation of Neurootological Equilibrimetric Society of India. Our two departments later cooperated on developing Transsphenoidal Pituitary Surgery and also Skull Base Surgery. Some other publications in this field[27-30].

In 1970s and 80s under the influence of propaganda by drug companies most patients with postural vertigo were diagnosed as Vertibro-basilar artery insufficiency secondary to Cervical Spondylosis and prescribed vasodilators. Following detailed studies of a number of such patients, many only 40-50 years old, along with our colleagues in ENT Department, we exploded this myth that this postural vertigo was not caused by Vertibro-basilar insufficiency, and ultimately I wrote an Editorial on the subject, though by this time the drug companies had earned enough[31].

Experimental Study on Spasticity

While the above studies provided some opportunities for planned research, I was still keen to start some experimental work. Having failed to find a collaborator for the study of neurogenic pulmonary oedema,

I tried to explore the possibility of initiating a study on spasticity of spinal origin prompted by the observations on the patients with lathyrism mentioned earlier. Around the same time publication of a study from the US that infusion of cold saline in the spinal subarachnoid space relieves spasticity I thought that if we could establish a model of disproportionate spasticity we could verify the utility of the cold therapy. I discussed this with Dr. Baldev Singh, who encouraged me to plan for this study and in addition he persuaded Dr. Desiraju, who was a Research Associate in the Department of Physiology, to help me in this effort. I approached ICMR for support which was approved. Without going in details I struggled hard trying various techniques in dogs – extradural balloon compression of the spinal cord, ligating intercostals arteries, even temporary clamping of thoracic aorta to produce ischaemic lesion in the cord. We could produce spastic paraplegia but not disproportionate spasticity. It was extremely difficult to maintain severely paraplegic animals. While we had some interesting pathological observations we obviously failed to establish the desired model. I regret to record that notwithstanding Dr. Baldev Singh and Dr. Anand's moral support the help expected from Dr. Desiraju# was wanting. Overall this was a frustrating experience. When time came to present the progress report to ICMR I had to accept my failure and inability to pursue the project further. It was even a greater disappointment to me since this failure had to be acknowledged in a committee chaired by the venerable Dr. Jacob Chandy. But to add insult to injury some of the observations made during this study, though never published by us, were later reported by another investigator from the US. We had observed that haemorrhage in the white matter following a traumatic lesion of the spinal cord extended on either side of the site of primary insult for several centimetres. If we had published this would have been the first report of this pathology.

To maintain at least some tempo for publication one had to fall back on clinical reports based on material collected earlier at Lucknow and added at AIIMS published in national journals[32-38] over the next two years, 1966-67.

Experimental Tuberculosis of the Central Nervous System

From the very beginning of the neurosurgery practice in Lucknow and later at AIIMS it was obvious that Tubercular lesions of the central nervous system (CNS) constituted a sizeable percent of our patient population. Reports from Madras, Bombay, Vellore, and Calcutta highlighted the variety of these lesions. This was then obviously an area of research to be explored. Extensive review of the literature revealed that most of the published work from India was in the nature of descriptive clinico-pathological aspects. Interest in the West in these lesions had waned. Instead of beating the well trodden path and still keenly looking for an experimental project I soon realised that there were many unanswered questions regarding the pathogenesis of the variety of clinico-pathological manifestations encountered. Thus, it was not known why a particular patient develops meningitis, another one a focal tuberculoma* and yet another both. Detailed study of Rich's original monograph, besides a lot of earlier publications, as also the pathological studies by Darab Dastur, made me suspect that it must have something to do with the host immune response.

#I hasten to add that this comment may not be appropriate since Desiraju is no more. Notwithstanding his unhelpful attitude I later helped him to be appointed as a Professor of Neurophysiology at NIMHANS, Bangalore.

*Tuberculoma: Tuberculosis producing a granuloma mimicking a brain tumour.

However, there was no experimental model of CNS tuberculosis reported in the literature. I, therefore, thought that this may be an area of research worth exploring. As usual I discussed this with Prof. Baldev Singh who arranged a meeting with Col. S.L. Kalra, Chief of Microbiology at the Institute. Col. Kalra himself an outstanding microbiologist and a very good friend of Prof. Baldev Singh, readily offered his help and assigned one of his postgraduate student Mohan Kumar to assist me in the study. I then submitted a properly thought out research program to ICMR for funding. During my presentation of the project to a committee headed by Prof. Ramalingaswami and including one of my favourite teachers and erstwhile colleague at Lucknow, Prof. R.M.L. Mehrotra. I thought it would be easy to have the Committee's approval. To my surprise and disappointment Prof. Mehrotra proposed rejection of the project remarking, "Nobody has succeeded in developing such a model so far and the study is thus unlikely to achieve the objectives". However, Dr. Ramalingaswami saved the day for me saying there is no harm trying again and even if he fails it will be a good experience for a clinician. The project was sanctioned with a "handsome" grant of few thousand rupees. With the active help of Col. Kalra and the day to day involvement of Mohan Kumar, who then took over this project for his Ph.D. thesis, the study took off much to my satisfaction. A strain of Mtb isolated from one of the surgically excised tuberculomas was used for the study. Initially we tried to explore the possibility of establishing the model in guinea pigs. Intra cardiac, intra cisternal and intra cerebral injections of Mtb were given to BCG vaccinated guinea pigs. While these succeeded to produce meningitis the rapid generalized dissemination of the disease resulted in early fatality. A tuberculoma like lesion was not observed. Being aware of the existence of brain tuberculomas in wild monkeys, we decided to use Rhesus monkey as an alternate model. Using unimmunized tuberculin positive, BCG hypersensitized and drug protected monkeys and using the same intracardiac, intracisternal and intracerebral routes of challenge, we succeeded in producing generalised meningitis, focal meningitis, generalised meningo-encephalitis and isolated focal parenchymatous lesions. It may be mentioned that these focal intracerebral lesions were, however, tubercular abscesses and not histo-pathologically characteristic tuberculoma. Nevertheless, it was a great personal satisfaction that atlast I had successfully completed an experimental study, planned and executed by me, no doubt with valuable contributions from the microbiology department. For a total cost of few thousand rupees only we finally had a unique model replicating most, if not all, clinico-pathological equivalents of human CNS tuberculosis. The humiliation felt following the spastic paraplegia study was atleast partially overcome. It may be mentioned that till today there is no other experimental model of CNS tuberculosis developed anywhere.

One of my regrets, retrospectively, is that for no obvious reason we did not publish this study in one of the international journals. I am sure it would have been accepted in Tubercle or Journal of Infectious Disease. But a much greater regret is that owing to premature death of Col. Kalra and unexplained reluctance on the part of other colleagues from Department of Microbiology, I could not peruse this very interesting study of great relevance to our country any further. However four papers were published on this study[39-42].

Needless to mention Tuberculosis of the Central Nervous remained a subject of clinical studies throughout my professional career and resulted in a number of publications. It may be worth quoting from a book – Infections of the Nervous System (eds.) PGE Kennedy and R.D. Johnson, Butterworth 1987, in which R. Kocen writing on Tuberculosis of the Nervous System stated, "In more recent years, the major contributions on both pathology and the varied clinical menifestations of tuberculosis of the brain and spinal cord have come from workers in India, in particular Dastur,

Tandon and Wadia". *[More of this subject later]*. These studies not just satisfied the scientific curiosity, or the ego to publish but actually improved our understanding of the disease of great interest to the country and laid the foundations for better diagnosis and treatment later adopted by others elsewhere in the world.

Studies on CSF Pathways & Neuroimaging

At the time of starting neurosurgery at KGMC Lucknow the only neuroimaging techniques generally available for diagnosis of intracranial lesions were Pneumoencephalography, Ventriculography and Angiography. Under the best of circumstances these were cumbersome, painful and at times even risky. In addition the images obtained, even with standard radiological equipment and in expert hands, were often of poor quality and difficult to interpret. The situation was worse for us. We did not have the state of art radiological equipment and no trained neuroradiologist. While at Lucknow I had to carry out all the diagnostic procedures myself with the able assistance of Dr. S.K. Ghosh, a recently qualified radiologist (MD Radiology), graciously assigned to me by Prof. B.N. Lall, HOD of Radiology & Radiotherapy. Under the circumstances we faced an unexpected diagnostic dilemma. A number of patients mostly adults presenting with raised ICP without any focal deficits and no intracranial space occupying lesion revealed by the above investigations but only dilated ventricular system forced us to label them as communicating hydrocephalus*.

In absence of the commercially available shunts (Pudenz or Holter) these patients were treated with ventriculo-peritoneal shunts using the red rubber tubes (Ryle's tube). The results were generally unsatisfactory. I suspected that our diagnosis was not correct since I had not seen identical patients in such frequency either at Oslo or Montreal. I wrote to Dr. Kristiansen and to Dr. Chandy for advice. Both agreed that there must be some problem of inadequate imaging. We realized that with the available facilities the pneumo-encephalograhpy or ventriculography we were not able to visualise the complete CSF pathways, specially the fourth ventricle. This was confirmed when on autopsy of one such patient we found a tumour in the posterior fossa which we had not suspected following the above investigations. We reviewed a paper by JWD Bull on Positive Contrast Ventriculography, published in Acta Radiol and another from Madras in 1960 by Menon *et.al*[43] and decided to utilise this technique, fully conscious of the possibility of deleterious effects of myodil on ventricular ependyma or delayed spinal arachnoiditis. It may be mentioned that at that time very few centres used this procedure, not only in India but also abroad. Neither at Oslo or MNI this was utilised. We decided to study a series of such patients in whom PEG studies had failed or were considered too risky for an already very sick patient. We standardised the technique utilizing fluoroscopic screen to follow the dynamics of the flow of contrast. Not surprisingly this improved our diagnostic capabilities but our earlier so-called "Communicating Hydrocephalus in Adults" disappeared![44]. We further modified the techniques at AIIMS and published another paper based on a larger series of cases[45].

*Hydrocephalus-dilatation of the ventricular system due to disturbance of CSF flow dynamics. It is called obstructive hydrocephalus when there is obstruction to outflow from the ventricles and communicative hydrocephalus when the CSF absorption is defective.

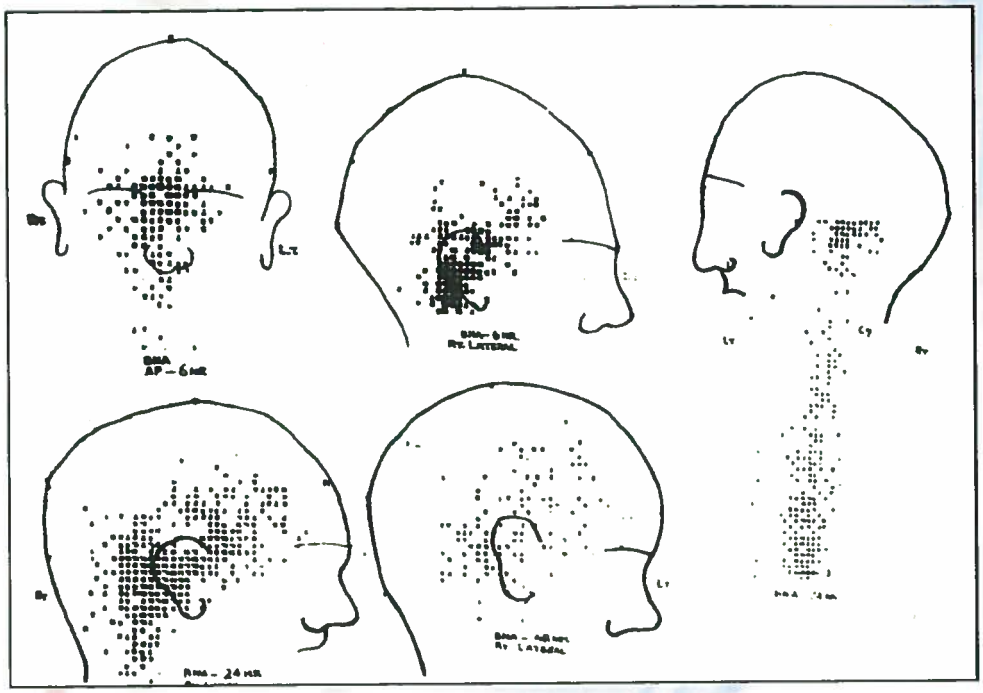


Fig.3: Isotope (RIHSA) cisternography: Visualising CSF Pathways in a patient with tubercular meningitis showing multiple blocks.

Another lesson we learnt was from a young boy with raised ICP whose positive contrast ventriculography revealed a pan-ventricular hydrocephalus due to obliteration of the foramina of Luschka & Magnedie – the openings in fourth ventricle through which CSF exits from the ventricular system. I deroofed the fourth ventricle surgically to allow the CSF to flow out in to the subarachnoid space from where it is absorbed. After a brief period of improvement the child died. I could not explain the outcome till it dawned on me that while I had relieved the ventricular obstruction I had no knowledge of the state of this child's subarachnoid space where most of the CSF is absorbed. The question remained unanswered till we were introduced to Isotope Cisternography, a technique developed by Di Chiro in 1964 and demonstrated to us by Franz Glasauer who visited our Department from Buffalo, USA. With some difficulty and personal contact with scientists at BARC we were able to get Radio Iodine Labelled Human Serum Albumin (RIHSA) and in the meanwhile we had managed to get a reasonable scanner under a grant from Swedish International Development Agency (SIDA). We were the first in India to introduce this technique which was still not commonly used abroad. We published a series of papers between 1972 and 1974[46-49].

These studies besides helping us in diagnosis of a variety of pathologies affecting the cranio-spinal axis provided invaluable knowledge about the pathophysiology of post meningitic (tubercular) hydrocephalus a very common sequlae of TBM seen in many of our patients. Thus in all cases of tuberculous meningitis with symptoms or signs of raised intracranial pressure or hydrocephalus a definite obstruction in the CSF pathways could be established. The site of obstruction in the CSF pathways could be single or multiple and varied from case to case. Such information regarding dynamics of CSF flow and absorption could not be obtained by any other diagnostic procedure then available. These studies not only explained the reason for failure of surgery on the patient mentioned earlier but it also helped us in planning appropriate treatment of our patients not only of post meningitic hydrocephalus, but also of a variety of developmental anomalies of the CNS –

encephaloceles*1, spinal dysraphism*2, traumatic or spontaneous CSF rhinorrhoea*3, normal pressure hydrocephalus, spinal arachnoiditis*4 etc.

Besides the usefulness of these studies on radio-isotope scanning for pathological lesions involving CSF pathways, new information was gathered regarding CSF flow dynamics under physiological conditions. These brought to our notice some unsolved problems regarding the dynamics of cerebrospinal fluid circulation. I was invited to give a talk at IIT Delhi during an Indo-French Symposium on Fluid Dynamics. During the discussion it became evident that physicists and other experts in the field were unable to explain our observations. On their request I decided to publish this work[50]. It must be acknowledged that these studies could not have been possible without the help from radio-pharmaceutical division of BARC and active collaboration by our Department of Nuclear Medicine. The equipment required for these studies was obtained through a generous grant from Swedish International Developmental Agency (SIDA).

With the advent of modern imaging technologies much of the information can be obtained from CT and or MRI studies.

PL40 Multicentric Study: Epilepsy in India

As is well known both at Oslo and Montreal there was special interest in surgery for epilepsy. Dr. Penfield was the uncrowned king in this field and Dr. Kristiansen who worked with him promoted this field in Oslo. As was usual for me I had read Dr. Penfield's and Dr. Kristiansen's books and some other publications on the subject while I was there. I had observed Dr. Penfield do these operations and assisted Dr. Rasmussen during surgery on several such patients. Montreal was the most renowned centre in this field globally. Both at Lucknow and Delhi I looked after patients with epilepsy and ultimately with the cooperation of Dr. P.C. Gupta, an Assistant Professor in Neurology, we finally managed to initiate surgery for epilepsy at AIIMS. Unfortunately with PCG leaving for US and not getting the necessary support from others in the Department of Neurology we lost the tempo for such activity. However, my personal interest in overall care of epilepsy patients persisted. I rarely referred such patients to neurologists. Besides surgery for temporal lobe epilepsy – a standard procedure, at least in one patient clinically diagnosed by me as focal epilepsy originating in supplementary motor area, confirmed by locally developed implanted electrodes, surgery relieved the patient of his medically intractable epilepsy. Similarly we surgically treated (later published) first three cases of Rasmussen Syndrome from India and biopsy confirmed a fourth one[51,52].

Isotope Cisternography technique permits the study of CSF flow dynamics.
*1Encephalocele-Herniation (protrusion) of the brain outside the skull through a developmental defect.
*2Spinal Dysraphism- Developmental defect in the vertebral column
*3CSF Rhinorrhoea- Leaking of CSF in to the nose through a developmental or traumatic defect in the base of the skull.
*4Spinal Arachnoiditis-Glueing together of meninqnges (membranes) covering the spinal cord usually, following an infection.

Prof. Baldev Singh, alongwith Drs. K.S. Mani (NIMHANS, Bangalore), Anil Desai (KEM, Bombay), T.K. Ghosh (Bangur Institute, Calcutta), B. Ramamurthi (Institute of Neurology, Madras) were awarded a major PL 40 grant along with Samuel Trufant and Earl E. Walker from USA, to study hospital referred patients in various predetermined geographical areas in India for comparison of etiology, type of epilepsy, socio-economic status, cultural and emotional factors and response to therapy. By the time the scheme was approved Prof. Baldev Singh had already retired from his position as Professor of Neurology. He, therefore, indicated that he would not accept to participate in this study unless I and Prof. S.N. Pathak, his successor in the Department of Neurology, would agree to share full responsibility for the conduct of the study, enrolling all patients fulfilling the predetermined criteria for diagnosis of epilepsy under our care. We started registering patients from November/December 1969 till June 1972 to permit a minimum of two years follow-up of the last patient enrolled. A total of 600 patients were registered at our centre. The five centres together studied 3439 patients with a follow-up of 78.2% for two years and 71.2% for four years. This was the first multicentric study we participated in. The preparation of the common research protocol, developed with the help of Prof. Walker was in itself a strenuous but a great learning exercise. In an era when use of computers had not yet entered biomedical research in the country the protocol was designed to be fully computerised to answer a large list of predetermined questions. A very detailed history, including family history and standard neurological examination was jointly supervised by three of us (BS, SNP, PNT) in a special OPD organised for this purpose. The research associates collected details on socio-economic aspects. Every patient was submitted to a battery of psychological test (IQ, PQ and DQ), X-ray skull and EEG were the only routine investigations. Every patient was jointly examined by Dr. Baldev Singh, Dr. Pathak (till 1975), Dr. Virmani (later) and myself. Each record was personally scrutinized. Prof. Walker on his annual visits to India randomly cross checked the entries in the data- sheets. Biostatistics division of ICMR supervised by Dr. A.D. Taskar computerized the data. An annual report, based on hundreds of computer generated data sheets, was submitted yearly. At the completion of the study a joint report of the five centres was to be prepared. The Biostatistics division of ICMR generated literally thousands of computer print outs comparing and contrasting data from the five centres. However, while each centre produced its individual report a comprehensive, multicentric report was not prepared for several years. Prof. V. Ramalingaswami, after taking over as DGICMR, embarrassed by the failure to get the joint report finalised by the five Principal Investigators, requested me (as a co-investigator of the Delhi Centre) to undertake this responsibility. On one hand my hands were full of the rapidly increasing clinical work load, the teaching and training responsibilities, the preoccupation with administrative requirements of planning and supervising the establishment of the Neurosciences Centre, on the other I was concerned that the Principal Investigators may consider this as stealing their credit. I was also familiar with magnitude of the task having been involved (alongwith Dr. Baldev Singh) in preparing the annual and final reports of the Delhi Centre. I discussed all this with Rama and expressed my reluctance to take up this responsibility. Rama was not going to take a no for an answer. He had already thought of his action plan. He told me that he had nominated me for a Jawaharlal Nehru Fellowship which would permit me to be relieved of my routine duties. I was left with little choice. The honour associated with this Fellowship and in addition handsome (by then prevailing standards) honorarium for two years was tempting enough. I had another condition that it must be ensured

that the five PIs were agreeable to this arrangement and the final report will be published as a Monograph edited by me. Soon after the Nehru Fellowship was announced, in addition to my clinical and teaching responsibilities I handed over all other time consuming duties to Dr. Banerji. Thus during 1984-85 I managed to wade through the voluminous data with the assistance of Basant Misra who had just completed his M.Ch. and ultimately produced a decent monograph "Epilepsy in India" published by ICMR. However, its publication was unduly delayed till 1989, just prior to the International Epilepsy Conference held at New Delhi. Fred Andermann, my friend from MNI, who was already a renowned epileptologist, found this report to be an unique contribution in the field. Prof. Earl Walker on receipt of a copy of the monograph wrote, "This study which Dr. Tandon has written up so well is truly an epic, which I hope will stimulate further investigations into the causes and treatment of seizures". In addition to the valuable information on effect of epilepsy on students, work status, personality adjustment, social relationship, and intellectual functions in our socio-cultural environment the most important knowledge gained was in respect to therapeutic response to the first line anti-epileptic drugs. Majority of patients were treated with phenobarbitone and diphenylhydantion either alone or in combination. Mysoline, carbamezapine and diamox were used occasionally, but not as primary drugs of choice. On this regime at the end of second year approximately half the patients (51.6%) were seizure free, less than one third (29.4%) improved, and 19% unchanged or worse. The corresponding figures at the end of the 4th year follow-up were 64.2, 21.1 and 14.7 percent. Needless to say this was a rewarding experience in planning, executing and analysing a very large multicentric study. It taught me many lessons concerning multicentric clinical research. In addition to the monograph[53,54] several other papers were also published based on our own data[55-58]. I was invited to give a talk on the subject at the 25th International Conference on Epilepsy, Lisbon in 2003.

Subarachnoid Haemorrhage & Intracranial Aneurysms*

Subarachnoid haemorrhage (SAH) due to intracranial aneurysms was one of the common clinical conditions encountered in neurosurgical practice in Oslo (and for that matter in Scandinavia itself) Figs. 4a, 4b and 4c. There were many unanswered questions about the pathophysiology and therapy of this condition. In fact in early sixties and seventies it was a hot topic of research in Europe and US. Dr. Kristiansen was particularly interested in exploring the etiopathogenesis of the vasospasm so commonly associated with SAH. During my couple of months stay in Oslo in 1960, on way back home from Montreal, he told me that the next World Congress of Neurological Surgery was to be held in Copenhagen in 1961 and he would like a joint paper to be presented by us. After some thoughts I suggested that on the basis of the clinical and autopsy records available we could prepare a paper on,"Preoperative and Post-operative circulatory disturbances in cases of ruptured intracranial aneurysms as studied by angiography and autopsy".

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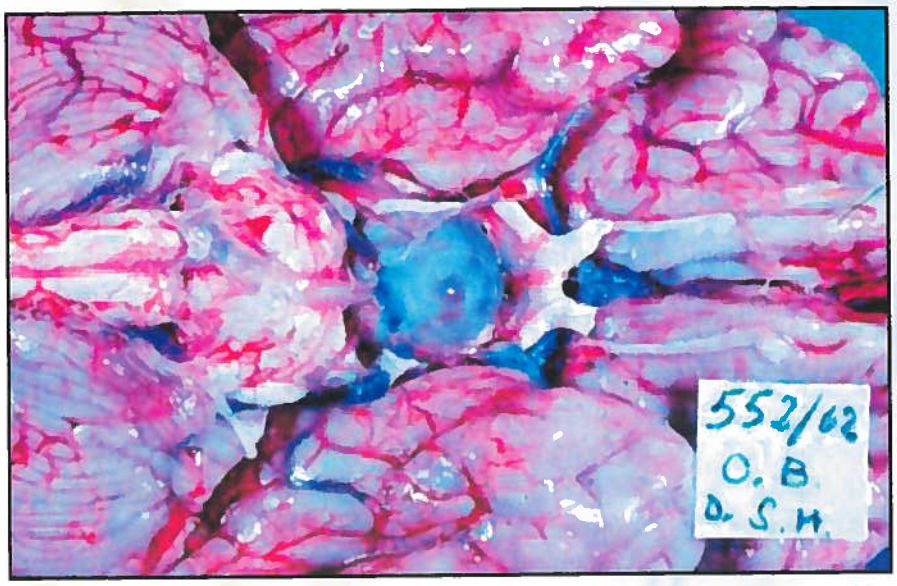
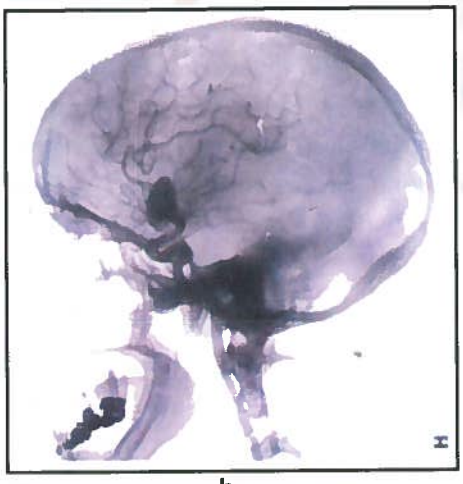
*Subarachnoid Haemorrhagic- Bleeding over the surface of the brain, in the potential space between the coverings of the brain (piameter and arachnoid)

*Aneurym-baloon like localised dilatation of an artery supplying the brain.



a

4 (a) : Autopsy specimen showing a large aneurysm at the basilar artery



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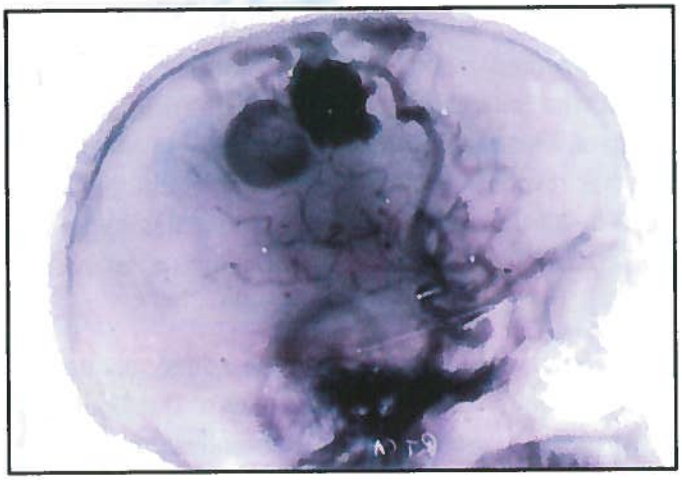


c

4 (b):Carotid angiogram showing aneurysm at carotid Bifurcation; 4 (c): Carotid angiogram showing an anterior-venous malformation

He fully approved of the topic and during my brief stay in Oslo. I collected the necessary data, briefly reviewed the literature and prepared a draft paper. It was later edited and presented by Prof. Kristiansen at the Congress even though he very much wanted me to present it. I was already in India and there was no way I could afford to attend the Congress. This study was published in the Proceedings of World Congress of Neurological Surgery, Copenhagen 1961]. On the basis of the data I had collected for this paper another paper was published in 1964[59].

Back home there were many other more important disease entities one had to deal with. For the time being I lost interest in SAH. As a matter of fact both Dr. Chandy and Dr. Ramamurthi had reported, "the low incidence of intracranial aneurysm as a cause of SAH in India". The latter initially wrote a paper on the subject in Neurology India in 1965 and another in Journal of Neurosurgery in 1970[60,61]. Similarly Mathai and Chandy in an analysis of over 10,000 admissions in the Departments

of Neurology and Neurosurgery at CMC Vellore during a 15 year period found only 47 SAH cases among whom there were 10 AVMs & 7 ruptured aneurysms[62].

In the early seventies, a relatively higher incidence of aneurysms was reported by Sambasivan from Trivandrum, who challenged the prevailing "myth" of low incidence of these lesions. Following discussions with Drs. Ramamurthi & Sambasivan we formulated a multicentric collaborative study and submitted it to ICMR for funding. We planned the study to assess the magnitude of the problem employing standardised methodology. In order to supplement the clinical study it was decided to simultaneously carry out a pathological study on random autopsies, to look for the incidence of aneurysms, as also the incidence of anomalies of the Circle of Willis and severity of atherosclerosis, predisposing factors postulated to be responsible for aneurysms. Clinical study was carried out at all the six centres Bombay, Calcutta, Chandigarh, Delhi, Madras and Trivandrum, but the pathological study was carried out only at Chandigarh and Delhi, between 1972-75*. Following submission of this proposal there was inordinate delay in its sanction by ICMR. One day I took the 'courage' to see Prof. P N Wahi, Director General, ICMR, to enquire about the fate of our proposal. He sarcastically said-"you neurologists and neurosurgeons think you are the only one who are interested in research. The Council has to consider diverse disciplines". I promptly rejoiced to say, "Sir, are you complaining or complementing us!" He readily complemented us and the proposal was sanctioned within a few days. I was the coordinator of the study. As with the Epilepsy project after completion of the project the final report was inordinately delayed since the data, which could be easily computerized, was not forthcoming from different centres. Thus it became another responsibility for me to complete during my Nehru Fellowship. It was ultimately published in 1987 by ICMR as a monograph "Epidemiological Study on Subarachnoid Haemorrhage in India" (1972-75). In its preface I summarised the findings as follows:

"The report shows clearly that the commonly accepted predisposing factors for development of a saccular aneurysm such an anomalies of the Circle of Willis, media defects at the junctional areas and atherosclerosis were found as frequently in Indian subjects, as reported from other parts of the world. The clinical study revealed that once the diagnosis of subarachnoid haemorrhage was suspected and the patients were fully investigated the frequency of intracranial aneurysms was much higher than was believed hitherto, though still not as high as reported from the West and Japan. The relative frequency of intracranial aneurysms and arterio-venous (AV) malformations in the present series was similar to that reported from other parts of the World".

Once this knowledge spread the number of patients with subarachnoid haemorrhage, and hence with aneurysms as its etiology, referred to neurology/neurosurgery departments all over the country, rapidly increased. It may be mentioned that visit by Hans Pia and E. Grote in 1978 from Germany on our request rapidly categorized use of microneurosurgery for surgery of these lesions.

*There lies an interesting tale. There was a photographer – a sikh gentleman in the Department of Surgery at KGMC. When I enquired from my colleagues about his competence and availability to help me in my clinical research, I was promptly told not to expect anything from him. I nevertheless approached him and he was not only helpful but produced reasonably good photographs for me. I later realized that this was the usual alibi of my colleagues, not only against him but other workers in the Department, for their reluctance to publish papers.

The team visited Bombay and Calcutta besides Delhi for hands-on training. For the sake of record, it may be pointed out that in a limited way we had already initiated microneurosurgery in our department. Visit by a team led by Charles Drake in 1984 further aroused interest in the field. There are several neurosurgical departments in the country including one at AIIMS who now treat more than 150-200 aneurysms a year, while between 1972-75 the six centres reported only 180 aneurysms among 661 patients with SAH[63-65].

Meningo-Encephaloceles*

While at Lucknow I saw an unusual number of cases of a developmental defect of the cranium in infants and young children – meningo-encephaloceles – too many in a short time compared to the four years of my stay at Oslo and Montreal (Fig.5). Even more remarkable was the fact that contrary to the reports in the Textbooks from the West there was a proportionately larger number of these in the frontal region as opposed to the occipital region. I kept a record of these patients alongwith their photographs*. When I came to Delhi I carried their records with me. One day I showed this to Dr. Banerji who had not seen such cases in his years at CMC, Vellore, undoubtedly the busiest Neurosurgical service in the country then. He prompted me to publish this material, which I did [66].

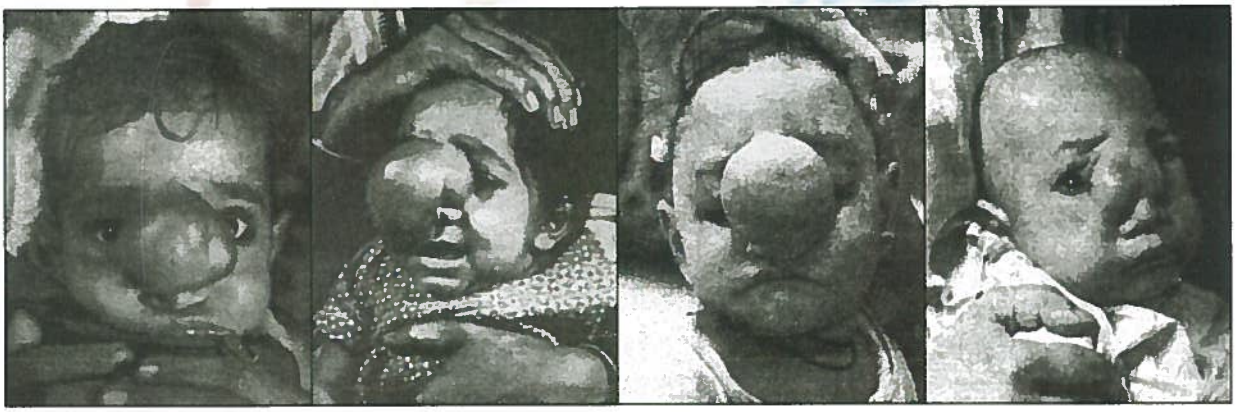


Fig. 5:Meningoencephalocele: Different presentations

Over the years we had many more such patients at AIIMS. During my visit to Oslo I showed those pictures to Prof. Kristiansen and gave a talk on the subject. He had not seen so many such type of patients in his long experience. He advised me to prepare a detailed paper for Acta Neurologica Scandinavica. By then we had surgically treated 40 such patients[67]. Review of the largest series of 187 cases of Encephaloceles from the most renowned Paediatric Neurosurgery Centre in USA revealed that there were only 21 cases of Fronto-nasal lesions[68]. In contrast among our 40 cases there were 11 such patients. Our series included some very rare entities like cranium bifidum occultum, congenital absence of skull and scalp, multiple lesions etc[69]. A similar disproportionate incidence of anteriorly situated lesions, was report by Charas Suwanvela from Thailand in 1965 and Acqaviva et al (1965) from Casablanca[70], while these constituted only a small percentage of cases reported by De Vet (1957)[71], Davis & Alexander (1959)[72] and Fisher et al (1952)[73] from Europe & USA.

*Meningo-encephalocele- a protusion (herniation) of the meninges (the membranes covering the brain) and brain through a developmental defect in the skull.

Detailed study of these patients not only permitted me to describe their pathological anatomy, propose a more precise classification and enunciates factors to be kept in mind while planning their management, on the basis of this knowledge a rational surgical approach to these lesions was described.

One of the major shortcomings of surgical treatment of the fronto-nasal variety of these defects was the post-operative appearance of the face due to deformed nose. Nearly a decade later Tessier, a plastic surgeon from France, described techniques for plastic reconstruction of cranio-facial deformalities. In consultation with our Plastic Surgeon Inder Dhawan we planned to utilise this type of surgery, initially on a patient with residual deformity following excision of a fronto-nasal encephalocele earlier. We later adopted and modified the procedure to carry out one stage operation for total correction of the defects alongwith excision of the encephalocele. It may be mentioned that this was a very major surgery lasting 10-12 hours on a small baby. However, our joint effort was successful. This being the first such surgery in the country. This was presented to the Neurological Society and subsequently published[74,75].

Over the years we successfully operated upon many such patients along with Prof. Dhawan, Dr. A.K. Mahapatra, who initially as a Senior Resident, assisted in this surgery after my retirement progressively acquired enough expertise to undertake such operations without the help of a plastic surgeon. He has by now accumulated unparalleled experience of such surgeries.

Delineation of Clinical Profile of Neurological Disorders in India

Soon after setting up the Neurosurgical Service in India it became clear that the clinical profile of neurological disorders I encountered in practice was quite different from what I saw at Oslo or Montreal. To delineate this was an obvious subject for research. There was only limited information available since there were so few Neurologists and Neurosurgeons in the country at that time, most of them having been trained abroad, overburdened with the professional workload with limited facilities at their disposal and having been in service for hardly a decade before me. In addition, in absence of complementary services in Neurology, Neuroradiology, Neuropathology etc the pioneer Neurosurgeons had to take care of these disciplines also. It way my good fortune that my training abroad covered most of these disciplines to some extent in addition to Neurosurgery. At Lucknow, though one of the faculty member – Dr. N.N. Gupta, on the basis of a limited exposure to 'Neuro-psychiatry' under a Fellowship abroad, claimed to be a specialist in the field, there was no regular Neurology service. It therefore fell to my lot, like other pioneer Neurosurgeons in the country to study the neurological disease profile. Thus a number of my earlier publications dealt with such subjects. These may not be considered high scientific contributions but certainly it was relevant clinical research. It was also not without reason. In order to arouse awareness of the subject and to spread knowledge about the possible scope of our discipline it was important to publish a lot of our work in national journals.

In contrast to the West we saw lot more patients with infective disorders brain abscess, meningitis, neurotuberculosis than neurodegenerative ones like multiple sclerosis, Parkinson's disease,

dementias etc. Even the manifestations or course of disease of some of the neurological disorders for example multiple sclerosis, motor neuron disease, developmental disorders were often at variance with what was seen abroad. It was for this reason that some of our earlier publications dealt with subjects like Etiological Survey of Paraplegia, Acute Transverse Myelopathy, Cauda Equina Syndrome due to lumbar disc prolapse, Post-meningitic spinal arachnoiditis or for that matter Infantile Tremor Syndrome or Meningo-encephalocele etc. Our publications also dealt with investigations based on allied disciplines like neuro-otology, neuroradiology, electrophysiology, radio-isotope studies or neuropathology. These studies were carried out in collaboration with colleagues from these disciplines.

However, a major area of research publications, not surprisingly, dealt with Infective Disorders of the CNS, specially Tuberculosis and its sequelae, brain abscesses, parasitic infections – conditions which we encountered so frequently and in which our colleagues in the West were not interested.

Neurotuberculosis

My interest in Tuberculosis was of long standing. I was suspected to be suffering from Tuberculous meningitis while I was a house-surgeon (1951), though it proved to be a drug modified pyogenic meningitis. Later in 1954 I worked as an Assistant Surgeon with a WHO Team at SJTB Hospital, Delhi, for one year. I had an opportunity to update my knowledge of the disease. It was during my stay at Oslo that after the World Congress of Neurosurgery at Brussels I learnt from Prof. Kristiansen about a much appreciated presentation of a very large series of intracranial tuberculomas by Dr. Ramamurthi. This brought to light the high incidence of this lesion in India. However, during my stay in Oslo and Montreal I had seen only one case of calcified tuberculoma of the brain.

On return to India, it was not surprising, that I started to encounter the varied manifestations of CNS tuberculosis – both cranial and spinal. This prompted a detailed review of the literature specially the clinico-pathological reports on CNS lesions, published in recent years from Madras, Vellore, Bombay and Calcutta. Armed with this knowledge it was obvious that this being a real problem in India deserved special attention for research.

As mentioned earlier, an etiological survey of paraplegia – 286 cases, admitted to Department of Medicine and Neurosurgical Unit at our hospital in Lucknow between January 1960 to October 1963 revealed tuberculosis as the commonest etiology accounting for (18% cases). These included 41 cases of Pott's disease*, more than one third of whom (39%) requiring surgery. In addition there were 5 cases of post-meningitic arachnoiditis, one case each of tubercular myelitis and intradural tubercular granulations. The important lesson learnt was that a sizeable percentage of these cases could be successfully treated medically if diagnosed early. Until this time there were only three series of over 150 cases of paraplegia reported in Indian literature. It may be mentioned that syphilitic lesions were still seen (16 cases) while there were only 5 patients with multiple sclerosis.

*Pott's Disease : Tuberculosis of the spine with or without paraplegia

Surprisingly we saw 35 cases (13.25%) of Acute Transverse myelitis among these 266 patients. This was an unexpected observation and hence was subject of a publication (referred to earlier).

Review of the literature had indicated that the prognosis of post meningitic spinal arachnoiditis was poor[76,77]. However, there was hardly any information about the treatment. Based on some experimental studies about the effect of cortisone on pia-arachnoid adhesions [78,79], we decided to treat our patients with intrathecal corticosteroids along with standard antitubercular therapy. Surprising recovery of some of our patients prompted a brief report on the subjects[80].

Another unusual manifestation of the disease encountered by us was superior orbital fissure syndrome* of tubercular etiology. We could find no such report in the literature hence we published our experience[81]. A well known sequelae of tuberculosis meningitis is hydrocephalus. I saw a large number of such children with my friend P.C. Bajpai at Lucknow. The V-A/VP shunts were still not available in the country. The results of medical therapy were dismal. In absence of any accepted regime we tried intraventricular corticosteroids along with standard chemotherapy in the hope of resolving adhesions in the CSF pathways. Regrettably unlike patients with post-meningitic arachnoiditis mentioned earlier, this combined regime failed to provide any relief from hydrocephalus. This study was thus discontinued.

Based on our accumulating experience with patients of tuberculous meningitis (TBM) and extensive survey of the literature indicated that enough is not known about the patho-physiology of CSF dynamics in this condition. The standard neuro-diagnostic techniques then available – PEG, VEG, Myelography, Angiography – were unable to provide the desired information. Hence, when we could introduce RIHSA scanning. This became one of important group of patients to be investigated. This was the first such study in the World literature (see earlier).

During a visit to AIIMS Dr. J.D. Spillane, a neurologist from UK, met me and discussed some disorders of the CNS of particular interest to us. On his return home he wrote to me requesting contributions for his proposed book on Tropical Neurology and specially wanted me to write a Chapter on CNS Tuberculosis. I was somewhat surprised to receive this request from a Neurologist – not to his counterparts in the Institute, who were his hosts. However, I requested Prof. Pathak to be a co-author. This Chapter was a detailed review on the subject based on our experience on Tuberculous Meningitis, Intracranial Tuberculomas and Spinal Tuberculosis. It included studies reported from other tropical countries on the subject. It was ultimately published in 1973 by the Oxford University Press[82].

*Superior orbital-fissure Infective lesion, in this case tubercular, affecting the tissues behind the eye ball resulting in protrusion of the eye and paralysis of the nerves supplying it.

This episode taught me another lesson as to how a neurologist from abroad visited some of the developing countries, developed contacts with colleagues there, requested them to contribute to the book he edited, on a broad field of Tropical Neurology – something we should done on our own. This became the first book on the subject for many years. It was not till 1999 that J.S. Chopra from PGI Chandigarh published a much more comprehensive Neurology in Tropics (B.I. Churchill Livingstone, New Delhi). On his request I contributed a chapter for this book [83].This knowledge was further elaborated in 1980s when the first CT Scan in the country was installed at AIIMS[84,85].

Over the years we continued to gather experience with a variety of tubercular lesions. Already in 1972 alongwith C.C. Kapila, D.K. Dastur, B. Singh and myself we edited a monograph based on the Proceedings of a National Symposium published by the Indian Academy of Medical Sciences (now called National Academy). I had contributed three papers to this volume. Yet another paper on the subject was published along with Dr. H.D. Tandon, Prof. of Pathology, who had earlier contributed on Abdominal Tuberculosis[86].

Few years later I received a request from Editors (PJ Vinken & GW Bruyn) of the Handbook of Clinical Neurology to contribute a Chapter on Tuberculous Meningitis to their "encyclopaedic effort" spread over 43 volumes. Once again it was a bit surprising that they selected a neurosurgeon like me for this task. It was easy for me to accept this request as we had already accumulated enough literature and clinical material on the subject. However, it may be pointed out that this was before the days of routine use of computers and internet. One had to manually search the volumes of Excerpta Medica to collect the references. To make "note cards" in the long hand following personally rummaging through the library for the desired papers and studying the papers in the library. To find time for all this from busy surgical and other professional duties, teaching responsibilities and other administrative chores was, to say the least, not an easy affair. To finally sit down to write the manuscript of over 70 printed pages, arrange for the illustrations and edit and re-edit the typed copies of it (not like now with the use of a computer) was painstakingly time consuming. Let me add to this, collating the references in the text and arranging these in the end took a week's time of my cooperative wife. There were no research assistant or post docs to do this job, which of course was far beyond the capabilities of the ever helpful office secretary Mr. C.P. Kumar. But miracle of miracles the task was completed within the permitted dateline. It was greatly appreciated by the Editors[87].

When I mentioned this to my friends at MNI during a visit to Montreal, I was pleased to learn that invitation to contribute to this monumental Handbook was considered a signal that "you have arrived at the international academic scene". I was requested to update this chapter a decade later, which I did along with Ravi Bhatia and Sneh Bhargava[88].

Intracranial Tuberculomas

As mentioned earlier there were already a number of studies on the subject from various parts of the country. One unusual observation at our centre was much lower incidence of tuberculomas among over 1000 cases of intracranial space occupying lesions (ICSOL) or brain tumours (only 4.4%)[89] compared to reports from Madars[90] and Bombay (20%)[91-92], and Calcutta and Vellore (8%)[93-94]. This discrepancy persisted even when we had over 2000 ICSOLS surgically treated. We, however, failed to find an explanation for this considering that the incidence of tuberculous meningitis and for that matter pulmonary tuberculosis was apparently no different from the other centers in India (Fig. 6).

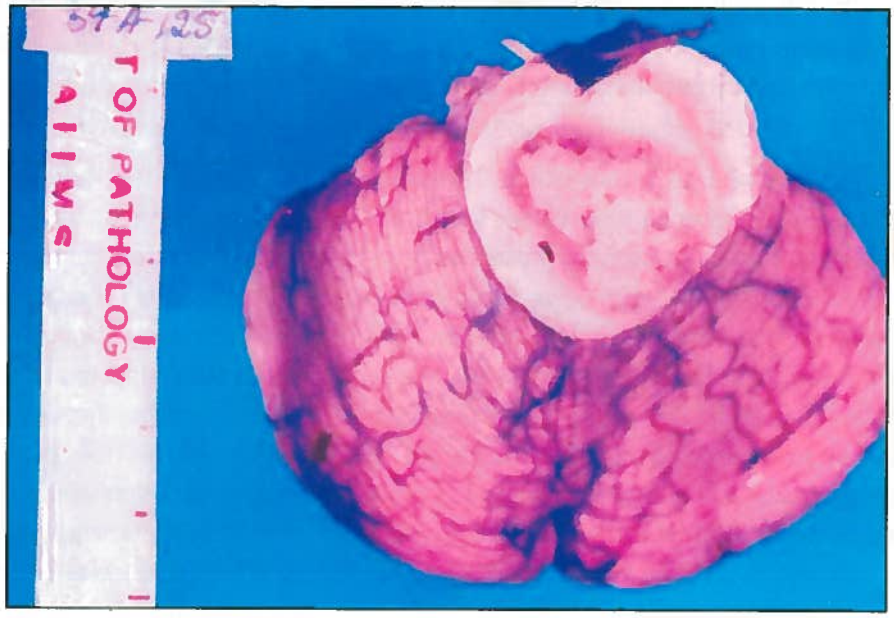


Fig. 6: Autopsy specimen of a tuberculoma of the brain stem

Till the advent of CT scan it was not possible to diagnose intracranial tuberculomas pre-operatively with any degree of confidence. Hence the standard treatment for these lesions was surgical excision as practiced by all of us[82,87,89,90,94]. Following the availability of CT scan 1978, we decided to initiate a study to determine diagnostic characteristics of tuberculomas as compared to other ICSOL. We described the image morphology of various types of intracranial tuberculomas which made it possible to arrive at a reasonably reliable diagnosis of these lesions non-invasively. This permitted us to try medical therapy instead of inevitable surgical excision. We were able to establish that unless vision or life was threatened by the advanced state of the disease there was full justification to try medical therapy. Surgery was thus limited to patients who failed to respond to medical treatment. The lesion resolved in nearly 80-90 percent of such patients thus escaping surgery. It has become the standard therapeutic regime for intracranial tuberculomas*[95].

There was a detailed publication dealing with the effect of medical treatment on intracranial tuberculomas after we had gained experience with a larger number of such patients. In this series of

*The ultimate gains from this research far outweigh the impact factor or citations received for such a publication. I would consider this an invaluable result of any research, an outstanding example of translation research.

50 patients 45 patients recovered fully, three failed to respond, one developed liquefaction in a solid tuberculoma requiring surgery and one died[96]. Mention may be made of another related publication which dealt with management of uncommon inflammatory lesions including tubercular ones in the depth of the brain relatively inaccessible for surgery[97]. Our accumulating experience on the subject was presented at the International Congress of Neurology 1989 and later published[98]. In later part of 1970s we were requested by editors of Operative Neurosurgical Techniques to contribute a chapter on the subject[99]. Similarly I contributed a chapter on surgery for intracranial Tuberculous Infection in Text Book of Operative Neurosurgery (eds) R. Ramamurthy *et. al.*[100]; an interesting, unusual manifestation of a tuberculoma in the brain stem was published in Oral Surgery[101]. A series of cases of focal epilepsy with a small, solitary, cortical or subcortical, less than 5 mm, ring or disc lesion on CT were investigated. Among these 25 cases atleast one proved to be tubercular in nature on biopsy, 11 responded to antitubercular drugs. While these "microlesions" could be of varied etilogy, e.g. cysticercosis, pyogenic abscess, focal encephalitis, the possibility of a tubercular etiology needs to be kept in mind[102]. A chapter on the subject was contributed to API Textbook of Medicine"[103]. An invited talk in a symposium on Tropical Neurology organised by the Tropical and Geographical Neurology Research Group of World Federation of Neurology and the Royal Society, London was later published[104]. (Fig. 7a,b) For other publications on the subject see references[105-108]. **[Our study of CNS Tuberculosis was abstracted in Infectious Disease Digest.]**

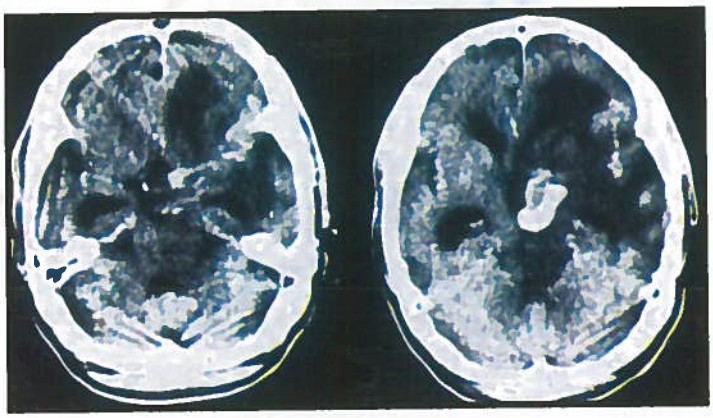
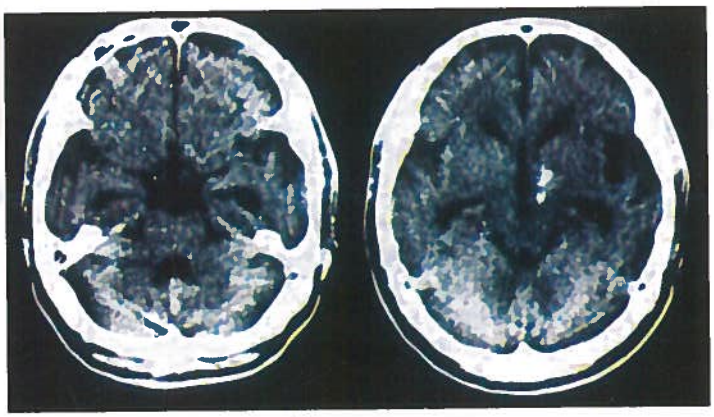


Fig.7 (a) CT Scan: Showing a brain tuberculoma in right thalamus



7 (b) CT Scan: Following medical therapy-resorption of tuberculoma

In addition to CNS Tuberculosis, two other infective disorders were subject of our studies:

Brain Abscess

Not surprisingly brain abscesses constituted a significant percentage of infective disorders of CNS in our country. Among our first little over 1000 cases of surgically treated ICSOLs, brain abscesses accounted for 85 cases as compared to only 44 tuberculomas. While the incidence of brain abscess had markedly gone down in the West delayed treatments of middle ear infection among our poor population was responsible for this high incidence of a pre-eminently preventable life threatening disease.

Prior to my joining at Lucknow most of these patients were treated by my teachers (Profs. Misra & Bhatia) in ENT Department as a part of surgery for middle ear infection. They had achieved creditable results even though from neurosurgical standards it would not be considered an ideal approach. To my surprise and satisfaction soon after my joining the college they voluntarily referred these patients to me. It was the same situation at AIIMS.

Between April 1965 and May 1972 we treated 55 patients with brain abscess of diverse etiology. Though middle ear infection constituted the most common cause, in this short series we had 12 cases of brain abscess secondary to cyanotic heart disease* (nearly, 22 percent of all cases). As compared to some of the series reported from the West, we hardly saw a patient with an abscess secondary to sinusitis and only 3 of pulmonary (lung) origin, the two most common causes in the West. The overall result of surgery – a mortality of nearly one third was a cause of concern. Delayed reference of the patients for treatment, high incidence of cyanotic heart disease as its etiology, and associated meningitis were found to be responsible for the poor result. At this time there was no consensus regarding the best way of treatment – repeated aspirations, primary excision or secondary excision. On the basis of a critical analysis of our experience, we were able to establish a management protocol and reduce the mortality significantly[109].

It may be mentioned that following the availability of CT, not only the diagnosis became easier but the therapy could be planned better. This resulted in dramatic improvement in both mortality and morbidity as reported by Ravi Bhatia in our larger series of 220 patients which was presented at the World Congress of Neurosurgery held at New Delhi in 1989.

Brain Abscess in Cyanotic Heart Disease: Till a detailed study by Taussig et al in 1971 on long term observations on the Blalock – Taussig Operation: Common Complications reported in Johns Hopkins Medical Journal, most reports on the subject were based on a few cases only. In 1966, I reported successful treatment of two such patients seen at Lucknow[110].This was the first such report from the country. Later the collective experience from our Department at AIIMS – 18 cases treated over a period of 12 years was published[111].In addition we reported successful treatment of a very rare case of Thalamic Abscess* in a child with cyanotic heart disease. There was no such case reported in the literature till then[112].

*Thalamus is a structure situated in the depth of the brain and represents the relay station of all sensory input to the brain.

Cerebral Cysticercosis**

Another common infective disorder, still prevalent in the country, as in other developing countries in Asia, South America and Mexico, was cerebral cysticercosis. Its manifestations, as also its management, had changed in recent years. This became a subject of some of our studies. Recognising our interest in this disease I was invited to organise a symposium during the First International Congress of IBRO held at Lausanne in 1982. This prompted me to review the world literature, analyse our own clinical material and high light the geographical differences in its incidence and manifestations. Around the same time I was invited to write a review on the subject by the Editor of Neurosurgical Review.

It became obvious that the same parasite, for reasons not well understood produced different clinico-pathological manifestations in different parts of the World. This in turn required different diagnostic and therapeutic strategies. We documented its varied manifestations as seen in our population and proposed appropriate therapy. This resulted in the following publications[113-115].

Neurotraumma – Head Injury

The day I joined AIIMS, by sheer coincidence, Dr. Susheela Nayyar, then Minister of Health and President of the Institute, happened to be there to inaugurate a National Seminar on Trachoma. She personally welcomed me to the Institute and remarked, "Now no one will die of head-injury untreated". She had recently lost her brother due to head-injury. In all hospitals these patients were admitted to general surgery departments and after much delay referred to the neurosurgeon even if one happened to be on the staff of the institution. Mõst neurosurgeons, often working alone, with limited number of beds and support staff gladly permitted this arrangement. Inspite of these limitations, because of my abiding interest in the subject, contrary to the practice in most institutions, we at AIIMS decided to admit all such patients directly in our service. Situated as we were on the periphery of the city at that time, initially we didn't have overwhelming demand for such service, yet it provided us valuable opportunity to undertake well planned studies. We did not have any ICU facilities (This infact proved to be a blessing in disguise – see later) but based on my experience at Oslo, and the studies carried out there, we planned a management strategy which included use of cerebral angiography (This was before CT era) for early diagnosis (as advocated in our Monograph mentioned earlier) in place of exploratory burr holes (wood-pecker surgery) – a common practice those days. This was one of the high-light commented in the Lancet Annotation on our Monograph. "Masterly inactivity" or "Wait and Watch" policy till clinical evidence of deterioration occurred was considered ideal management strategy at that time. Following our study we advocated active intervention for any patient who following injury failed to show continuous improvement or manifested any evidence of secondary regression. It may be mentioned that 1960s witnessed a flurry of research activity on this subject globally. Dissatisfied by the results of current

**Cysticercus is the larval stage of tape worms that invade the brain and forms multiple cysts scattered all over it.

management strategies as advocated by acclaimed neurotraumatologists like Brock (1950)[116], Gurdjian and Webster (1958)[117], Rowbotham (1964)[118] a variety of new therapeutic regimes were experimented upon. These included intracranial pressure-monitoring, use of measures to reduce it like IV manitol, urea, intratracheal intubation and artificial ventilation, corticosteroids, barbiturates, either singly or in combination. In some centres abroad a combination of these practices became mandatory for the management of unconscious patients (GCS 8 or below).

However, based on critical evaluation of the current literature and our earlier experience we chose not to blindly adopt these practices often called "aggressive treatment" as advocated by Gordon (1971)[119], Becker *et.al.* 1977[120], Marshall *et.al.* 1979[121]. As a matter of fact already in 1969 at the International Congress of Neurosurgery at New York, we questioned the value of routine use of corticosteroids then generally advocated or of ICP monitoring and artificial ventilation. Our paper was selected for televising on the closed circuit network of the Conference Hotel.

Realising that even within the country there was no consensus on the management of severe head – injury Dr. Ramamurthi and I decided to undertake a prospective study under the aegis of ICMR, based on a pre-determined mutually acceptable protocol capable of computerised analysis. Unfortunately owing to premature retirement of Dr. Ramamurthi the study could not be completed at Madras but during a 20 month period from 1977 to 1979 we prospectively studied 551 cases of head injury admitted to our service at AIIMS. None of our patients was submitted the so-called "aggressive management" practices mentioned above. We elected to establish prompt diagnosis using early angiography and appropriate surgery where indicated – primarily for evacuation of intracranial haematomas. (This was prior to the CT scan era).

Dr. John Jane, a well-renowned Neurotraumatologist from Charlottesville, Virginia, an old friend from Montreal days, during his visit to our Department, was appraised of our overall management strategy for head-injured patients. He looked at some of our records. He remarked that though he personally believed in our strategy – "less is better", he, being part of a multicentric US study has to follow the so-called "aggressive management" referred to above. Since the patients records at both centres were capable of computerised analyses and comparison, it was decided to request the Biometeric Division of NIH to undertake this task. Accordingly, a joint proposal was made to ICMR & National Institute of Health, USA (NIH) for this purpose. After a prolonged bureaucratic wrangle, the proposal was approved. A senior scientist from NIH visited us to carefully scrutinize our records and declared that the format of our clinical records and those of John's had more than 80% similarity and hence could be used for comparative analysis. All our records were photocopied by the US Embassy New Delhi and transferred to NIH. After much delay at the US end a joint paper was published. Its conclusions are summarised below.

There was striking similarity in mortality rates at both centres when comparing patients with least severe head injuries and those with the most severe injuries according to the motor score of the Glasgow Coma Scale (GCS M). However, in the group with an abnormal but purposeful motor-response (GCS M=5), the mortality rate was 12.5% in New Delhi versus 4.8% in Charlottesville ($p<0.01$). The relative absence of prehospital emergency care and delay in admission after head injury in New Delhi and denial of the so called aggressive treatment were cited as two possible

causes for the differences in mortality rates in this subgroup of patients with "moderate" head injuries[122].

A prospective study to confirm these findings could not be carried out even though in a report on Indo-US S&T Collaboration over a Decade brought out by the US Embassy quoted our study as the best example of bilateral co-operation for mutual benefit. The study at least strongly supported the idea that the very costly, high tech ICU care for all patients of head-injury did not confer definite advantage for these patients, this not withstanding its advocacy by many neurosurgeons abroad.

In the meanwhile I had independently analysed the data from our centre in much greater details. Alongwith our cumulated experience on the subject for two decades, I decided to present it as my Presidential Address at the 35th Annual Conference of the Neurological Society. This was published in Neurology India soon after[123].

The detailed analysis provided further evidence to challenge the routine use of the so-called "aggressive" treatment regimes mentioned above.

Faced with continuing reports of high mortality (30 to 50 percent) or even more for patients admitted with GCS of 8 or less, inspite of the use of "aggressive" treatment strategies, a host of investigators began to explore the molecular aspects of head injury in experimental animals. On the basis of these studies a variety of therapies were advocated. A number of compounds like antioxidants, free radical scavengers, Vitamin E and C, Catalase etc proved to minimise the secondary brain damage in the experimental model of head injury. As a matter of fact Larry Marshal in an Editorial in Neurosurgery in 2000 commented, "Future improvement in care of patients with head injury will increasingly be dependent on advances in molecular neurobiology .....". I published a detailed review on the subject[124].

The most surprising fact that emerged from all these experimental studies was that the beneficial effects observed in animal models following therapy based on targeting the molecular abnormalities did not prove to be useful in human subjects. The reason for this variable effect is not yet available.

Faced with this dilemma the National Institute of Neurological Disorders and Stroke (NINDS) USA, sponsored a Workshop to explore the reasons for this paradox. The participants included virtually all "who is who" of neurotrauma research. We were of course not invited. The extensive report of the workshop acknowledged the lack of clinical benefits from any of these therapeutic measure (s) either singly or in combination[125]. It is worth mentioning that our clinical studies had already provided reliable evidence for this[123,124] and yet none of these, including the paper in J. Neurosurgery (1989)[122] was even mentioned[126,127].

Acute subdural haematoma (ASDH) and temporal lobe Lesions (TLL)

One of the unique features of my Oslo study was the availability of detailed clinical notes and 100% autopsy on fatal head injury patients. At that time it was generally accepted that ASDH carried a mortality of 90-95%. I was intrigued by this fact and wanted to find an explanation for this. The meticulous autopsy records provided a clue for a possible explanation. Every single case of ASDH,

succumbing even after prompt "successful" evacuation of the subdural clot, was found to have varying extent of contusion/laceration of the brain. It appeared logical to believe that the cause of death was not the subdural clot – which in majority of cases was not sizeable (often a thin layer). The most common sites of this contusion were the temporal lobe and/or frontal lobe. The contusion was associated with varying degree of oedema, parenchymal haemorrhages/hematoma which predisposed to tentorial herniation*, so frequently observed in the fatal cases.

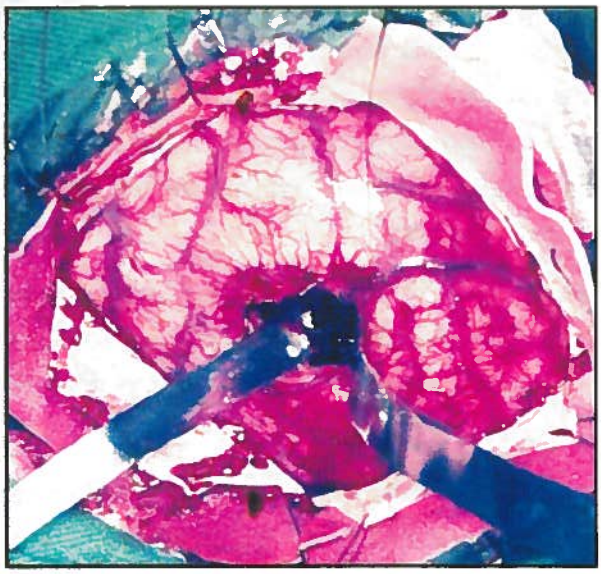
Thus in 1960 we wrote: "A large majority of these cases had a thin layer of subdural blood overlying the damaged brain. This subdural layer is in itself innocuous. The progressive deterioration which may be immediately reversed by operative evacuation of the intracerebral haemorrhage leaves no doubt that these cases deserve the merit of being classified in a separate group". Furthermore, we pointed out that, "from a pathological standpoint it is difficult to draw a clear cut distinction between a lesion which could be called a cerebral contusion with haemorrhage and a real intracerebral haematoma". It occurred to me that the best way to treat such patients was not the commonly practiced (multiple) burr hole evacuation of the subdural blood, but to perform a formal craniotomy to simultaneously evacuate the damaged brain along with any intracerebral haematoma (see later). As in those days unlike most others we routinely used cerebral angiography for diagnosis, it was easy to assess the extent of the subdural clot and the associated parenchymatous pathology. The parenchymatous lesions commonly affected anterior part of the temporal lobe including its pole and under surface and/or the frontal lobe – orbito-frontal (base) and dorsilateral surface. The injury thus, primarily involved non-eloquent parts of the brain the so-called "silent areas", hence its removal was considered justified to save a life. To our surprise such lesions constituted the most common indication for surgery in our large series of severe head injury patients. Reports in the literature did not mention this as a distinct diagnostic category obviously being mistaken for ASDH and treated as such. Textbooks on Head Injuries (Rowbotham 1964[118], Brock 1950[116], Gurdjian & Webster 1958[117] did not mention it. As late as 1970s, our colleagues from India, especially those interested in neurotraumatology reported no such patients in their series of head injury patients.

However, as early as 1942, Courville[128] in a detailed report on pathology of head injury had documented such lesions as traumatic intracerebral haemorrhage. He found contusion of the temporal lobe in 70 percent of the fatal head injuries. Lewin (1966)[129] referred to the focal oedema and contusion of the TL which could be so severe as to cause extensive secondary ischaemic damage of the TL. Leeds *et. al.*(1966)[130] called it, "traumatic encephalomalacia", Botterell in 1973[131] labelled it as "pulped temporal lobe" and Jamieson (1991)[132] gave an even more dramatic label e.g. "exploded temporal lobe". In my Presidential Address to the Neurological Society of India 1985, I summarised our experience with 236 cases of surgically treated TL leisons[123].

*Tentorial Herniation- Skull cavity is divided by rigid membranous (dural) septa- one between the two cerebral hemispheres (Falx) and another between the cerebral hemispheres above and the cerebellum below (tentorium). There is a gap in the tentorium through which the brain stem passes. In case of a mass lesion (haematoma, tumour etc/ above the tentorium part of the cerebral hemsphere (temporal lobe) herniates through. The opening in the tentorium thus compressing the brain stem, the most vital part of the brain which results in coma and threat to life.

For patients with ASDH and associated temporal lobe pathology – a common finding in our cases – we planned a formal fronto – temporal craniotomy, an anterior temporal lobectomy* and section of the tentorial edge to prevent any herniation (Fig.8 a & b). I may add that this strategy was the result of detailed discussions with the other colleagues in the department and was adopted as a policy. Many of our visiting colleagues disbelieved our observations and some even warned us against such surgery predicting that we would end-up with many vegetative individuals. Attempts to treat such patients with large bilateral frontal decompressive craniotomy had not been rewarding.

8 (a) Operative photograph showing contusion of the temporal lobe in a patient with Acute subdural Haematoma



8 (b) Operative photograph showing an intracerebral clot underlying a contusion

There hangs an interesting story about it. We decided that our younger colleague Dr. Brahm Prakash, should present our experience at the Annual Conference of the Neurological Society at Jaipur. For a variety of reasons neither Dr. Banerji nor I could attend this conference. On his return from there Brahm was very unhappy and crest fallen, since not only he was severely criticised but

*Temporal Craniotomy-Cutting open the skull just above the ear and turning it as a trap-door.
Temporal Lobectomy- Removing the damaged part of the temporal lobe of the cerebral hemisphere.

persons like Kalyanaraman who had earlier reported a very large series of head-injured patients from the Madras Neurology Institute claimed not to have seen such cases. On his way back to Madras, Kalyanaraman dropped in my office. We got talking about Brahm's presentation. It so happened that angiograms of all the patients included in Brahm's paper were still with me in the office. I showed those to Kalyanaraman and asked him if he still doubted the entity we were talking about. He was convinced and realised that since exploratory burr-holes and evacuation of any subdural haematoma encountered through these was the standard procedure in their department the incidence and gravity of the concurrent parenchymatous lesions was likely to have been overlooked and not given its due importance.

It is worth mentioning that most neurosurgerons in Europe de Vet 1976 [133], Lanksch et al 1979[134], Vigouroux and Guillermain 1989[135] and Papo *et.al.* 1982)[136] considered surgery on such patients within 24 hours after injury to be futile. A high mortality, nearly 90-100 percent had been earlier reported for cases of post-traumatic intracerebral haematoma operated during first 12-24 hours (Loew & Wustner 1960[137], Tonnis et al 1963[138], Stender and Schulze 1965[139]). Ultimately in 1978, we published our series of 85 cases, 56.7 percent of whom could be saved. Ten out of 22 patients operated upon within 24 hours also survived [Tandon *et.al.* 1978][140]. We, therefore, had no hesitation in advocating early surgery of the type we had practiced for such patients. This was later confirmed in a much smaller series reported by Seelig *et.al.* (1981)[141]. They reported that early surgery specially within 4 hours of injury reduced the mortality to 30 percent. Not only did we succeed in dramatically reducing the mortality for the so called ASDH, but we did not face the high incidence of vegetative state predicted by others. The surviving patients were left with no discernable neurological deficits. It must, however, be acknowledged that our efforts to get a proper psychometric and psychiatric evaluation of such patients did not succeed. It still remains a subject of great research interest[142]. **This paper was abstracted in Neurology, Neurosurgery, Abstracts. It was referred to in their book on Head injury (Eds) Brian Jennett and Graham Teasdale[143], who commented that our description of this entity was one of the best.**

It will be seen that a hypothesis based on observations gathered from systematically conducted autopsy on all fatal cases of head-injured patients prompted the development of a therapeutic strategy. This over a period of a decade and half proved to be successful in bringing down the mortality of so-called "ASDH" from 90-95% to nearly half-approximately 45 percent[142,144].

At the time when this strategy was adopted there was a common belief that early surgery on such patients was doomed to failure and hence contraindicated. This rewarding research was no doubt possible because of the routine practice of cerebral angiography for diagnosis of head injured patients adopted by us (prior to the CT era), instead of the exploratory burr-holes (then generally practiced) and the tradition of autopsy on all hospital admitted fatal cases then prevalent at Oslo. A careful correlation of clinico-pathological data led to the evolution of the novel therapeutic strategy much against the prevailing teaching or practice. This required no big-budget scheme nor the need for high technology facilities, but simply an intuitive leap of logic, there being no previous reference in the literature.

With the availability of CT scan the diagnosis of these lesions became easier and more direct. It may be worth quoting from the last paper published by me on this subject,[144] "it was pointed out that acute subdural hematoma is a well-entrenched nosological entity implying subdural collection of blood following acute head-injury." Pathologically, it is usually associated with or, for that matter, it is secondary to cerebral contusion and laceration. Based on cumulated experience, clinical and pathological studies, it is proposed that, for too long the neurosurgeons have put emphasis on the clot rather than the totality of the pathological anatomy and they have focussed their therapeutic strategy on removal of the accumulated blood, unmindful of the associated parenchymtous lesion. Not surprisingly, such attempts have been associated with a very high mortality. On the basis of nearly four decades of our experience and critical review of the literature, evidence has been provided that to reduce the mortality of this condition, it is necessary to adopt a strategy, not only to evacuate the clot but to comprehensively deal with the associated parenchymatous lesions and the cascade of secondary insult to the underlying brain. It is gratifying to note that our observations as early as 1960 and repeatedly reinforced over the years ultimately found confirmation in recent publications [Phuenpatham *et.al.*1993[145], Wilberger *et.al.*1991[146], Crooks 1991[147], Yanaka *et.al.* 1993[148]]. Purists may not like to accept it as scientific research since it was not based on a randomized double-blind control trial. For us it was a most rewarding exercise resulting in saving lots of lives. Recently in place of our surgical approach for this condition alternate strategy of decompressive craniotomy has been advocated Sinha *et.al.*[149] Nevertheless, comparative results in its favour are not available. Nevertheless, even this new approach is based on the recognition of the fact that removal of the subdural blood alone is not enough to treat this condition.

Depressed Fracture of the Skull & Growing Fracture Skull (Cranio-Cerebral Erosion)*

According to the traditional teaching and prevalent practice a fracture of the skull depressed below the normal surface of the skull, greater than 5 mm, was to be surgically elevated (Fig. 9). It was believed that pressure on the underlying brain by the depressed fragment was responsible for progressive, persistent neurological deficit and that it predisposes to post– traumatic epilepsy later in life. During a visit to our ward at Ulleval Hospital, Oslo by Dr. Lamar Roberts from Montreal, who questioned why the depressed skull fracture of a patient was not elevated, Dr. Kristiansen commented the that he did not believe in either of the above contentions. He pointed out that the associated neurological deficit was not caused by pressure from the depressed fragment but was the result of the force of the initial injury itself and the post-traumatic epilepsy, if it developed, was the result of damage to the underlying brain at the time of the impact. Both these sequelae could not be eliminated by surgical elevation of the depressed fragment. These observations, contrary to the prevailing views, were no doubt based on his personal experience. I wondered if there was any objective evidence to support this view. A review of the literature failed to provide the answer. I then proposed to Dr. Kristiansen to review and follow-up such patients treated in the Department earlier. He readily encouraged the idea. As mentioned earlier the meticulously maintained hospital records could be retrieved and as long as the individual was still in Norway, he/she could be contacted using the national register. I, therefore, started collecting the necessary data.

*Depressed Fracture Skull-is one in which the fractured segment of the skull is driven in to press on the brain.
Growing Fracture-is when the separation between the edges of a linear fracture progressive increase over time.

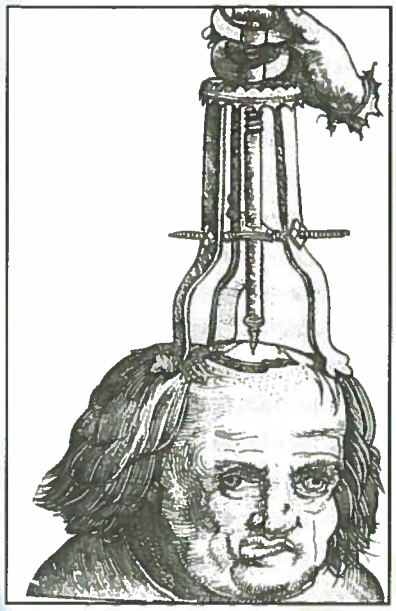


Fig. 9: A historical picture showing surgery for elevation of depressed fracture

The initial review confirmed Dr. Kristiansen's contentions as was recorded in our 1960 monograph. Among 21 patients with depressed fracture skull which were not elevated only 1 developed post traumatic epilepsy. But I did not think that the number of cases studied were enough to merit a separate publication at that time. In any case, I was too preoccupied with the larger task of completing the monograph mentioned earlier. However, I kept the data with me with a view to collect some more information later. Several years later, back home, I decided to present a paper on the subject at the Annual Conference of the Neurological Society of India held at Vellore. Most senior neurosurgeons including Dr. Chandy, Dr. Ramamurthi etc were present. Discussion following my presentation elicited a great deal of scepticism at the proposed expression of futility of surgery. We in our Department at AIIMS continued to follow this practice and collected further support for this idea, which was published later[150]. Except, when required for cosmetic purposes we did not elevate depressed fractures. At the same time we looked for corroborative evidence among patients with focal epilepsy. This extended data was presented at the National Seminar on Epilepsy held at Bangalore in 1975[151].To the best of my knowledge, elevation of closed depressed fracture except for cosmetic purpose is no more practiced by most neurosurgeons.

Growing Fracture Skull: Cranio-Cerebral Erosion

Linear fracture of the skull with more than a few millimetre of separation of its edges along with a tear of the underlying dura in infants and young children had been known to enlarge with passage of time. I had seen a couple of such cases treated at Oslo and Montreal. It had been variously called, "Growing Fracture Skull", "Meningocerebral Cicatrix", "Leptomeningeal Cyst" while Dr. Penfield gave it the designation of "Cranio-Cerebral Erosion" (Fig. 10 a & b). He hypothesised that in absence of dural cover the pulsating brain against the fracture edges resulted in the widening of the bony defect – the so called "Growing fracture".

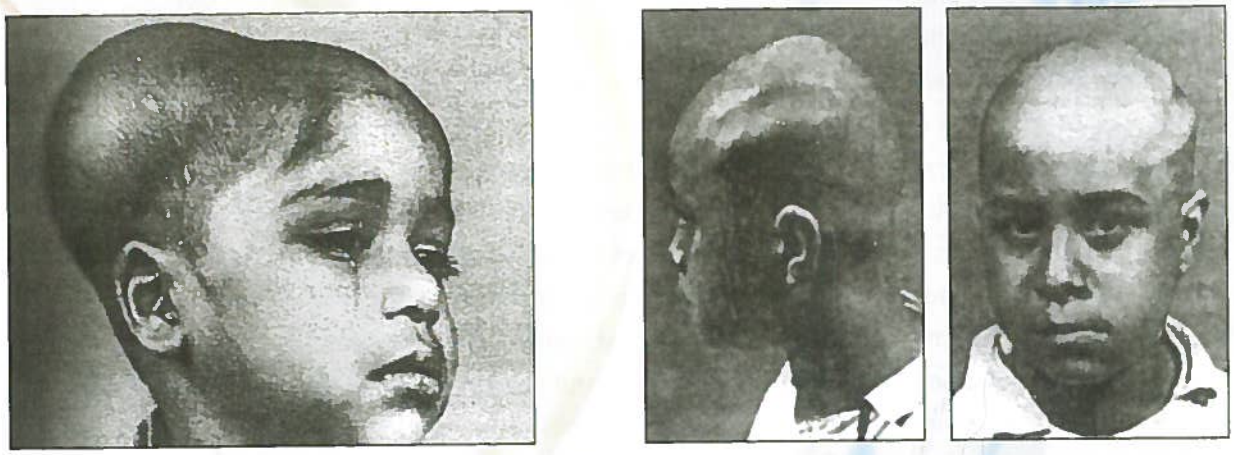


Fig. 10 (a) Clinical photographs of patients with cranio-cerebral Erosion

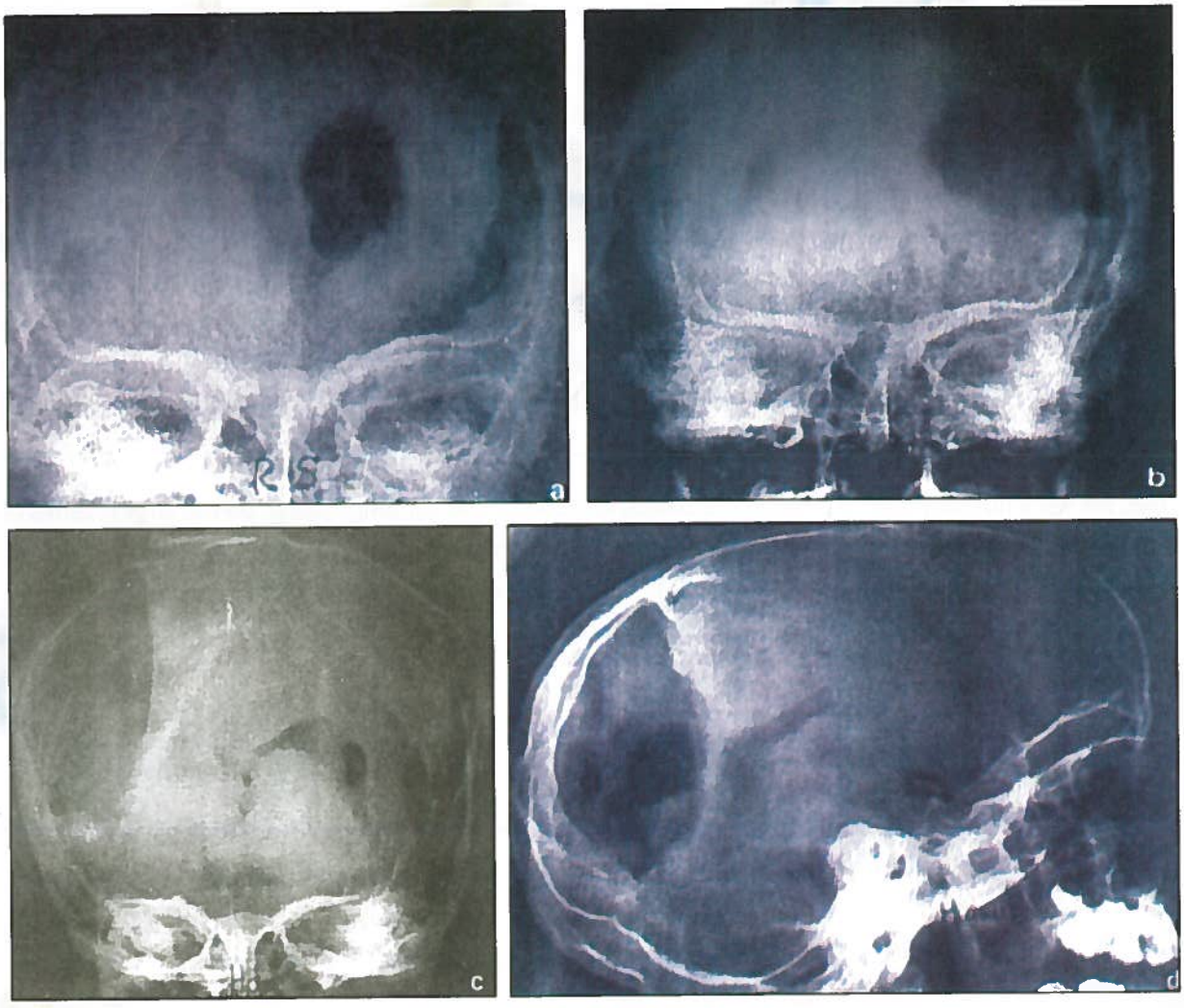


Fig. 10 (b) X-rays showing growing fracture skull

Most reports on the subject were based on a few cases only. For reasons explained later we tended to see many more such patients and hence it became the subject of careful study. We observed that most of these patients were below 2-3 years of age at the time of injury, which was generally a

result of fall from a height, often from a roof top. Following the injury there was a soft swelling - ? Blood? CSF or both – overlying the fracture which if, left untreated resulted in, the gap between the fracture edges to increase. At times it was associated with a cystic swelling overlying the defect. Depending upon the location of the fracture a number of these children would develop focal epilepsy and some even a progressively increasing neurological deficit. At surgery for the repair of the skull defect we found the scalloping of the bone along the edges of the fracture. The dural defect was wider than the bone defect and the underlying brain, devoid of its meningeal coverings, was gliotic and often cystic and covered with fibrous cicatrix at the edges. The ipsilateral lateral ventricle invariably migrated towards the defect. Surgery thus, required a major operation consisting of removal of damaged brain, duraplasty for repair of the dural defect and cranioplasty for the skull defect and not just repair of the skull defect as was often practiced. It may be mentioned that there was a paucity of reports on surgical management of such patients except in respect to techniques for cranioplasty. Not only did we see an unusually large number of such patients we saw some bizarre variants of the same. We first published this in 1967[152-154].

Most neurosurgeons had limited experience with the condition and some even questioned the need for surgery. Doubts were expressed about the progressive nature of the defect particularly about the progressive brain damage. We therefore decided to study the pathology of the lesion – no such detailed report being available in the literature. It became obvious that some of pathological descriptions – like "lepto-meningeal cyst", "meningocerebral cicatrix" – were obviously not based on proper pathological studies. As mentioned above the meningeal covering over the affected brain was invariably missing and a cyst was not an essential feature of the lesion. In addition we were able to provide unequivocal evidence of progressive injury to the skull as well as the underlying brain indicating the need for early, prophylactic surgery. It may be mentioned that this view was initially contested by Dr. B. Ramamurthy, till we provided the evidence based on our pathological studies[155-156].

Thus, we were not only able to provide the clinical features of this condition based on the largest series of this condition reported so far, defined it pathogenesis and the pathology but our studies established the rationale for surgical management. The same principles could then be applied when we had to deal with some "grotesque" variants of this condition[157].

BRAIN TUMOURS – NEUROONCOLOGY

An important component of a neurosurgeon's professional work is to deal with patients with brain tumours which not only threaten life but are potential source of morbidity. Harvey Cushing[158], often called father of modern neurosurgery, who was responsible for making surgery for brain tumours safe and respectable commented, "The surgery of brain tumours may be liked, without being trivial, to a form of major sport which is played against an invisible but utterly relentless antagonist quick to take advantage of every misplay and faulty move". The management of such patients required a team work involving neurologists, neurosurgeons, neuroradiologist, neuropathologists, neuroanaesthetist, radiotherapist etc. The few centres existing in the country in early 1960s, when I

initiated this service at Lucknow, by and large had limited facilities and expertise as regards the ancilliary support. The rising expectations of the patients forced most of us to undertake this responsibility fully conscious of our limitations. My mentor from Oslo – Prof. Kristiansen – following a visit to Lucknow in 1964, in a talk delivered soon after at MNI – Montreal commented, "If I had not seen with my own eyes Prakash's patients alive I would not believe that neurosurgery was possible with such limited facilities".

During the interview for the post of Professor of Neurosurgery at AIIMS, I was asked about the mortality rate of patients of brain tumours operated upon by me at Lucknow. With all honesty I said, "I am sorry it is still high around 25 percent". Dr. Baldev Singh who was an expert in the selection committee remarked, "Dr. Tandon should be congratulated for this". As a matter of fact in an Editorial in 1970[159], I had pointed out the following:

"Large series of cases reported from all over the world illustrate a very high immediate postoperative mortality of 20-40% (Grant 1956[160]; Tonis & Walter 1959[161]; Ley and Co-workers 1962[162]; Chandra and co-workers, 1957[163]; Jelsma and Bucy 1967[164]; Kunicki, Szwagyzyk and Ladzinska 1969[165])." I mention all this to provide a back-drop of the circumstances and challenges faced by anyone attempting to establish an acceptable neurosurgical service in those days. The efforts required for this weighed heavily against pursuing any research.

Delivering the Fourth Institute Day Oration at Madras Neurology Institute in November 1975, where I summarised our results of surgery on 1029 patients with intercranial space occupying lesions, tumorous or tumour-like (ICSOL)*, I had to humbly comment, "Unlike those who can afford the best, let us ask what best we can achieve with what we have". By this time our surgical mortality for several tumours had come down significantly, notwithstanding the very advanced stage of the disease of our patients. Thus, the overall mortality for tumours, in and around the sella (Pituitary Adenoma, Craniophanyngioma etc) was already below 5 percent[89].

Thus, in the early years our efforts were primarily directed towards improving our surgical results reduce mortality and minimise morbidity. But this is not to say that we lost sight of contributing to new knowledge whenever an opportunity arose. Initially we concentrated on reporting unusual or uncommon entities, like Trigeminal Neurofibromas in Adolescents(1969)[166]; Chondrosarcoma of the meninges (1972)[167]; Subarachnoid ependymal cyst (1972)[168]; Aneurysmal bone cyst of the spine (1973)[169]; Craniopharyngiomas treated by surgery and radiotherapy (1974)[170]; Tumours in and around sella,1974[171]; Third Ventricular Chromophobe Adenoma with normal adenohypophysis (1976)[172]; Craniopharyngioma in childhood (1976)[173]; Multiple Primary Tumours of the Brain (1977)[174]. As we accumulated data on larger series of specific tumours like gliomas, pituitary adenomas, craniopharyngioma etc. we carried out more in depth studies of some specific aspects of these tumours not in common knowledge. Before describing some of these detailed studies let me point out that even case reports, often not considered as research, require a serious intellectual effort. One must be knowledgeable enough to recognise the uniqueness of the observation, paucity of literature on the subject, efforts required to search the literature and then to highlight the lessons learnt from it. Only then it is accepted for publication in a reputed journal.

*Besides me these patients were operated upon by my colleagues Drs. A.K. Banerji, Ravi Bhatia and Brahm Prakash.

*Gliomas of the Brain

These constitute the most common type of brain tumours. Since 1884 when first such tumour was submitted to surgery, voluminous literature had accumulated on the subject regarding its classification, histopathology, clinical manifestations and treatment. Yet till today a cure is not in sight. Taking advantage of the vast clinical material at our disposal, our efforts were directed to find ways and means of reducing the mortality and morbidity and to prolong useful life utilizing the knowledge gained from critical analysis of our experience. Thus our research publications were focussed on these aspects.

The Therapeutic Approaches

More than hundred years after the Godlee's first operation in 1884 for such lesions, the utility and extent of surgery for supratentorial hemispherical gliomas remained controversial. Majority of neurosurgeons in England considered biopsy and radiotherapy as the best treatment, while both my mentors Dr. Kristiansen and Dr. Elvidge believed in adequate internal decompression. The British surgeons felt that the decompressive surgery did not provide any worthwhile long term survival. On the other hand taking into consideration the socio-cultural and economic milieu in the country we felt that prolonging life even for a year or so was worth the efforts. In addition most of our patients presented in the advanced stage of the disease with markedly elevated intracranial pressure threatening vision and life. The mortality and morbidity associated with biopsy, alone under these circumstances was reported to be very high. Furthermore, the then available diagnostic procedures – PEG, VEG, Angiography, EEG or even recently introduced Isotope Encephalometry – failed to provide reliable preoperative diagnosis of the nature of the tumour, specially to differentiate neoplastic lesions from the curable infective intracranial space occupying lesions like tuberculomas, chronic brain abscess etc so common in our population.

We from the beginning, therefore, practiced radical surgical decompression of these tumours as the most desirable therapy alongwith post-operative radiotherapy. In 1981 at the National Seminar on Neurooncology, sponsored by WHO & NIMHANS held at Bangalore, I presented our collective experience from AIIMS on "Surgical Decompression of Supratentorial Gliomas" and provided evidence of its usefulness in a large series of unselected patients[175].

In my presentation at this National Seminar I conceded that, "The management of gliomas is a matter of philosophy and not a matter of science. There are no statistics which can be considered sound in terms of pure science." And, "Therefore this philosophy has to be guided by your conscience and your milieu more than anything else". This sentiment was partly echoed in my presentation at the 2nd Conference on Biology of Tumours held at London in 1984. (See later).

At the same Sminar at NIMHANS Dr. Ramamurthi remarked, "The future of neuro-oncology in India is closely linked to a more positive approach towards the treatment of gliomas". And further, "While technical advances help in surgery of benign lesions, the malignant ones still elude solution". At the same

*Gliomas are the intrinsic tumours of the brain involving the brain parenchyma. They are the most common brain tumours, and more than 50% are malignant.

Seminar I had also presented our views on "Classification of CNS Tumours: The surgical point of view". Notwithstanding a number of classifications of brain tumours provided by Bailey & Cushing (1926)[176], Penfield (1931)[177] Kernohan & Sayre (1952)[178], Zulch (1965)[179], Russel & Rubinstein (1971)[180], and WHO, there was no consensus specially in respect to grading of gliomas. This made comparison of the result of treatment between different series rather difficult. This was best illustrated by my interaction with my friend Prof. Ansgar Torvik, a distinguished neuropathologist of Norway. During one of my visits to Oslo I had taken a few dozen randomly selected histopathology slides of gliomas with me for his opinion. It became obvious that he graded many of our cases to be of higher malignancy than the grading ascribed by our neuropathologists Dr. Subimal Roy and his colleagues.

In 1983 during my visit to UK under INSA-Royal Society exchange programme I was invited to deliver a talk at the Neurology Centre, Newcastle General Hospital, Newcastle. I chose to present our experience on 'Surgery for Supratentorial Gliomas'. I was already informed by my friend Robin Sen Gupta, a faculty member there, about the prevailing attitude on the subject in that Centre. Prof. Henkinson, Chief of Neurosurgery, who chaired the lecture, had personally invited the Prof. of Neurology and his colleagues for this event. At the end, after a spirited discussion, Prof. Henkinson not only congratulated me but pointedly requested the neurologists, "that at least now you would have been convinced of the role and utility of surgery for these unfortunate patients and in future will refer them to us for proper management". In 1984, I was invited to give a talk on the subject at the Second International Symposium on Biology of Brain Tumours, held at London on the occasion of the Centenary of the Godlee's Operation. The title of my presentation was, "Radical" surgical decompression of supratentorial gliomas: Do the results justify the operation? In addition to providing enough proof justifying our approach based on one of the largest series reported (500 patients) of such patients, I also briefly referred to our results on such tumours involving the dominant hemisphere*, something most neurosurgeons, even outside UK, considered contraindication for surgery. These 500 patients constituted a consecutive series of patients with supratentorial gliomas treated in our Department between January 1973 and June 1982. 237 of these (47.4%) involved the right hemisphere, 222 (44.4%) the left (i.e. dominant) hemisphere, and the remaining affected other sites mainly midline. The overall surgical mortality was 14.34% for the right and 13.96% for the left hemisphere tumours.

The overwhelming response I received from the participants reassured me of the value of our contribution. This study was later published in a book based on the selected presentations made at the Symposium[181].

Surgery for Gliomas Involving Speech Areas

As mentioned above there was a general reluctance, even strong opposition, to operate upon gliomas of the dominant hemisphere, even if there was no evidence of speech impairment preoperatively. Based on

*Dominant Hemisphere: The cerebrum is divided in to two halves, the right and the left. The half that has the speech centre, usually the left one has right handed persons, is called dominant.

the experience gained under Dr. Elvidge at MNI, we had rarely denied surgery to such patients. Surprisingly even Dr. Elvidge did not publish his experience on the subject, though he used to say that the location of the tumour was not a contraindication for surgery for gliomas _____ "my finger can go where a tumour can go". A "Medlar" search for publications on the subject for the previous six years in 1993, failed to reveal any sizeable series on the subject. We, therefore, decided to present a detailed account of our experience with surgery on gliomas involving speech centre at a Conference of the Academia Eurasiana Neurochirugica held at Budapest. This was later published in Acta Neurochirurgica[182] (Figs 11-13).

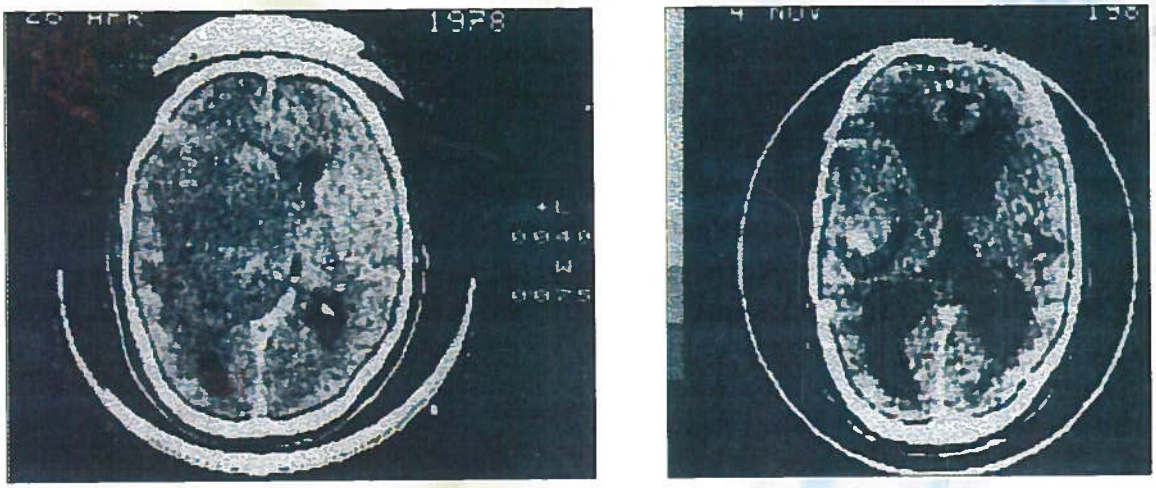


Fig. 11 (a) CT Scan. Glioma left hemisphere, April 1978; Fig. 11 (b) CT Scan. Post operative November 1980

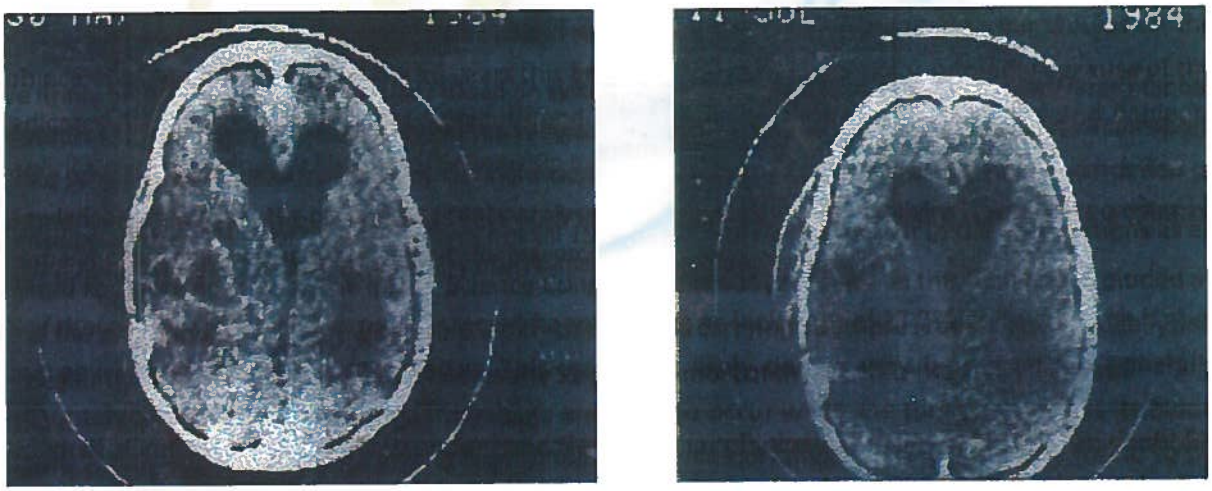


Fig. 12 (a)CT Scan Preoperative. Glioma left hemisphere 30.5.1984; Fig. 12 (b) CT Scan Post operative: No tumour seen 11 July 1984

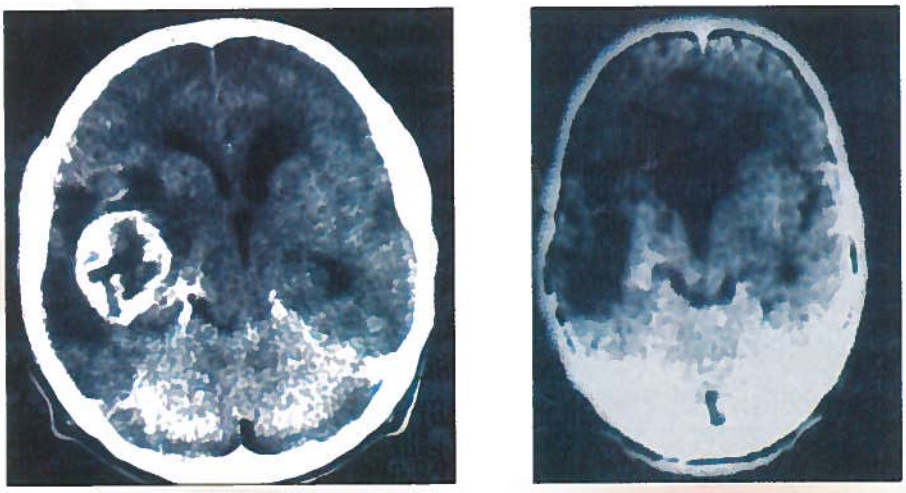


Fig. 13 (a) CT Scan. Pre-operative Glioma left hemisphere; Fig. 13 (b) CT Scan post operative Tumour radically removed.

It may be worth quoting some part this paper which highlights our contribution:

"With all limitations, "radical" surgical removal of supratentorial hemisphere gliomas is now generally recognised as a desirable approach for their management. However, even amongst those who advocate surgery reservations are expressed regarding tumours involving the speech areas, for fear of producing or exacerbating an existing speech defect". Thus, Pastzor (1980)[183] while advocating surgery for gliomas stated, "we do not operate when the central region, the area of Broca and Wernicke Centre*, or when deep midline structures are infiltrated". Garfield (1986)[184] commented that, "traditionally, severe and distressing focal deficit, such as aphasia has been regarded as a contraindication to attempts at tumour removal".

Among the 100 patients with tumours in and around the speech areas reported by us in the publication referred to above there were 58 with preoperative evidence of speech defect. Postoperatively 65% of them improved and only 15% deteriorated with regard to their speech function. "Even amongst those with deterioration, there was none who developed complete aphasia. Most of them had reasonable degree of comprehension and expression to be able to carry on with at least the activities of daily living"[182]. We therefore, concluded that, "As long as surgical reduction of the tumour mass remains a desirable goal of management of gliomas, the authors do not find any justification for denying it to those with lesions producing a speech defect". It may be mentioned that for a variety of reasons it is seldom possible to totally excise a glioma. It is a matter of great satisfaction for us that even Garfield who seriously doubted our views on the subject, initially, in his contribution on Gliomas in the well known British publication, "Northfield's Surgery of the Nervous System" edited by I.D. Muller (1987) made the following observation.

"However, the more traditional view that surgery in itself will not lessen deficits such as aphasia impairment of speech and hemiplegia (paralysis of one half of the boy) has been challenged (Tandon 1984)**, and if tumour removal by suction is restricted to the obvious tumour tissue even severe deficits may improve". Our observations found further support from our later studies.[182]

At the London Conference (referred to above), the session I was to present my paper was Chaired by a renowned British neurosurgeon Mr. Garfield. He obviously was one of those who felt that surgery of gliomas was of little use. While introducing me in the usual formal customary manner, as I stood up to go to deliver my talk, he requested me to wait and added a somewhat sarcastic comment. The conference was held in a building attached to the famous London zoo-The Regent Park. He mentioned that when we go for our lunch in the Park's cafeteria we pass the cages of baboons. He proceeded to add that one characteristic of baboons is that they can be taught to do anything but can't be taught not to do

*Broca and Wernicke centres are areas of the brain in the left hemisphere responsible for speech.

**1984 refers to the year when I presented our study at the London Conference mentioned earlier. Garfield had presided over the session in which our paper was presented. This was later published in 1986[181].

something. He then gave me the floor. The obvious implication of this rather typical British satire was meant to indicate our inability not to operate on patients on gliomas. After thanking the Chair for his other complementary comments about me I opened my presentation by mentioning that "baboons may have their own reasons for the behaviour and added that medicine, is still not a perfect science and its practice must take into account the socio-cultural, economic milieu during its planning. I then proceeded with my formal presentation. Just as the paper was opened for questions and comments, I was amazed at the number of hands that went up associated with a cacophony by a number of other participants claiming "I am another baboon" notwithstanding that the session was to break for proverbial British "elevenses" Coffee break, the questions and many complementary comments continued at the cost of the break. I have seldom received so many laudatory remark after a 20 minute paper at an International conference. Mr. Garfield personally came over to thank me profusely and mentioned that the "baboon" comment was just meant to provoke the audience. The best complement I received was by an Indian origin scientist-Dr. Patel who was working in the prestigious institution-The Queen's Square- who said. "This lecture today has made me proud to be an Indian".

We firmly believe that our contributions based on systematically collected observations on a very large number of unfortunate patients, who trusted their lives to us, though not part of a protocol based randomised controlled study, provided us valuable insights to reduce the morbidity and mortality of gliomas and advanced frontiers of knowledge. In a sense in the course of our daily professional duties we utilised the living laboratories created by the malaficence of nature as an opportunity for research.

Recurrence of Supratentorial Gliomas

Inspite of all recent advances in biomedical sciences a cure for gliomas has not been found. Recurrence is the most common cause of death in a patient treated for a glioma. Hence one of the aims of treating such patients is to minimise and / or delay recurrence not only to prolong life, but to provide a useful life with least possible morbidity. Unfortunately our clinical experience posed a number of questions like incidence of recurrence vis a vis the extent of tumour removal at surgery, correlation of recurrence free survival time with the tumour grade, the pathological features of recurrent tumour, the scope of reoperation for the recurrent tumour. Surprisingly, there was a paucity of information on these issues in the literature. This prompted us to study a series of 200 randomly selected patients of supratentorial gliomas followed up for more than one year (for 1 to 3 years. for 118 cases, 3 to 5 years. for 46 cases and more than 5 years for 36 cases) after radical surgical decompression and postoperative radiotherapy to answer some of these questions.

The series included 82 cases of astrocytomas, 46 cases of mixed gliomas (oligoastrocytomas), 33 cases of malignant astrocytomas, 31 cases of glioblastomas and 8 cases of oligodendrogliomas. The recent availability of CT Scan made it possible to objectively study the extent of tumour removal, its site and the timing of tumour recurrence. Such a study would not have been possible prior to the CT era[185].

The study confirmed, what was already known that recurrence of the tumour was the cause of death in all

except 2 cases. Recurrence was at the site of the original tumour removal in most patients, spread of the tumour in cranio-spinal axis far removed from its original site was observed only in four patients. However, there were a number of unique findings. As expected, the recurrence was earlier in patients with malignant astrocytomas and glioblastomas as compared to the relatively benign groups (astrocytoma, oligoastrocytoma, oligodendroglioma). But quite surprisingly, for a given patient the course was unpredictable. Thus, recurrence was observed within one and a half years in a histologically very benign looking fibrillary astrocytoma with classical microcystic changes. On the other hand it was delayed for as long as 16 years after operation in a case of malignant astrocytoma and for 6 years in a case of glioblastoma. What is even more remarkable that absence of any residual tumour seen in a post-operative scan does not imply that it will not recur? Residual tumour on the other hand may remain quiescent for several years and then suddenly start to grow. Attempts to correlate the clinical picture, duration of the illness prior to operation, CT appearance, size and extent of tumour failed to provide any significant correlation with recurrence free intervals. This knowledge not available earlier is very relevant for overall management strategy for these patients.

Recurrence is usually characterised by a dedifferentiation of the tumour to a higher grade of malignancy. Based on our experience with reoperation following recurrence on 46 patients, 5 of these twice, a subject on which very limited information was available, we formulated the criteria for selection of patients for reoperation with useful outcome. On the basis of this study we advocated reoperation for recurrence of a glioma for patients with initially relatively benign tumour (astrocytoma, mixed glioma, oligodendroglioma) who have had good quality survival for more than 1 ½ to 2 years, and the recurrence was in an accessible region. We were thus able to provide additional useful survival for one or more years to at least one third of the patients[185]. Following this study Dr. Chitra Sarkar our Distinguished Neuropathologist looked for biological markers and carried out cell kinetic studies in-vitro to answer some of the questions raised by our clinic-pathological studies referred to here. Using latest techniques of molecular biology, genomics and tissue culture they have provided interesting insights on this issue.

SUPRATENTORIAL GLIOMAS AND EPILEPTIC SEIZURES

One of the common clinical manifestations of supratentorial gliomas is epileptic seizures. Nearly 60 percent of these patients suffer from seizures during the course of their illness – sometime as a presenting symptom, and sometime during the preoperative or postoperative period. While there were quite a few papers dealing with occurrence of seizures in different types and grades of tumours, surprisingly, there was a paucity of information regarding the effect of surgical treatment of these tumours on seizures. This information was relevant in deciding to whom and for how long antiepileptic drugs were to be prescribed post-operatively. We, therefore, decided to seek this information among 200 surgically treated patients for whom follow-up information was available for at least one year or more.

We found that epileptic seizures were the only symptom or the initial symptom in nearly half (46.5%) of these patients. The incidence was higher among the relatively slow growing tumours (astrocytomas

75.5%, mixed gliomas 60.8%, oligodendrogliomas 62.5%) as compared to the rapidly growing malignant astrocytoma (54.5%) and glioblastoma (29.0%)[186].

A review of our series challenged many of the commonly held beliefs regarding the diagnostic significance of epileptic seizures in respect to brain tumours.

Among the patients who had history of epileptic seizures preoperatively surgical decompression of the tumour resulted in relief of seizures in the majority. Seizures persisted in only 18 percent following operation. The duration and frequency of seizures preoperatively did not influence the postoperative seizures status. Only a small percentage of patients who did not have history of seizures postoperatively these occurred at the time of recurrence of tumour, often heralding the recurrence, even prior to any other manifestation of recurrence[185].

While primarily concerned with clinico-pathological studies and the result of surgical treatment, some of our investigations were directed to understand the biology of selected tumours. It may, therefore, be mentioned that the opportunities provided by the rich clinical material prompted our pathologists and basic scientists to explore their basic biology. (These studies are not detailed here).

Let me just mention a few of these studies in which we actively participated:

OLIGODENDROGLIAL TUMOURS: AN IMMUNOHISTOCHEMICAL AND ELECTRONMICROSCOPIC STUDY

We had a growing clinical impression that we had more than generally believed number of patients with mixed gliomas, (Oligoastrocytomas) which clinically behaved differently than either astrocytomas or oligodendrogliomas. Following discussions with our Neuropathology colleagues a series of 55 cases initially diagnosed as mixed gliomas (39 cases) and oligodendrogliomas (16 cases) were submitted to immunohistochemical and electronmicroscopic investigations. This study led us to conclude, "Most of the tumours in both of these groups immunohistochemically showed many neoplastic oligodendroglial cells with GFAP-staining (generally recognised as a characteristic of astrocytes) in their cytoplasm. By EM study too, many tumour cells showing features of oligodendroglial cells contained intermediate filaments. These observations suggested the presence of a transitional form of cells in these tumours, implying that both oligodendrogliomas and oligoastrocytomas (mixed gliomas) arise from a common progenitor cell capable of differentiation into both oligodendrocyte and astrocyte. While we knew that astrocytic tumours have a great propensity to become malignant and that oligodendrogliomas do so infrequently, we expected the mixed gliomas to biologically behave in between these limits, unfortunately we could not verify this or explore their biology further"[187].

IMBALANCES IN T CELL SUBPOPULATIONS IN HUMAN GLIOMAS

There had been a growing interest in utilizing immunotherapy as an adjunct in the management of gliomas. It was therefore desirable to study immunobiology of these tumours. Primary intracranial

tumours had been shown to manifest a variety of anomalies in cell-mediated and humeral immunity. A study on 39 patients with glioma and 21 healthy controls was therefore conducted to estimate serum immunoglobulins (IgG and CD4+, CD3+ & Pan B+cells). The study revealed normal numbers of B cells but a marked reduction of T-cells lymphopenia in the peripheral blood of glioma patients. The CD3+ and B cells remained within the normal range irrespective of the type and grade of the tumour. The Ig G levels were within normal range in patients with malignant astrocytoma and glioblastoma, but there was an increase in the IgM level with astrocytoma. It is unfortunate that this study was not perused to explore further the pathogenesis of these aberrations nor their clinical implications specially in respect to therapy[188].

DISTANT SPREAD OF CEREBRAL ASTROCYTOMAS

A distant leptomeningeal or an ependymal seeding by way of the CSF is not a commonly reported feature of astrocytomas, though it is known to occur in patients with medulloblastoma and glioblastoma. The first such case was reported in 1930. We reported 4 such cases along with a survey of the literature. A variety of factors responsible for this spread have been surmised[187]. The reason to mention this study here, which may not be considered much of a research, is to highlight an unresolved feature of malignant gliomas. It is well known that surgical intervention is responsible for dissemination of tumour cells into the CSF. This happens frequently enough. A systematic study in 1966 had shown that the percentage of tumour cells in the CSF in benign, malignant and metastatic tumours of the CNS was fairly similar. Yet another study had demonstrated presence of malignant cells in the venous blood in the neighbourhood of the glial tumour at the time of surgery. However, there has been no explanation available as to the infrequency of the distant spread or metastasis in these patients. This could be a fascinating question to investigate. Believing that this would imply some kind of host immune mechanism to be responsible for it, I approached our colleagues in cytopathology and immunology to help me to investigate this biologically interesting and clinically valuable research question. But I could not get the necessary collaboration. The question remains unanswered even today!

Let me mention yet another brief but biologically interesting study[189]:

Another paper based on 6 cases of a relatively uncommon neuroectodermal tumour of the cerebral hemispheres, often described under different nosology, discusses the unusual biological features of differentiation and de-differentiation in an otherwise malignant tumour. A survey of such cases reported in the literature was included. Though biologically interesting there were no obvious clinical implications. However, a detailed study of this isolated observation could provide interesting information of brain – immune interaction on basic developmental neurobiology and cancer immunology[190].

Let me conclude this aspect of our contributions on supratentorial gliomas by a brief reference to a detailed review of the subject, presented by me as Ramamurthi Oration delivered on 17 December 1993 during the Annual Conference of the Neurological Society of India. While summarizing our

experience over the years, a further analysis of 639 such patients treated in our Department between 1982-1989, (a year prior to my retirement) was carried out. It is gratifying to record that by now our surgical mortality had come down to 8.4% from 13.8% reported by us in 1986. This is not withstanding the fact that even now most of our patients presented in late stage of the disease and that in nearly 20% of these patients the tumour crossed the midline, or involved the basal ganglia (deeper regions of the brain) or both which makes them inaccessible. It once again revealed that in contrast to reports from the West the relative incidence of glioblastomas in our series was lower. It reconfirmed our earlier contention regarding the usefulness of surgery even for tumours of the dominant hemisphere, including those in and around the speech area. Not only did the existing speech impairment improved in the majority of cases, the same applied to preoperative hemiparesis. Equally interesting was the improvement in mean survival with or without recurrence (astrocytoma 154 months, Mixed glioma 141 months, malignant astrocytoma 57 months and glioblastoma 59 months). The reason to record this is that others reporting their results in future would need to improve on these figures while utilizing newer management strategies.

Lastly let me quote our concluding comments on future direction, "More than three decades of personal experience supplemented by knowledge gained from the writings of a large number of leaders in this field, I am convinced that while improved methods of diagnosis, and technically high standards of surgery made possible by the recent additions of LASERS, CUSA, operating microscope, image guided surgery etc., have continuously improved our ability to provide greater relief to the unfortunate victims of supratentorial gliomas, the ultimate solution is unlikely to come from "Sharper knife" or more powerful source of radiation, but from a better understanding of the biology of these tumours". It is gratifying to note that work in this direction is already going on in atleast a few centres in the country[191].

PITUITARY ADENOMAS *

Pituitary tumours constitute approximately 8-10% of intracranial tumours. Based on the earlier staining characteristics the anterior pituitary was found to have three different types of cells – chromophobe, acidophil and basophil. Cushing produced an elegant co-relation berween the tumours arising from these individual cell types and their clinical manifestations.

This classification continued to be accepted unquestioned till 1970s. Reports then appeared in the literature describing new pituitary dependent entities that did not fit with the existing classification. In the meanwhile availability of electron microscopy and emerging technique of immune-histochemistry promised to resolve some of these discrepancies. Dealing with a sizeable number of patients with pituitary adenomas and having achieved a respectable surgical result – a mortality of around 5 percent (even though many of our patients harboured "giant" adenomas which carried a very high mortality in the

*Pituitary gland is an endocrine organ situated in the base of the brain in a hollow space (sella) of the skull. It secretes a number of hormones which control other endocrine organs like thyroid, adrenal, gonads etc. It has therefore been called the "Master of the Endocine Orchestra".

best of hands) we could happily rest satisfied. We were, however, concerned with associated morbidity due to hormonal disturbances accompanying these tumours (Tandon 1977[89]). I lamented at that time, "the neurosurgeons are happy to relieve the symptoms of pressure on the optic pathways, ensure improvement in vision, but are we able to ensure a normal human being?" And further,, "Having reduced the mortality of surgery, and achieved reasonable success in improving vision, we will have to direct our attention to the endocrinological problems of our patients and thus arrange to develop endocrinological facilities if we have to add to the happiness of our patients". Till Dr. Kochupillai from Department of Endocrinology returned from Dr. Y.S. Yalow's (NL) lab to establish Radio-immunoassay (RIA) technique we were unable to investigate this critical and clinically significant aspect for the holistic care of these patients.

In the meanwhile Subimal Roy, our Chief of Neuropathology, developed expertise in EM studies and a little later he alongwith his colleague and successor Chitra Sarkar established the techniques of immunohisto chemistry. Thus already in 1977, Subimal Roy published a paper in Journal of Pathology (Vol. 122, pp 219-223) on the "Ultrastructure of chromophobe adenomas of the human pituitary gland". This study was later extended to other types of these adenomas and he contributed a chapter on the subject in Progress in Neuropathology (ed. HM Zimmerman 1983). Likewise already in 1978, Kochupillai alongwith Dr. Yalow published the technique of radioimmunoassay. The time was thus ripe for us to bring together this expertise and explore the so far neglected component of these tumours*. In 1984, at the 2nd Conference on Biology of Brain Tumours, in London (referred to earlier) we were able to present our preliminary experience in this regards. It was gratifying to note that alongwith our poster were those by Kovacs and Horvath, the acknowledged pioneers of such studies.

The number of patients included in our study, was greater and the technical quality of our micro-photographs was as good if not better. A comprehensive Clinico-Pathological study of Pituitary Adenomas based on one hundred patients with pituitary adenomas using light microscopy, electronmicroscopy (EM), immunohistochemistry (IH) and serum hormone estimation was published by us[192]. The study provided unequivocal evidence that the time honoured classification of these tumours, based on light microscopic examination and staining characteric, is inadequate to assess the clinical and endocrine status of these patients. EM studies could not be fully relied upon particularly with respect to the nature of secretary function of these tumours. Localisation of hormone in the adenoma cells with immunohistochemistry in combination with estimation of the hormone level in serum and the tumour itself provided a more comprehensive evaluation of these patients. The study revealed that contrary to earlier belief 40 percent of tumours were plurihormonal, growth hormone (GH) and prolactin (PRL) being the commonest combination. Though many patients with chromophobe adenomas were clinically "non-functioning", a number of others showed evidence of hormone anomalies. Thus at least 6 patients,

*During a visit to Oslo, where I presented our studies on pituitary adenomas the endocrinologist there offered to provide antibodies for some of the hormones. Chitra Sarkar fully utilised these to standardise gold-labelled immune electron microscopy for the first time in India.

diagnosed to be cases of chromophobe adenoma on the basis of light microscopy, presented with galactorrhea (secretion of milk). Immunohistochemistry revealed strongly positive reaction to PRL in many tumour cells. Serum PRL level was markedly raised. It became clear that IH demonstration of hormones in pituitary adenomas may not always be reflected in the serum and / or clinical picture. The biological significance of this observation obviously needs further exploration. Based on our studies we proposed a new classification of these tumours[193].

This was based on 122 cases of surgically treated large pituitary tumours. Preoperatively their endocrine status was assessed clinically and by specific RIA's of the pituitary and target gland hormones e.g. PRL, GH, LH, TSH, Testosterone, Estradiol, T3, T4 and plasma cortisol. Extract of the tumour tissue obtained at surgery was also assayed for various hormones in 80 out of 122 cases. The expression of multiple hormones in the same tumour as observed in our immunohistological study was confirmed and an attempt was made to explain its genesis.

HAEMORRHAGE INTO PITUITARY ADENOMAS

Acute haemorrhage in a pituitary adenoma resulting in "Pituitary Apoplexy", even though uncommon, was a well known clinico-pathological entity. However, we observed a significantly higher incidence of haemorrhage in the tumour than was reported in the literature. We, therefore, undertook a clinico-pathological study of 70 cases of pituitary macroadenomas treated surgically.

18 of these were found to have prior or recent haemorrhage an incidence of 27.7%. This was much higher than any of the earlier reported series. This was most likely due to very large tumours generally encountered by us. Necrosis and haemorrhage are likely to occur when the tumour outstrips its blood supply. It was therefore not surprising that tendency to haemorrahage and necrosis was found to be directly related to the size and vascularity of the tumour rather than to the type of adenoma. On the basis of our findings we divided these cases into four categories, (i) acute, (ii) acute or chronic, (iii) chronic, and (iv) acute episode in the past, and correlated their clinical manifestations and prognosis[194].

Dr. Zimmerman, an internationally renowned Neuropathologist considered this as a most comprehensive contribution on the subject.

Over the years with improved diagnostic capabilities an increasing number of smaller tumours as well as micro-adenomas were seen. Dr. Banerji and Dr. Bhatia developed transsphenoidal approach to these tumours initially alongwith our ENT colleagues.

One of our postgraduate students studied the incidence of microadenomas in routine autopsies and not surprisingly found a number of these[195].

Dr. Banerji reported one of the largest series of the "Giant" pituitary adenomas and their management at the IX World Congress of Neurosurgery held at New Delhi in 1989.

Other Brain Tumours

Management of brain tumours constituted a major part of our professional activity. For years more brain tumours were operated upon in our Department than any single hospital in North American Continent. This number has kept on increasing and in recent years this has gone upto 700 per year. Hence, besides the major contributions in respect to gliomas and pituitary adenomas from time to time our publications included others relatively uncommon tumours like Trigeminal Neurofibroma (1989)[196], Brainstem Neurofibroma (1980)[197], Intracranial tumours of infancy, childhood and adolescents (1984)[198], Craniopharyngiomas (1976)[172], Chondrosarcoma of the meninges (1972)[167], Differentiating medulloblastomas (1977)[199], Multiple Primary Tumours (1977)[174]. These reports were made because of paucity of information about these in the national and international literature. A couple of these constituted the only such report in the world literature. Some other publications dealt with newer diagnostic procedures as these became available e.g. ENG in Post Fossa Tumours (1972)[200], Auditory Brain Stem Evoked Responses in CP Angle tumours (1987)[201]. In addition there were reports on some unusual or uncommon tumours of the spinal cord. A major contribution on neurooncology was really made by our colleagues from Neuropathology unit in which our contribution was primarily in providing clinical features and in catalysing / promoting such studies. Hence these are not detailed here[202-204]. It may be mentioned that these were some of the earliest studies on markers of brain tumours in the country. While such investigations have now become routine in most neuropathology laboratories, Chitra Sarkar and her colleagues have since introduced several other markers to improve our diagnostic and prognostic capabilities and to throw some light on the biology of these tumours by utilising cell culture, molecular biology and genomic studies.

FOETAL NEURAL TRANSPLANTS

Over the years owing to the pressure of professional work and time consuming responsibilities to develop the Neurosciences Centre I had drifted away from my interest in and involvement with basic neurosciences. This was suddenly revived as a result of two events. I was invited to give a talk on "Neurosciences: Future Trends" by the National Academy of Medical Sciences in 1981. This made me review the basic science literature of the last decade. This was later published[205].

It became obvious that neurosciences, from being the strictly discipline oriented studies like neuroanatomy, neurophysiology, neurochemistry etc was now becoming a holistic multidisciplinary subject involving molecular biology, immunology, genetics, as also a host of newly introduced sophisticated investigative technologies. In 1982, I was invited to participate in the First International Congress of "International Brain Research Organization" (IBRO) at Lausanne to organise a symposium on

parasitic diseases of the nervous system. It gave me an opportunity to listen to the "Who is Who" of neurosciences giving an account of the latest advances in the whole field. This provided me an opportunity to bring myself upto-date in theoretical knowledge. I was already primed up to imbibe this new knowledge.

However, what impressed me most were the advances in the field of neural transplantation presented particularly by Gopal Das from USA and Anders Bjorklund from Sweden – the two pioneers of this potentially revolutionary field of immense clinical relevance. In personal discussions with Gopal Das, it became obvious that this emerging field, still in its infancy, should be persued by us in India. Other participants from AIIMS in this conference – S.K. Manchanda, Gomathi Gopinath, Usha Nayyar, Mohan Kumar – all agreed to join hands and establish a multidisciplinary group to initiate this activity. With the timely help from Dr. S. Ramachandran – Chief of the newly established National Biotechnology Board, we arranged to invite Gopal Das to AIIMS, establish a dedicated laboratory and conduct hands – on national workshops in 1985 & 1986. With his help we initiated our studies on the subject. For the next approximately 10 years this became a focus of our activity, primarily because of the dedicated involvement of Gomathi Gopinath and two of her Ph.D. students A.H. Shetty and Ranjeeta Banerji and later during my Bhatnagar Fellowship my Post doc V. Sable.

Considering the nature of the work it was not till 1988 that I first presented our initial observations as an invited key-note address at the Indian Science Congress[206]. Already research in this field had exploded all over the world though initially we were the only one in India carrying out these studies systematically and persistently. Over the years we published nearly 15 papers, most of these in international journals[207-222].

Our studies initiated with a view to understand the basic neurobiology of such transplants, no doubt for its ultimately application for the treatment of human diseases, revealed a number of hitherto, overlooked observations, of great relevance for their clinical application. Very early in the course of these investigations it became obvious that from 'rat to man' was a big leap. Hence, not withstanding a number of reports from abroad, particularly Mexico, Cuba, East European Countries and even UK, about human trials, we withstood the temptation to rush this procedure to clinical practice. This decision later proved to be the correct one.

The reasons for overlooking the limitations of foetal neural transplants for therapy by others were that (i) unlike our studies which followed the fate of the transplants in rodents, up to 18-24 months, nearly all other investigators abroad terminated their observations in 3-4 months; ii) hardly anyone did as detailed morphological studies as we did, which included light and electron microscopy, histo-fluorescence and immunohistochemistry, HRP and Golgi technique and quantitative morphometery. Surprisingly in spite of voluminous literature that had accumulated on the subject during the previous decade, such detailed morphological studies, as also long term follow-up of such grafts, were conspicuous by their absence[215].

Our long term observations revealed that like others the initial success rate of foetal neural transplants in

rodents was nearly 90% in our hands also. It unequivocally demonstrated that such grafts "take, grow, develop at least limited two-way connections with the host brain, produce appropriate neurotransmitter, and to a variable extent restore functional deficits resulting from disease or damage to the host brain". The results of these rodent experiments were so tantalizing that a number of neurosurgeons uncritically jumped from the rat to the man. Backlund and his colleagues had attempted autologus adrenal medullary transplants in striatum in couple of patients with Parkinson's disease already in 1981-1983. Madrazo from Mexico who initially used adrenal medullary transplants in 1989, had already used foetal ventral mesencephalon grafts in 1991. Many others had jumped on the band-wagon around this time. It may be mentioned that Bjorklund whose initial laboratory studies prompted these operations concluded already in 1991, "With respect to the clinical perspective, however, there is still a long way to go".

While awaiting long term results of our rodent studies, we decided to study the fate of the foetal neural transplants in sub-human primates. We chose rhesus monkey for this investigation. At that time no information was available on this species, though there were some reports on successful transplants in African green monkeys and squirrel monkeys. We were disappointed to observe that unlike rodents the success rate, in rhesus monkeys, after a number of trials, was no more than 20-30% (Gopinath et. al. 1989)[211].

A satellite symposium on foetal neural transplants was held at Pecs (Hungary) at the time of 2nd International Congress of IBRO in 1990, in which I participated. During informal discussions with other participants it became obvious that none of them was aware of any successful transplant in Rhesus monkeys.

Coming back to our rodent studies, the healthy growth of transplants observed during the first 3-4 months, developed changes compatible with premature ageing of the transplants leading to neuronal loss at varying intervals. These changes were characterised by appearance of clear spaces, membrane bound vacuoles, paucity of organelles specially rough endoplasmic reticulum and increasing accumulation of lipofuscin granules in the cytoplasm. Such changes continued to increase in frequency and severity with passage of time, so that at the end of 18 months and 2 yrs. majority of surviving transplanted neurons were so affected. In addition we observed thickening of blood vessel walls, perivascular cuffing with lymphocytes and macrophages loaded with tissue debris, degenerating neurons, and hypertrophic astroglia containing dense granules. The transplants of longer duration had progressively increasing amount of intracytoplasimc ageing lipofuscin pigment. These changes suggested premature ageing since these abnormalities were far less in age-matched host nigral neurons[216].

These changes in all the long term transplants were suggestive of premature aging or a slow rejection. Surprisingly this premature ageing was not reported by any other scientist till several years later when it was confirmed by another independent group abroad. The reason for this, no doubt, as mentioned earlier, was that most investigators failed to study the transplants beyond 3-4 months and did not carry

out as comprehensive a morphological study as was done by us. These observations thus questioned the possibility of long-term survival of the transplant and consequently its ability to provide continued functional relief. The loss of transplanted neurons both in rodents (Lawrence et al 1990) and monkeys (Helm et al 1993) was confirmed by some others who conducted longer-term studies. The same was found true for surgically transplanted human subjects who came to autopsy. While we had no proof, but there were enough indications, that this loss of transplants after a variable period of growth, was due to immune rejection. This obviously challenged the belief that brain is an immunologically privileged organ because of the existence of blood-brain-barrier. It is now generally agreed that this privilege is not absolute. This observation, therefore, acquired practical significance. The need for immuno-prophylaxis for patients undergoing any kind of allograft becomes obvious.

Another disheartening observation of direct relevance for therapeutic use of such transplants, not commonly commented upon, was the degree of neural connectivity achievable by such grafts. While our studies, like several others including those by Freund et al (1986), confirmed the development of neuronal processes which increased in density constituting a respectable neuropil and even acquired myelin with passage of time. Neuronal processes were also observed extending from the host into the graft. However, these processes seldom extended beyond 2-3 mm. A large number of synapses could also be demonstrated by electron microscopy, but majority of these were of the asymmetric variety containing clear round vesicles, suggesting their origin within the graft rather than as a result of connection with the host (Gopinath, Shetty, Tandon 1991 [216], Tandon and Gopinath 1994 [219]).

Recognising the fact that most neural functions depend upon complex neuronal connectivity, it is unlikely that such neural transplants could really help restore complex brain functions. The unquestionable behavioural improvement reported by a host of workers, primarily on animal models of Parkinson's disease, could not have been due to restoration of neural connectivity, but due to the secretion of appropriate neurotransmitter (dopamine) or some kind of trophic effect on the surviving host neurons. There were a number of other unanswered questions which came to the light during the course of these studies and also referred to in our publications. Many of these are still relevant for any kind of neural transplant based therapy, be it embryonic stem cells or their more recent alternatives (adult mesenchymal cells derived from bone marows, adipose tissue, skin etc., or induced pluripotential cells). One may question the relevance of these observations now that these types of transplants are no more used clinically owing to their failure to provide consistent long term relief. The reason to highlight these observations now is to forewarn the recent hype regarding the use of embryonic stem cells or their alternatives for a variety of diseases of the nervous system.

THEORETICAL NEUROSCIENCES

NEUROBIOLOGY OF CONSCIOUSNESS – BRAIN – MIND RELATIONSHIP

According to the tradition, the President, Indian National Science Academy, is expected to deliver an Anniversary Address based on his/her life-long contributions on a particular scientific subject preferably one of more general interest. In 1991, I chose to present our work on Neural Transplantation. In view of a variety of studies related directly or indirectly to neural mechanism of consciousness punctuating throughout my professional career, I decided to chose this as the subject for my presentation in 1992. Being aware of the importance of such lectures, preparations had to be started long time ahead. As mentioned elsewhere the first half of the twentieth century had witnessed a resurgence of scientific activity exploring the neural basis of consciousness as characterised by the work of Magoun, Moruzzi, Jasper, Penfield, Brodal, Eccles etc. Hence during my training at Oslo and Montreal around this time, I had read most of their works. Probably as a consequence a number of my own studies described earlier were influenced by this knowledge. Hence I thought that there was enough personal material to do justice to this subject.

Following a review of our personal contributions and the related literature, as per my usual practice I embarked upon exploring the literature from allied disciplines e.g. psychology, philosophy, physics, even religion etc. I was amazed at the wealth of such literature. I consulted over two dozen books and hundreds of papers since by now I had retired from my official position and I had accepted the prestigious Bhatnagar Fellowship, I could find enough time to indulge in his new found activity. I soon realised that until now my knowledge of the subject was confined to neurosciences only while over the years – even a millennium – the subject had attracted the attention of some of the brightest minds from diverse disciplines. I, therefore, decided to broaden the horizon of my talk under the somewhat confusing title: "Consciousness: Clinical and Beyond". Let me quote from the introduction of this talk to elaborate this point.

"Reflecting on the clinical encounters with a wide range of patients with brain disease made us realise that there are many more aspects of consciousness than those of day to day concern to the neurosurgeon". And "I am personally not aware of any other subject which could claim followers from so many disciplines. Thus not only biologists, neuroscientists, psychologists, psychiatrists and cognitive scientists, but physicists, chemists, mathematicians and more recently computer scientists and above all philosophers and sages, have all been attracted to this subject".

It, therefore, became imperative for me to atleast familiarise myself with these diverse contributions. Realizing my inherent limitations, and those of the occasion, my presentation provided only a glimpse of this vast subject. Briefly summarising our experience with clinical observations on head injured patients, studies on brain stem dysfunction and lesions in our patients, the evidence gathered from the cold caloric test (vestibulo – ocular reflex), electrographic study of sleep in cases of prolonged unconsciousness

provided the background. To this were added studies on some specific neurological syndromes like Anoxic Brain Damage, Epileptic Automatism, Global amnesia, Korsakoff psychosis, Locked-in Syndrome, Brain stem tumours which provided some additional insights into the neural mechanisms possibly involved in human consciousness.

A rather lengthy discussion that followed included the most difficult problem of the definition of consciousness and the prevailing confusion of a variety of terms used from time to time included under this rubric or even used interchangeably like mind, mental forces etc. There seemed to be no consensus as to what constitutes consciousness. On the basis of our clinical experience it could be stated, without fear of contradiction, "that awareness, attention, cognition, discrimination, memory, responsiveness, volition etc. are atleast some of the definable constituents of the unitary state of consciousness". A deeper look into this led to the obvious conclusion "that individually none of the(se) components amenable to empirical study could be equated with consciousness". And, therefore it was obvious "that collectively a variety of psycho-physiological factors are responsible for maintenance of full consciousness, singly none of these could account for it, nor be equated with it".

A discussion on State of Consciousness based on the writings in Upanishad and Vedas, writings of Charaka and Budhism along with the pioneers of neuropsychology William James, Hughlings Jackson, Sherrington, Penfield among others instead of providing a unified concept only led to scientifically unverifiable entities. Recourse to knowledge gained from neurobiological, psychological, psychobiological and cognitive studies provided interesting information but not an unquestionable insight on the subject. From whatever I could understand from no doubt limited study, the various philosophical hypothesis monistic and dualistic concepts of brain – mind – consciousness relationship, the riddle of consciousness remained unresolved.

Whatever else it achieved or not achieved, it aroused a renewed interest in me to explore this subject in greater depth. Not only I have read a lot more, tried to crystallize my thinking on the subject and participated in a number of multidisciplinary symposia on the subject. While the purist may not consider these contributions as hard – core science but if the inputs from these deliberations can stimulate such multidisciplinary discourse or help to provide some basis for future studies, utilising the latest techniques and technologies, to unravel the mystery of mind – the last frontier of human ignorance, I would consider the time and effort spent on exploring this unsolved problem, to be worthwhile.

Over the years, based on invited talks at such multidisciplinary symposia, the following papers were published[223-233].

Discussion:

A number of scientometric studies have established the relatively unsatisfactory status of bio-medical research in the country. Reddy et al (1991)[234] in their paper on "Research in Indian Medical Institutes" found that between 1981 and 1988 only 6 (4.7%) institutions had over 50 articles per year included in the Science Citation Index; 33 (26%) had 5 to 50 articles included, 43 (38%) had 1 to 5 articles and 41 (32%) had less than one article included. Seven medical colleges had none. Only the All India Institute of Medical Sciences, New Delhi and Postgraduate Institute of Medical Education and Research, Chandigarh could be compared with world leaders. A few years later S. Arunachalam in his paper, "How relevant is medical research done in India? a study based on Medline", analysed 19,952 papers published between November 1987 to December 1994. Fully conscious of the need for exercising caution in using international data bases in evaluating indigenous research performance, he arrived at a more or less similar conclusion. He not only observed quantitative and qualitative deficiencies but found, "there was a substantial mismatch between the needs and where work was being done". In conclusion Arunachalam (1997)[235] stated, "as compared to agriculture, medical research in India appears to be limping and off-target". In an Editorial in Current Science, P. Balaram (1997), commenting on Arunachalam's paper, observed, "This is hardly surprising since biomedical research has never been a major thrust in our medical institutions, with one or two important exceptions". He went on to add, "large number of clinicians produced today have 'only a limited appreciation of the capabilities of modern science in biomedical research". A similar medline search by ICMR in 2004 revealed vast differences in research output of various medical institutions. Thus when compared to 313 papers published by AIIMS, there were 190 by PGI, Chandigarh, 98 by SGPGI, Lucknow, while KGMC, Lucknow at number 8 among top ten had only 38 publications to its credit. As in previous surveys many had hardly any!

In recent years I have had the opportunity to review the research output of a large number of medical colleges – both public and private – in my capacity as a member of various committees of MCI, ICMR, MHRD, DST, DBT, CSIR, I am appalled at the apathy for medical research and in many cases total lack of knowledge of research methodology, research planning and conduct among their faculties. It is not surprising that some years ago to qualify for appointment as a Professor in a medical college MCI required only 4 publications by the prospective candidate. I gather this has recently been increased to eight. Recent efforts by ICMR to organise workshops on research methodologies, writing research protocols and providing support for establishing centralised laboratories in state medical colleges are steps in the right direction. But the real remedy lies in inculcating a spirit of enquiry, a zest for advancing knowledge, a recognition that disease pattern in different geographical, socio-cultural environments may be different than those in countries whose education system, medical knowledge and practices often followed by us are not necessarily directly applicable to ours. The Greek philosopher Socrates admonished that, "To live on the ideas of others is a sickness". This is especially true for medical practitioners. Let me hasten to add that this does not mean that outstanding nationally relevant and internationally competitive research has not been or is not being carried out in the country. It is not surprising that the most highly cited papers,

from India are really those which dealt with the problems of direct concern to India[233]. These were the ones mostly dealing with tuberculosis, malaria, diarrhoeal diseases, and malnutrition.

Often I have been asked, "What is the need for research, when so much knowledge is being generated by those better equipped to do so". Surprisingly it is not realised that the type of diseases, their manifestations, their natural history and even their response to therapy are not necessarily identical to what prevails elsewhere. Our diseases have their own characteristics which only we can find out. Research is needed to acquire, adapt and accelerate the application of the appropriate existing knowledge and technologies to suit our needs. At the same time it is often necessary to develop new technologies and new tools, taking advantage of recent advances to tackle previously unsolved problems or deal with the emerging new diseases like AIDS, Avian flu, diseases of demographic transition etc. Some years ago it was estimated that global investment for research on health was US$30 billion, only 5 percent of it (1.6 billion) was devoted to health problems of the developing countries, which account for 93 percent of the years of potential life lost in the world. Even though science knows no national boundaries, the fact is that problems relevant for national interest need national efforts to solve them. This is especially true in the field of biomedical research. It is not only a question of national pride but national need. Pandit Nehru, the patron saint of Indian science remarked, "It is inherent obligation of a great country like India, with its tradition of scholarships and original thinking, and its great cultural heritage, to participate fully in the march of science, which is probably mankinds greatest enterprise today".

The present monograph has been prompted by two different motives. Firstly requests from many friends and colleagues to record our experience of what they considered a very successful effort of doing research not withstanding our others responsibilities. Secondly it is to illustrate that the common excuse offered by many clinicians, even those holding academic positions, are mostly alibis for lack of motivation and efforts to do any research. The most common of these alibis is the burden of patient care not permitting time for research. The second alibi is lack of infrastructure and funds. Though both these are true to a certain extent, it may be pointed out that the author of this monograph was no less burdened by the demands of patient care and most of the interesting studies did not require extraordinary facilities and were conducted with none or very little funds. Furthermore, whatever funds were required were obtained through competitive grants from funding agencies. Let me hasten to add that not only the present author but practically all neurologists and neurosurgeons in the country who contributed to the majority of publications in the field (or are currently doing so) were the busiest clinicians. It may be added most such individuals including the author in addition to their service load developed some of the best training and teaching centres, while building specialised units or centres and even full-fledged institutions, simultaneously contributed to the promotion of the discipline nationally and representing it internationally. Furthermore, unlike recent years, in the earlier days the number of funding agencies and the amount of funds available were far more scarce. Among all those researches published in over 250 scientific papers except for the study on experimental tuberculosis, epilepsy, molecular biology of

pituitary tumours and foetal neural transplant there were no research funds involved. Majority of studies were based on careful clinical observations, faithfully recorded and critically analysed to answer some specific questions raised during day to day care of our patients, to improve their outcome or search for a cause of our failure. One of the major difficulties we faced was the problem of long-term follow-up of our patients who came from far corners of the country. The greatest source of our success was willingness of colleagues from diverse disciplines not only within the Institute but also from outside to collaborate, help and advise without which very little could be achieved. It will be observed that most of our studies were carried out, and co-authored, with colleagues from diverse departments within the institutions where I worked (KGMC, AIIMS) and some from other centres in the country (Bombay, Chandigarh, Calcutta, Madras, Trivandrum). Within our institutions these included basic science departments – anatomy, physiology, biochemistry, microbiology, pathology, nuclear medicine, radiology, as also several clinical department ENT, Ophthalmology, Neurology, Cardiothoracic surgery etc. it required persuasion, motivation and a spirit of cooperation, not always easy in our institutions. Without this cooperation it would not have been possible to publish what we could inspite of a very heavy load of patient care in a discipline like neurosurgery, at the same time developing a training programme and establishing a full-fledged clinical neuroscience centre.

In addition to the research publications, our academic activities included editing and contributing to 22 textbooks and monographs and nearly 70 invited chapters in addition to over 250 papers.

While it will be for others to judge the quality of our research and its practical utility. I hope that this monograph will provide enough evidence that a very busy clinician can significantly contribute to scientific research which leads to better patient care. This requires a desire to identify unanswered questions, humility to seek help from other colleagues, commitment to work as a team, patience to pursue untrodden paths, courage to challenge unproved dogmas, tenacity to face failures. This effort resulted in continuous improvement in the care of our patients, education and training of our students, leaving behind a legacy of research traditions and demonstrating that nationally relevant and internationally competitive research is not only possible but the need of the hour. From personal experience I have no hesitation to say the reward for this extra effort was uniquely soul satisfying.

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An (brief) introduction to the Author

Prof P. N. Tandon is an outstanding medical man who combined excellent professional competence as a Neurosurgeon with internationally acclaimed scientific research. He is credited to have played a critical role in comprehensive development of Neurosciences in India.

Born on August 13, 1928 at Shimla, Prof. Tandon received his medical education at K.G. Medical College (now University), Lucknow. Standing first in the University in the MBBS examination (1950), he was awarded the prestigious Hewitt Gold Medal and five other Gold Medals along with a number of prizes. Obtaining the M.S. Degree in 1952 (Lucknow University), he was awarded FRCS England in 1956. He then received specialty training in Neurosurgery and allied Neurosciences at the Ulleval Hospital, Oslo University, Norway (1957-58) and the Montreal Neurological Institute, McGill University, Canada (1959-60).

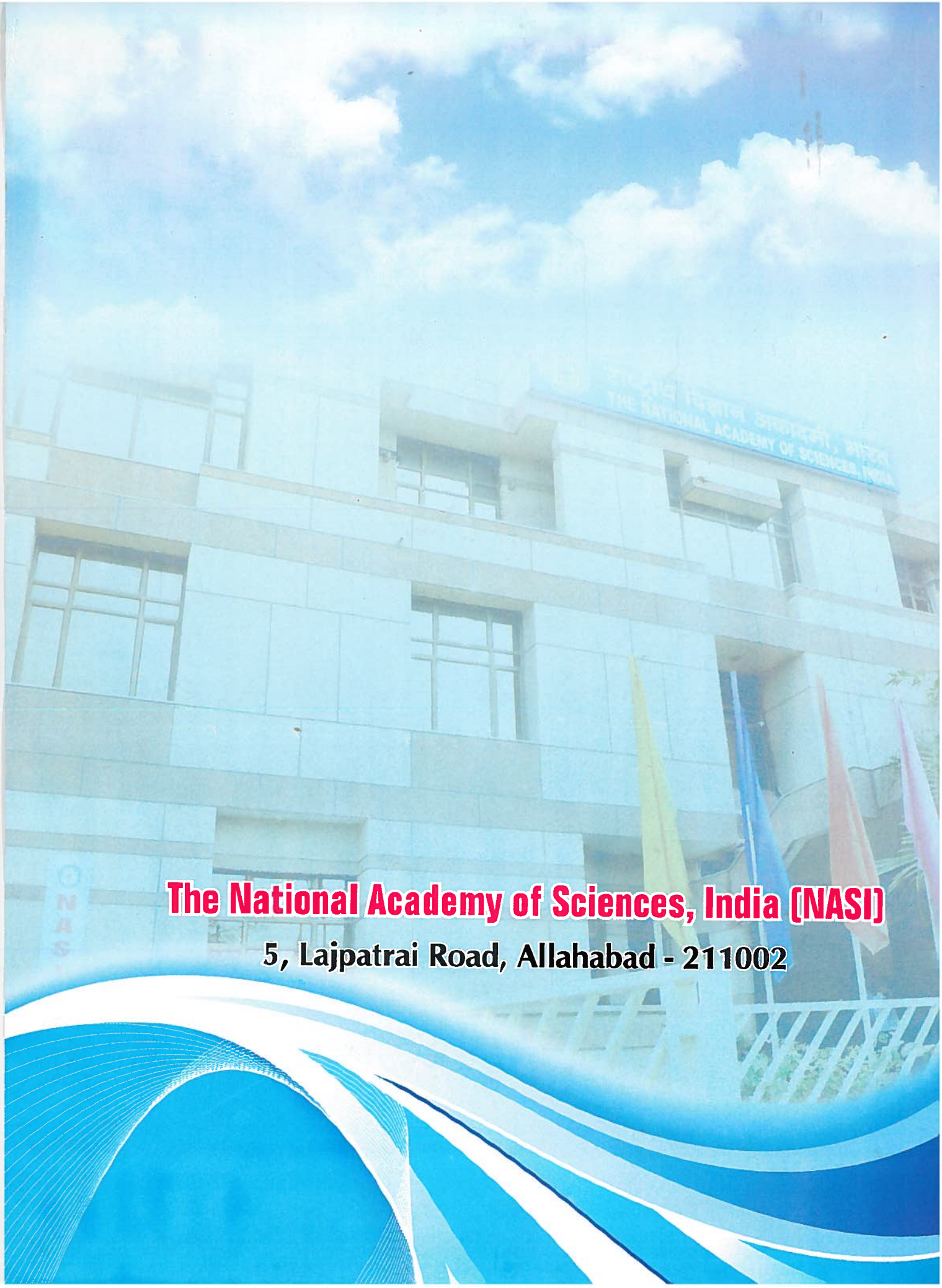
Declining several rewarding offers abroad, he returned to India to start the first Neurosurgical Service at his Alma Mater in 1961. In 1965, he was appointed Professor and founded the Department of Neurosurgery at the All India Institute of Medical Sciences, New Delhi. Under his leadership, this department grew to be the country's premier Neurosciences Centre. He is the Founder President of the National Brain Research Centre (NBRC) at Manesar under the aegis of Department of Biotechnology, GOI.

Notwithstanding a very heavy clinical workload and teaching responsibilities, Prof. Tandon was deeply committed to advance the frontiers of science. His major research efforts dealt primarily with neurological disorders of the nervous system of national relevance. These included developmental defects, head injury, CNS Tuberculosis, subarachnoid hemorrhage, and experimental foetal neural transplant. These have resulted in 270 scientific papers, over two dozen monographs and more than 70 chapters in National and International text books. He is the co-editor of the Text Book of Neurosurgery and Consulting Editor of Text Book of "Operative Neurosurgery". He trained more than fifty neurosurgeons, several of whom initiated and/or headed the departments of Neurosurgery in all over the country.

OTHER CONTRIBUTIONS: Prof. Tandon has been the President of Neurology Society of India, National Academy of Sciences, India, Indian National Science Academy, Indian Academy of Neurosciences. He has served as a member of the Governing Body of the Council of Scientific and Industrial Research (CSIR), Indian Council of Medical Research (ICMR), Indian Council of Social Science Research (ICSSR) and nominated Member of the University Grants Commission. He has been chairman of the SAC of CDRI, CCMB, NARI and NBRC. He was the founder Co-chairman of the Inter Academy Panel (IAP) of The World Science Academies, a member of the ICSU – Review

Committee, Indo-US VAP, Indo-US S&T Forum (Governing Body). He was elected Fellow of the National Academy of Medical Sciences (1973), served on its Council and as Vice President. He was elected a Member of the Norwegian Academy of Sciences, 1987, Honorary Member, Society of Neurological Surgeons, USA, 1987, Foreign Member of the Royal Society of Medicine, London, 1992, Member American Association of Advancement of Science, USA (2002), Honorary Life Member of the Indian Institute of Advanced Study, Shimla, 2002. Currently he is Emeritus Professor at AIIMS, Emeritus Professor National Academy of Medical Sciences, & National Research Professor.

AWARDS & HONOURS: Padma Sri (1973); **Hon. Surgeon to the President of India** (1977-80); **B.C. Roy Award** for Developing a speciality (1980); **M.N. Sen Oration**, ICMR (1980); **UGC National Lecturer** (1982); **FICCI Award for Life Sciences** (1983); **Jawaharlal Nehru Fellowship** (1984-85); **Member Science Advisory Council to the Prime Minister** (1986-89); **Dhanwantari Prize**, INSA (1986); **Outstanding Alumnus Award**, K.G. Medical College, Lucknow (1987); **O.P. Bhasin Award** for Medical and Health Sciences (1988); **Padma Bhusan** (1989); **S.S. Bhatnagar Fellowship** (1990-95); **Basanti Devi Amir Chand Prize**, ICMR (1991); **B.C. Roy Award** for Eminent Medical Scientist, MCI (1993); **Sir C.V. Raman Medal of INSA** (1997); D.Sc. (h.c.,BHU); **G.M. Modi Award** for Innovative Science (1998). **INDO-ASEAN** Eminent Persons Lecturer (1999), **M.N. Shah** distinguished Fellow (2000-2005), **Firodia Award** for Excellence in Science & technology (2003), **New Millennium Plaque of Honour in Medicine and Physiology** (Indian Science Congress: 2002-2003), **Prof. Bachhawat Lifetime Achievement Award**; Indian Academy of Neuroscience: 2003, **NASI President's Gold Medal** (2006), **Padma Vibhusan** (2006). **INSA Gold Medal** for Promotion & Services to Science (2011) **Lifetime Achievement Award** by All India of Medical Sciences (2014), **National Research Professor** (2014).



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