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Clinical Research: Reasons, Rewards and Regrets (Personal Experiences)

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"To gather knowledge and to find out new knowledge is the noblest occupation of the physician. To apply that knowledge with sympathy born of understanding, to the relief of human sufferings is the loveliest occupation" *Sir Edward Archibald*

In this era of modern biology with an emphasis on reducing all life processes to their molecular and genetic level, researches on the whole human being tend to be relegated to a second place. This paper, based on author's long involvement with clinic research, highlights the reasons and rewards of this field of research. Drawing upon personal experience in three major fields of investigations - head injury, neurotuberculosis and aneurysmal subarachnoid haemorrhage - it is attempted to illustrate that good clinical research involves no less intellectual inputs or scientific rigour than any frontline laboratory studies. Furthermore, there are many important questions that can only be answered by properly planned clinical studies, with or without support from laboratory investigations. It is regretted that clinical research has not attracted enough attention or recognition in the country.

Key Words: Clinical Research, Head injury, Traumatic lesions of temporal lobe, Neurotuberculosis, Aneurysmal subarachnoid haemorage

In this era of high-tech biomedical research at the molecular and genetic levels, concerned with basic building blocks of life and their functional correlates, the individual as a whole seems to be getting farther and farther removed from the focus of attention. Unless one's researches deal with genes and their products, chemicals and their receptors, proteins and their configurations one risks to be overlooked, even if not derided, by the high priests of modern science. William James once remarked, "Many persons now-a-days think that any condition must be scientific, if the arguments in favour of it are derived from the twitchings of frog's legs–especially if the frogs are decapitated

and that –on the other hand–any doctrine chiefly vouched for by the feelings of human beings–with heads on their shoulders–must be benighted and superstitious". Today the frog's leg has been replaced by genes and their products. Instead of the recordings of the jumping leg, it has to be producing monoclonal antibodies or producing "knock out" or transgenic mouse to be accepted as high class research. Painstaking investigations on whole individuals, in health or disease, intricately embedded in the complex socio-cultural-ecological milieu, though presenting greater difficulties for unravelling their hidden secrets than the discovery of a single gene, a transmitter or a receptor, may fail even to acquire the dignity of being called scientific research specially amongst the elites of academia. It is with the idea of bringing the individual itself rather than any one of the myriads of molecules it is made up of to the center-stage that I decided to devote this talk to clinical research, to honour the man for whom the blue colour of the sky and water of the sea was the prime motivator rather than intricacies of the optics or spectroscopy which no doubt he utilized in his quest for truth. In the opinion of Claude Bernard, considered to be the father of biomedical research, "while the hospital, the library provide an opportunity for making and recording observations but only the laboratory provides the area where these can be tested by carefully designed experiments". For Hughlings Jackson, whose penetrating clinical observations provided new insights into the working of the human brain, as relevant today as when these were made, disease was the nature's experiment upon the brain—we should be wise enough to learn from it. Lest I am misunderstood to be an advocate of only one of these two approaches, let me hasten to add that many different paths can lead to truth—the search for which is the ultimate goal of all sciences. Clinical research deals with questions raised at the bedside of the patients, often needing the help of the laboratories to resolve, while the results of biomedical researches originating in the laboratories acquire their full significance when they ultimately find their use for improving our understanding of human health and relief from abberations. I take this opportunity generously provided by you to present some personal endeavour in clinical research to illustrate the reasons and the rewards of such an enterprise. At the sametime I would share with you some unfulfilled expectations which throw some light on reasons for the frequently bemoaned status of medical research in the country. For this purpose I propose to draw upon some areas of my major interests — Head Injuries, Central Nervous System Tuberculosis, and Aneurysmal Subar-achnoid Haemorrhage, to which, along with a host of colleagues, I devoted a large part of my professional and research efforts. It is not intended to present the technical details of these investigations, most of which are already published, but to provide an overview to illustrate the justification and joys of clinical research.

Head Injuries

Patients with head injuries constituted a large part of the clinical work in our

neurosurgical service when I started my training at Oslo, Norway. This also happened to be an area of interest for my chief Professor Kristian Kristiansen. On the face of it, considering the number of books, monographs and research papers already published on the subject, one would have thought that nothing much will emerge from initiating further studies on this well-explored subject. A standard management regime had been established in the department. It appeared that the primary role of a neurosurgeon was to treat open wounds, promptly diagnose an intracranial haematoma and evacuate it. Professor Kristiansen had already established the role of cerebral angiography for prompt and reliable diagnosis of extradural and subdural haematomas. Once these aspects of head injury had been taken care of, the surgeon could do little to alter the outcome. Notwithstanding a diligent implementation of these practices a significant number of these patients died. This aroused two questions in the beginner's mind — what caused the death of fatal cases and could this be predicted in the early post-traumatic period. A review of the available literature revealed that adequate answers to these questions were not available. The excellent documentation of the clinical course of these patients and nearly 100% autopsy rate on fatal cases, available in the department provided an opportunity to attempt to answer these questions.

A consecutive series of 3000 cases of head injuries were reviewed. Two hundred and sixty five patients with severe cranio-cerebral injury, including all surgically treated and fatal cases, were identified. Their clinical and autopsy records were carefully scrutinized. An analysis of their clinical, angiographic, operative and autopsy data revealed a number of interesting findings, not only of direct relevance for diagnosis and therapy, but also having some bearing on the first question as to the nature and extent of pathology resulting in fatal outcome (Kristiansen & Tandon 1960). The lessons learnt from this study may be summarised as follows:

(i) There was a need for better clinico-pathological classification of head injury syndromes.

(ii) It was not possible to correctly diagnose the various types of intracranial pathologies on clinical grounds alone. Cerebral angiography was by far the best diagnostic procedure available then to promptly diagnose surgically treatable intracranial haematomas.

(iii) Cerebral contusion, a common pathology observed in fatal cases, either on its own or in association with intracranial haematomas, contributed significantly to poor prognosis.

(iv) The so-called "acute subdural haematoma" was seldom an isolated lesion. It was commonly associated with cerebral contusion/laceration which was not only the cause of the haematoma in majority of cases but was responsible for poor outcome. It was therefore not surprising that simple evacuation of the surface clot, as commonly practiced then, carried a high mortality of 70–85% in most reported series.

(v) Intracerebral haematomas, hardly acknowledged as a distinct clinico-pathological entity, and hence seldom mentioned as an indication for surgery at that time, was not an uncommon lesion. Moreover, like acute subdural haematoma, which often masked these lesions, the intracerebral haematomas, were also a consequence of brain contusion and laceration. It was not possible to differentiate intraparenchymal haematomas from contused oedematous swollen brain acting as a mass lesion, even after angiography. There were no published series of sizeable number of surgically treated patients with this lesion available at that time.

(vi) Clinical picture of brainstem lesions, mostly secondary to transtentorial herniation, may be observed in absence of observable structural pathology. Hence these symptoms and signs should not be accepted as evidence of irreversible brain damage.

Some of these observations, radically different from the prevailing beliefs, concepts and practices, prompted *'Lancet'* of February 18, 1961, to editorially comment, "The treatment of severe head injury clearly becoming less the province of the inactive master than it has been hitherto". Needless to say that this comment by one of the most prestigeous medical journals was a source of great personal satisfaction. What was even more gratifying was the practical application of this knowledge for day to day management of head-injured patients which resulted in reduced mortality (Tandon 1986). At the same time leads obtained from this initial study needed to be further elaborated, confirmed and submitted to clinical validation. Thus, followed a series of investigations spread throughout the years of my active professional and academic life. Most of these observations found further support from our own investigations (Tandon 1964, 1967, 1984, Tandon & Kristiansen 1965, Tandon et al. 1972, 1978, Mahapatra et al. 1985, Mahapatra & Tandon 1987, Colohan et al. 1989) and those of others.

For purposes of illustration I would just take a couple of examples.

Post Traumatic Temporal Lobe Lesions

As mentioned above at the time of our initial study the precise incidence and significance of this lesion were not generally recognised. To quote our monograph of 1960, "In spite of several papers on this subject during recent years, the clinical and therapeutic aspects have not attracted enough interest". Furthermore, "From a pathological standpoint it is difficult to draw a clear-cut line between a lesion which could be called cerebral contusion with haemorrhage and a real intracerebral haematoma". Based on the study of only 18 such patients it was emphasized, "that there is a group of cases among closed head injuries whose clinical picture is chiefly, if not totally, dependent on this lesion alone, which in some cases is amenable to surgical treatment". It was pointed out that these lesions were often mistaken as acute subdural haematoma

and hence subjected to inadequate surgical management. It is interesting to note that in the ensuing years this lesion was described under a variety of names, "intradural haematomas" (Phillips & Azariah 1965), "exploded temporal lobe" (Jamieson 1971) and "traumatic encephalomalacia" (Leeds et al. 1966). Skepticism about this entity continued to prevail for another decade. In 1978, we published a comprehensive review on the subject, based on our experience with a series of 85 cases, which was further elaborated in 1986 on the basis of 236 surgically treated cases (Tandon et al. 1978, Tandon 1986). It is worth pointing out that inspite of increasing acceptance of this lesion as the single most common indication for surgery in patients with closed head injury (Jenett & Teasdale 1981, Becker et al. 1982, Papo et al. 1982), controversy regarding indications and timing of surgery persisted till very late (de Vet 1976, Vigouroux & Guillermain 1981, Lanksch et al. 1979, Papo et al. 1982). Even though, already in 1961, Mc Laurin and Tutor (not aware of our earlier publication) pointed out "that the neurological picture (of acute subdural haematoma) was primarily, if not completely, the result of associated direct brain injury", many well known neurotraumatologists (Ramamurthi 1976, Harris 1971, Richard & Hoff 1974, Cooper et al. 1976, Lewin 1976, Rosenorn & Gjerris 1978, Bagchi 1980) continued to advocate its management by multiple burr hole evacuation. Not surprisingly, the mortality remained in the neighbourhood of 80%. Advent of CT scan finally provided a confirmation of our observations regarding the incidence, pathogenesis and treatment of this lesion. The mortality rate, though still high, has been reduced to around 40%.

Brainstem Lesions in Head Injury

One of the most dreaded complications of closed head injuries, which was commonly accepted as inevitable evidence of fatal outcome, was another condition, which attracted my attention as a result of the initial study mentioned above. Frequently observed in fatal cases, at that time there was no way of demonstrating its existence in those who survived. This no doubt contributed to its ominous significance. However, a series of clinico-pathological studies led us to challenge the prevailing belief. We concluded, that, "A similar clinical picture is also seen, though less frequently, in both fatal and surviving cases without brainstem haemorrhage". As a corollary, while the clinical signs suggesting brainstem involvement had ominous prognosis, they did not necessarily imply a fatal outcome (Tandon 1964, 1967, Tandon & Kristiansen 1965). Additional support for this view was provided by our studies on brainstem reflexes (Jadav et al. 1971, Tandon et al. 1973). It needs to be pointed out that most neurosurgeons, under the mistaken belief of the inevitable poor outcome, developed an attitude of fatalistic resignation once this diagnosis was suspected. On the basis of our studies we advocated a policy of not giving up and were rewarded by unexpected favourable outcome even in some patients with generally accepted poor prognosis (Mahapatra et al. 1985, Tandon 1986, Mahapatra & Tandon 1987). Availability of CT scan ultimately provided us the

opportunity to establish the validity of our earlier observations.

Instead of discussing individual clinico-pathological entities, let me now provide a glimpse of the overall consequences of the management strategies which evolved as a result of application of the results of these and several other clinical investigations. Such studies demand precision in documenting clinical observations, carrying out appropriate state-of-art investigations, critical analysis of the data with an open mind to test your hypothesis or develop new one for future testing. At a given moment of time there may be no techniques or technologies available to advance the investigations any further, but one must be prepared to exploit any new developments when the opportunity arises. At times, this very lack of latest technology, instead of proving a hurdle, may prove to be an unexpected boon as illustrated by the following example:

Notwithstanding several new management strategies evolved by neuro-traumatologists, towards the end of 1970s, it became obvious that there was no significant improvement in the outcome of severely head-injured patients. This prompted Langfitt (1978) to proclaim, "There is in fact very little evidence to support the belief that a large decrease in the mortality from head injury has occurred in the last 50 years". This led others to advocate an "aggressive" management regime consisting of elective artificial respiration, intracranial pressure monitoring, large doses of corticosteroid, and use of intravenous barbiturates in an ICU setting for all such patients (Becker et al. 1977, 1982, Marshall et al. 1979, Miller et al. 1981). Not having such facilities available to us at that time we of necessity had to be satisfied with prompt diagnosis and treatment of intracranial haematomas and relying on conventional means of care of the unconscious patients. A careful record of all our patients was maintained on properly coded proforma. A visit by an old friend, Dr John Jane from the USA, a recognized authority in the field, who followed the "aggressive" treatment mentioned above, provided an opportunity to compare and contrast our results based on these radically different management regimes. Records of consecutive series of patients treated at the two centres (541 from AIIMS, Delhi and 821 from University of Virginia, Charlottesville) were independently analysed by the Biostatistics Division of the National Institute of Health, USA. Without going into the details of this comparative study which are already published (Colohan et al. 1989), it was revealed that except for a small group of patients there was no significant difference in the outcome in these two series. It is a pity that these leads could not be persued to their logical conclusion. During the last decade, enough evidence has, however, been produced from different centres questioning the rationale of indiscriminate use of most of the individual components of the "aggressive" treatment owing to some of their adverse consequences (Muizelaar et al. 1991, Bouma et al. 1991, Rosner & Colely 1991, Sapolsky et al. 1985, 1986, 1988, Shapira et al. 1992, Hall 1992). Recent years have witnessed a series of reports suggesting

totally new strategies to reduce the mortality and morbidity of these patients (Tandon 1994). However, no randomised clinical trials are yet available to confirm these observations. It is a matter of regret that inspite of a number of centres in the country with the necessary clinical material and infrastructural facilities we have not taken the lead in doing so.

It is a matter of personal satisfaction that these clinical investigations and several others not included here (for the sake of brevity) have helped to improve the overall management of ever increasing number of patients with severe head injury. The incalculable reward is the number of valuable lives saved and their morbidity reduced. We are conscious that clinical studies alone will not provide newer insights into the molecular and biochemical basis of the cascade of events triggered by the injury, which result in secondary brain damage. These are no doubt responsible for the currently unacceptable morbidity and mortality associated with such injuries. In addition to providing a scientific basis for our therapeutic strategies, these studies help in reducing the cost of treatment. It is, however, a matter of regret that even in this era of "evidence based medicine, established traditions and entranched prejudices have often inordinately delayed utilisation of the results emanating from such studies, especially if these emanate from developing countries (Tandon 1986).

Tuberculosis of the Nervous System

This brings me to another field of clinical research specially relevant for our country. Having received all my neurosurgical training abroad, on resuming work in India, I was suddenly faced with diseases and clinical syndromes not encountered earlier. It soon became obvious that approximately one in every five patients presenting to us was suffering from some form of tuberculosis of the nervous system. It became imperative to gather all possible knowledge about these disorders, initially from the literature and the experiences of the few colleagues in the country at that time. Clinical studies, systematically carried out, helped to delineate the disease profile as seen in our patients. Soon these led to identification of specific problems requiring detailed investigations. These have been the subject of a series of studies published from time to time throughout my professional career. However, this presentation is restricted to only a few examples.

Postmeningitic Hydrocephalus

This devastating sequelae of tuberculous meningitis, a cause for very high mortality and morbidity, accounted for a large number of neurological and neurosurgical patients in most centres in India. In absence of the availability of the recently developed CSF shunting devices, a rational management of such patients was a frustrating experience. The clinico-pathological studies carried out by us and others in the country not only helped to develop appropriate management regimes for these unfortunate patients but have received much international recognition. As a matter of fact, in one of the recent books on infections of the central nervous system it has been stated,

"In more recent years, the major contributions on both the pathology and the clinical manifestations of tuberculosis of the brain and spinal cord have come from workers in India, in particular Dastur, Tandon and Wadia" (Kocen 1987). To mention one such study prompted by our unfortunate experience with a young child whose investigations revealed a panventricular hydrocephalus with a blocked fourth ventricle secondary to tuberculous meningitis. It appeared a simple surgical exercise to remove the mechanical obstruction by deroofing the ventricle to reestablish the flow of CSF. Much to our dismay a "successful" operation resulted in a fatal outcome after few days. A repetition of similar experience with another identical case made us suspect the rationale for the operation since technically the surgerey was flawless. Observations on other patients with post meningitic hydrocephalus, utilising the then availlable modes of investigations (ventriculography, pneumoencephalography), indicated that the pathogenesis of this condition is ill-understood. A need for a better understanding of the CSF dynamics and not just the pathology became obvious. There was, however, no technique then available to study this in patients. This became possible a few years later when isotope cisternography was introduced. We promptly used it to investigate a series of patients of tuberculous meningitis to establish the incidence and pattern of alterations in CSF dynamics in these patients. This for the first time demonstrated that the site of obstruction in the CSF pathways and the resulting alterations in flow dynamics varied from patient to patient. Besides providing a better insight regarding the pathophysiology of post meningitic sequelae, it also explained why we failed to help our patients with blocked fourth ventricle by the deroofing operation. This operation converted an obstructive hydrocephalus into a communicating one without relieving the intracranial hypertension (Tandon et al. 1973, 1975). Even though the availability of CSF diversion devices fortunately provided a reliable means of relieving hydrocephalus by a standard operation irrespective of the nature, extent and site of obstruction it does not reduce the scientific value of these investigations.

It may be pointed out this knowledge could only be gained by study of human patients and not by studies in experimental animals which we had initiated around the same time.

Experimental Tuberculosis of the Central Nervous System

Impressed by the protean manifestations of tubercular infection of the central nervous system observed in our patients one wondered why one patient developed meningitis and another a tuberculoma. While some developed focal lesions only others had a diffuse lesion, some had a single lesion and others multiple ones. We hypothesised that the nature of lesion was probably an outcome of a complex host-parasite relationship. Since there was no way of manipulating these interactions in our patients, we planned to study this in experimental animals, where one could control the various parameters related to the host and the

organisms. A survey of the literature revealed that there was no animal model for investigating these questions earlier. Several well meaning colleagues and seniors tried to dissuade us from embarking on such a venture in which others had not succeeded as was apparent from the literature. Following some initial studies in guinea pigs which proved to be unrewarding, we decided to explore the possibility of utilising monkeys for this purpose considering their evolutionary proximity to man. Without going into details of these experiments published elsewhere, (Tandon et al. 1970, 1973) in brief, we manipulated the immune status of different groups of monkeys (unprotected, BCG vaccinated and tuberculin hypersen-sitized) and varied the doses and routes of injection of the bacilli (intracardiac, intracisternal and intracerebral). We thus hoped to produce the diverse pathology observed in our patients. Our efforts were rewarded to a great extent. We observed that CNS lesions failed to develop unless tubercle bacilli were injected either in the CSF pathways or directly in the brain. Unprotected animals developed acute diffuse meningitis following intracisternal injection, the BCG-vaccinated ones reproduced the pathological picture of chronic, basal meningitis similar to the one commonly observed in humans, the hypersensitized animals manifested hyperacute reaction with massive necrosis and oedema akin to tuberculous encephalopathy earlier described by Dastur and Udani (1966) in their paediatric patients. We were able to produce a localised lesion in the brain, reminiscent of a tuberculoma, which on histology proved to be a tuberculous abscess.

It is worth pointing out that till today there is no better experimental model of CNS tuberculosis. At the sametime it is a matter of regret that we not only failed to produce a classical cerebral tuberculoma, but owing to circumstances inherent in pursuit of science in our country, this line of study could not be pursued further to explore in depth the more basic questions of the course and pattern of cellular and humoral immune responses, their significance in development of the variety of lesions, their response to drugs. Let me add that paucity of research funds or lack of investigative capabilities and infrastructure were not responsible for discontinuing this promising line of research. These required a multidisciplinary effort which was not forthcoming inspite of all attempts. Such studies which have currently acquired renewed interest owing to the resurgence of tuberculosis in association with HIV/AIDS epidemic, lie burried in some of our low impact journals in the country.

Computerized Tomographic (CT) Investigations of CNS Tuberculosis

The difficulties of reliably diagnosing CNS tuberculosis was, and to some extent even today is, a matter of great concern to clinicians all over the country. With our own abiding interest in this subject, when in 1978, the first CT scanner was installed in the country at our Institute, we promptly initiated investigations to assess its utility in diagnosis of such lesions. Not unexpectedly at that time

only a handful of preliminary reports were available on the subject. For all practical purposes we had to establish our own diagnostic criteria based on careful correlation of clinico-pathological findings with image morphology. For the first time we were able to non-invasively visualise these lesions directly. It was not long before we were able to lay down reliable diagnostic criteria and utilise the same to study therapeutic response objectively. Characteristic basal exudates could be demonstrated in 80–90% of cases with tuberculous meningitis. These could be graded for their severity which helped to predict the prognosis. Co-existence of hydrocephalus, tuberculomas or cerebral infarcts, which influenced therapeutic management, could be determined (Bhargava & Tandon 1980a, Bhargava et al. 1982, Tandon et al. 1988). These were no doubt important contributions widely cited. However, it was in respect to intracranial tuberculomas, that our studies ushered in a radical change in the management strategies. While earlier it had been surmised that atleast some intracranial tuberculomas may resolve under medical therapy, lack of reasonable proof of diagnosis and inability to objectively demonstrate the same dictated the need for surgery for these cases (Ramamurthi 1956, 1973, Tandon & Pathak 1973). Following a systematic study of patients with intracranial tuberculomas it could be unequivocally established that majority of these patients can be cured with antitubercular drugs alone. The role of surgery was limited for patients with imminent threat to life or vision due to raised intracranial pressure, those who fail to respond to medical therapy and if the diagnosis is in doubt (Bhargava & Tandon 1980b, Tandon & Bhargava 1985, Bhatia et al. 1986, Tandon 1990, 1996). This management regime independently confirmed by others is now universally accepted. It has thus saved a large number of patients from unnecessary risks, inconvenience and expense of surgery. It is obvious that only well planned clinical research could provide this valuable information. It is true that even today some degree of uncertainty remains regarding the scientifically acceptable diagnosis based on CT alone. One would have wished that a reliable immunodiagnostic test was developed to provide a more definitive diagnosis. Inspite of several groups working in the country, a sensitive and specific test has so far elluded these efforts.

Aneurysmal Subarachnoid Haemorrhage

Till as late as mid seventies most neurosurgeons believed that subarachnoid haemorrhage (SAH) due to intracranial aneurysm was far less frequent in India than elsewhere (Mathai & Chandy 1965, Ramamurthi 1970). Sambasivan's experience at Trivandrum for the first time cast doubts on this presumption. A multicentric national study involving six centres was therefore planned under the aegis of the Indian Council of Medical Research (ICMR). The aims of the study were to investigate all hospital-admitted patients with subarachnoid haemorrhage to establish its etiology, and to assess the incidence of atherosclerosis and congenital anomalies in the circle of Willis, which

were believed to predispose to aneurysm formation. These investigations were carried out as per a mutually agreed common protocol, utilising universally accepted methodology. Notwithstanding some inherent limitations of this study, contrary to the prevalent views, it revealed that once the diagnosis of SAH was established and the patients were fully investigated, intracranial aneurysm was its most common cause. At the sametime we observed that atleast in Chandigarh and Delhi the incidence of atherosclerosis and anomalies of the Circle of Willis, including medial defects were also identical to the reports from the rest of the world (ICMR 1987). A greater awareness of this entity, consequent upon this study, has been responsible for increasing number of such patients now being diagnosed and successfully treated in most major neurosurgical centres in the country (Sambasivan et al. 1984, Prakash 1988, Kak et al. 1988, Ranganadham et al. 1990, Rout 1996). Many lives have thus been saved from this eminently treatable life-threatening condition. For some unexplained reasons, intracranial aneurysms continue to be diagnosed infrequently in Madras. Regretably no concerted effort has yet been initiated to investigate this matter further, which if confirmed promises to provide interesting insights into the pathogenesis of this order.

In conlcusion, I hope I have been able to illustrate that while preoctupied 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 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. No doubt sophisticated laboratory investigations and experimental studies may be required to provide additional support or confirmation of such studies. It often fails to be recognized that good clinical research involves no less intellectual inputs, or rigours of observation and analysis than any frontline laboratory studies. On the other hand, clinical investigations are beset with a number of inherent handicaps. The research parameters are not under the control of the investigator and cannot be manipulated at will. No procedure should add to the discomfort or slightest risk to an already sick individual. Any deviation from the prevailing standard diagnostic or therapeutic procedures should conform to the highest code of ethical norms. Necessary controls, the essential component of any experimental study, are most often not available. Paucity of quality-controlled laboratory investigations, socio-cultural obstacles for long-term follow-up and autopsy studies, and excessive burden of service load prove additional deterrants for well planned prospective clinical studies. However, properly conducted clinical studies can provide invaluable insights into the disease process and thus help reduce its morbidity and mortality. On the face of

it these may not always match the scientific sophistication of basic research, yet in terms of their practical utility for reducing human misery they deserve due recognition. It will be presumptuous on my part to recount the generally accepted motivations for pursuit of scientific research which are equally applicable to clinical research. I trust I have been able to illustrate the special needs for such studies. Many diseases prevalent in our country are of little interest to others who have better resources to investigate these. It may be mentioned that out of the worldwide investment for health research estimated to be 30 billion dollars, only 5% (1.6 billion) is devoted to health problems of developing countries, which account for 93% of the world's burden of preventable mortality. Same disease prevalent in different parts of the world may not present identical problem, thus requiring locale specific studies. Different ethnic populations, different genetic make-up and socio-cultural-ecological environment modify the manifestations and therapeutic responses which demand re-evaluation of knowledge generated elsewhere. Without the indigenously carried out clinical studies one would not have discovered the limitations in our population of the standard prophylactic regime of BCG or oral polio vaccine practised elsewhere. By exploiting the opportunities and strengths provided by our vast clinical material we not only serve a societal need but can more easily acquire international scientific leadership than by attempting to replicate the work on conditions being investigated elsewhere. It is regretted that the medical profession in the country by and large has failed to utilize these unparalleled opportunities and challenges to make our researches either socially relevant or scientifically excellent.

References

Bagchi A 1980 *An Introduction to Head Injuries* pp 5859, (Calcutta : Oxford University Press)

Becker D P, Miller J D, Ward J D 1997 The outcome from severe head injury with early diagnosis and intensive management; *J. Neurosurg.* **47** 491-502

-------, -------, Young H F 1982 Diagnosis and treatment of head injury in adults; in *Neurological Surgery*, Vol **1** pp 1938-2083 (Philadelphia : W B Saunders Company) Vol **1** pp 1938-2083

Bhargava S and Tandon P N 1980 Intracranial tuberculomas - a C T study; *Br. J. Radiol.* **53** 935-945

------- and ------- 1980 C N S tuberculosis - lessons learnt from C T studies; *Neurology India* **28** 207-212

-------, Gupta A K and Tandon P N 1982 Tuberculous meningitis - A C T study; *Br. J. Radiol.* **55** 189-193

Bhatia R, Tandon P N and Mishra N K 1986 Inflammatory lesions of the basal ganglia and thalamus; *Neurosurgery* **19** 983-988

Bouma C J, Muizelaar J P and Choi S C 1991 Cerebral circulation and injury, the elusive role of ischaemia; *J. Neurosurg.* **75** 689-693

Colohan A R T, Alves W M, Gross C R, Turner J C, Mehta V S, Tandon P N and Jane J A 1989 Head injury mortality in two centres with different medical services and intensive care; *J. Neurosurg.* **71** 202-207

Cooper P R, Rovit R L and Ransohoff J 1976 Hemicraniectomy in the treatment of acute subdural hematoma. A reappraisal; *Surgical Neurology* **5** 25-28

Dastur D K, Udani P M 1966 Pathology and pathogenesis of tuberculous encephalopathy; *Acta Neuropathologica* **6** 311

de Vet A C 1976 Traumatic intracerebral haematoma; in *Handbook of Clinical Neurology*, **24** 351-368 eds P J Vinken, G W Brugen (Amsterdam : North-Holland Publishing Company) **24** 351-368

Hall E D 1992 The neuroprotective pharmacology of methylprednisolone-a review; *J. Neurosurg.* **76** 13-22

Harris P 1971 Acute traumatic subdural haematomas; in *Head Injuries* 321-326 (Edinburgh : Churchill Livingstone)

Indian Council of Medical Research 1987 *Epidemiological study on subarachnoid haemorrhage in India* (1972-75), New Delhi pp. 1-34

Jadhav W R, Sinha A and Tandon P N 1971 Cold caloric test in altered states of consciousness; *Laryngoscope* **81** 391-395

Jamieson K G 1971 Diagnosis and treatment of head injuries in *Head Injuries;* (Edinburgh: Churchill Livingstone) 294-297

Jenett B and Teasdale G 1981 *Management of Head Injuries* (Philadelphia : F.A. Davis Company)

Kocen R 1987 Tuberculosis of the nervous system; in *Infections of the Nervous System* eds P G E Kennedy and R T Johnson (Butterworth: London)

Kristiansen K and Tandon P N 1960 Diagnosis and surgical treatment of severe cranio-cerebral injuries; *J. Oslo City Hospital (Suppl)* **10** 107-213

Langfitt T W 1978 Measuring the outcome from head injuries; *J. Neurosurg.* **48** 673-678

Lanksch W, Grumme T H and Kazner E 1979 *Computed Tomography in Head Injuries* (Berlin: Spring Verlag)

Leeds N E, Reid N D and Rosen L M 1966 Angiographic changes in cerebral contusion and intracerebral hematomas; *Acta Radiologica* **5** 320-327

Lewin W 1976 Changing attitudes to the management of severe head injuries; *Brit. Med. J.* **2** 1234-1239

Mahapatra A and Tandon P N 1987 Brainstem auditory evoked response and vestibulo-ocular reflex in severe head injury patients; *Acta Neurochirurgica (Wien)* **87** 40-43

Mahapatra A K, Tandon P N, Bhatia R and Banerji A K 1985 Bilateral decerebration in head injury patients; *Surgical Neurology* **23** 536-540

Marshall L F, Smith R W, Shapiro H M 1979 The outcome with aggressive treatment in severe head injury: 1. The significance of intracranial pressure monitoring; *J. Neurosurg.* **50** 20-25

Mathai K V and Chandy J 1965 Incidence of subarachnoid haemorrhage; *Neurology India* **13** 40-41

McLaurin R L and Tutor F T 1961 Acute subdural hematoma. Review of ninety cases; *J. Neurosurg.* **18** 61-67

Miller J D, Butterworth J F and Gudeman S K 1981 Further experience in the management of severe head injury; *J. Neurosurg.* **54** 289-299

Muizelaar J P, Marmaron A and Ward J D 1991 Adverse effects of prolonged hyperventilation in patients with severe head injury; *J. Neurosurg.* **75** 731-739

Papo I, Caruselli G, Scarpelli M and Luongo A 1982 Mass lesions of frontal lobes in acute head injury. A comparison with temporal lesions; *Acta Neurochirurgica (Wien)* **62,** 47-72

Phillips D G and Azariah R G S 1965 Acute intracranial haematoma from head injury; *Brit. J. Surgery* **52** 218-222

Prakash B 1988 *Surgical Approach to Intracranial Giant Aneurysms;* Paper presented at *38th Annual Conference of Neurological Soc. India,* Chandigarh

Ramamurthi B 1956 Experiences in tuberculomas of the brain; *Indian J. Surgery* **18** 452

------- 1970 Incidence of intracranial aneurysms in India; *J. Neurosurgery* **30** 152-157

------- 1973 Tuberculomas of the brain. Summary of a twenty years experience; In *Tuberculosis of the Central Nervous System.* eds C C Kapila, D K Dastur, B Singh, P N Tandon, (Indian Academy of Medical Sciences) p.85

------- 1976 Acute subdural haematoma; in *Handbook of Clinical Neurology* pp 279-296. eds P J Vinken, G W Bruyn (Amsterdam: North-Holland Publishing Company)

Ranganadham P, Mahapatra A K and Banerji A K 1990 Analysis of 129 cases of intracranial aneurysms. A 10 years study of AIIMS; *Neurology India* **38** 15-24

Richard T and Hoff J 1974 Factors affecting survival from acute subdural haematoma; *Surgery* **75** 253-258

Rosenorn J and Gjerris F 1978 Long term review of patients with acute and subacute subdural haematomas; *J. Neurosurg.* **48** 345-349

Rosner M J and Colely I B 1991 Cerebral perfusion pressure, intracranial pressure and head elevation; *J. Neurosurg.* **75** 689-693

Rout D, Nambiar U and Nair S 1996 Vascular malformations; in *Textbook of Neurosurgery* pp 633-657 eds B Ramamurthi, P N Tandon, R Ramamurthi, K Sridhar (Livingstone New Delhi: B I Churchill) pp 633-657

Sambasivan M, Nair S K R and Sanal Kumar P 1984 Analysis of 1000 cases of subarachnoid haemorrhage and experience with intracranial aneurysms; *NeurologyIndia* **32** 17-25

Sapolsky R M 1986 Glucocorticoid toxicity in the hippocampus, temporal aspect of synergy with a kainic acid; *Neuroendocrinology* **43** 440-444

-------, Packan D R and Vale W W 1988 Glucocorticoid toxicity in the hippocampus : *in vitro* demonstration; *Brain Research* **453** 367-371

------- and Pulsinelli W A 1985 Glucocorticoids potentiate ischaemic injury to neurons : Therapeutic implications; *Science* **229** 1397-1400

Shapira Y, Artru A A, Yalid G and Shohami E 1992 Methylprednisolone does not decrease eicosanoid concentrations or edema in brain tissue or improve neurological outcome after head trauma in rats; *Anaesthesia Analgesia* **75** 238-244

Tandon P N 1964 Brainstem haemorrhage in cranio-cerebral trauma; *Acta Neurologica Scandinavica* **40** 375-385

------- 1967 Pahtophysiology of brainstem disturbances following head injury; *Neurology India* **15** 20-23

------- 1984 Head injuries. A quest for preventable morbidity and mortality; Annual Number. The National Academy of Sciences, India, 59-68

------- 1986 Management of head injury: Fads, fasions and facts; *Neurology India* **34** 1-30

------- 1990 Intracranial tuberculomas. Unresolved problems; in *Advances in Neurology* eds J S Chopra et al. (Elsevier Science Publishers BV / Biomedical Division) p 299

------- 1996 Nervous system tuberculomas and their surgical treatment; *Neurological Infect. Epidemiol.* **1** 109-117

------- and Bhargava S 1985 Effect of medical treatment on intracranial tuberculomas - a CT study; *Tubercle* **66** 85-97

-------, Bhatia R and Banerji A K 1973 Vestibuloocular reflex and brainstem lesion. A clinicopathological study; *Neurology India* **21** 193-199

-------, Bhatia R and Bhargava S 1988 Tuberculous meningitis; in *Handbook of Clinical Neurology* **8**, pp 195-226 ed A AHarris (BV : Elsevier Science Publishers)

------- and Kristiansen K 1965 Clinicopathological observations on brainstem disorder in cranio-cerebral injuries; *Excerpta Medica, Int. Cong. Ser.* **93** 78

------- and Pathak S N Tuberculosis of the central nervous system; In *Tropical Neurology* pp 37-62 ed. J D Spillane (London Oxford : Oxford University Press)

-------, Prakash B and Banerji A K 1978 Temporal lobe lesions in head injury; *Acta Neurochirurgica* (Wien) **41** 205-221

-------, Rao M A P, Pathak S N and Dar J 1973 RIHSA cisternography in the management of tuberculous meningitis in: *Tuberculosis of the Nervous System*: p 55-57 eds C C Kapila, D K Dastur, B Singh, P N Tandon: (Indian Academy of Medical Sciences) p 55-57

------- , Rao M A P, Banerji A K, Pathak S N and Dar J 1975 Isotope scanning of the cerebrospinal fluid pathways in tuberculous meningitis; *J. Neurolog. Sci.* **25** 401

-------, Singh B, Bhatia R and Banerji A K 1972 Electroencephalographic study of sleep in cases of prolonged unconsciousness; *Neurology India* **20** 261-266

-------, Singh B, Mahopatra L N and Kumar M 1970 Experimental tuberculosis of the central nervous system; *Neurology India* **18** 81-85

-------, ____, Mahopatra L N and Kumar M 1973 Effect of 'immunization' and 'sensitization' on tuberculous lesion of the central nervous system eds CC Kapila, D K Dastur, B Singh, P N Tandon. (Indian Academy of Medical Sciences) pp 213

Vigouroux R P and Guillermain 1981. Posttraumatic hemorrhagic contusion and laceration; in *Progress in Neurological Surgery*. **10** 49-163 eds H Krayenbuhl, P E Maspci, W H Sweet, (Krager, Basel)