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Doctor–Patient Relation

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Mr. Chairman and friends, I consider it one of the most fulfilling and yet humbling experience of my life to have been elected and serve as the President of the NAMS. In that capacity, it is my privilege to deliver the Academy Oration of this year. I have chosen to talk on **"Doctor-Patient Relation"** a subject dear to my heart. At this time I would like to recall and pay my homage to some of those superb teachers of Medicine and great human beings from whom I learnt the alphabet and art of Medicine. I would like to dedicate this Oration to those inspiring men of Medicine: Dr. K.L. Wig, Dr. R.P. Mehrotra and Dr. P.N. Chhuttani.

Ladies and gentlemen, doctor-patient relation is one of the most unique and privileged relations. The only relation to my mind which can stand above this relation is the "mother and child" bond which of course, is the most satisfying, full of love, kindness, sacrifice and is almost a divine relation. The third relation which I can imagine reaching somewhere near these two would be the "teacher-taught" relation. A patient to a doctor is at once a dependent child, an eager student, a friend and a person needing advice, help, sympathy, understanding and hope. In the last 37 years and two months of my professional career since I graduated, I have had the privilege of enjoying this relation. I would not wish to have any other profession if I were to live my life all over again.

The doctor-patient relation is based on rich traditions, experience and history of our profession, with some modifications and refinements taking place all the time. But I do believe that the dynamics of doctor-patient relation cannot change in its basic ingredients. We all start with *Hippocratic Oath* enunciated 2500 years ago. The words ring true and pure even today - *"I swear by Apollo physician, by Ascelpius, by health, by heal-all, and by all the gods and goddesses, making them witnesses, that I will carry out, according to my ability and judgement, this oath and this indenture"*. And thus it goes on to say about the regard for the teacher, his children, his family, treating the sick according to his ability, not to use poison

*Academy Oration (1998)

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under any provocation or suggestion, not to enter any house except to help the sick and without any intention of wrong doing especially while treating the woman, to treat the patient information completely confidential and so on.

However, we often forget that in our own culture, there is a rich heritage of professional ethics and medical traditions and perhaps even more elaborate and complete. The divine physician Charaka, laid down the qualities of a physician and went beyond the Hippocratic Oath while describing the conduct, behaviour and even personal qualities of the physician. He talked of love and sympathy for the patient. He required the physician to be fearless, merciful to the poor, tolerant to unpalatable words and conquer the very root of hatred. He forbade adultery, disclosure of secrets and defects of the patients. He had elaborate advice for the physicians which included how to dress, how to speak, how to behave with the patients and people. In fact his instructions covered every conceivable kind of activity in the daily lives of men and women. Compassion, however, was the central core of his professional conduct-*"A good physician nurtures affection for his patients exactly like the mother, father, brothers and kins. The physician having such qualities gives life to the patients and cures their diseases"*. He condemned negativism and nihilism as undesirable and urged wise persons to see things properly with the lamp of wisdom.

Galen and his thinking dominated the European Medicine for many hundreds of years till the dawn of the scientific era starting in the 15th century. With the foundation of modern Medicine laid down by Vesalius, William Harvey, Virchow, Claude-Bernard, Louis Pasteur, Robert Koch and many others, towards the end of 19th century, we entered the beginning of modern era of medicine. As an epitome of this era, I would like to refer to Sir William Osler, a physician, a teacher, a researcher and writer par excellence. His example of doctor-patient relation is perhaps one of the most shining examples for any student of medicine to emulate. If you go through his biography by Harvey Cushing and see his *"Textbook of Medicine"*, you will find endless examples of how he viewed his patients with utmost compassion, understanding, devotion and helping attitude. In fact, one can talk for the next one hour about his qualities as a physician, but I will mention only a few. One of the most touching examples of his love for his patients was about a young English man who had come to Montreal in 1875 on a visit and fell ill. Sir Osler, having diagnosed malignant small pox, moved him into the hospital and looked after him. Since he was a foreigner and friendless, Dr. Osler sat by his bed side holding his hand till he breathed his last. He then went on to write to his family giving minute by minute account of this young man's illness and his last moments so that the family to this man had the consolation that their loved one was cared for and did not die as an abandoned individual in a foreign land. His letter is worth reproducing in full:

"My dear Sir, No doubt before this, the sorrowful intelligence of your son's death has reached you, and now, when the first shock has perhaps to a slight extent passed away, some further particulars of his last illness may be satisfactory. On the evening of Thursday 22nd, and on the following day, I discovered unmistakable evidence of the nature of his disease. On Saturday, in consultation with Dr. Howard-the leading practitioner of our city, his removal to the smallpox hospital was decided upon. I secured a private ward and took him there in the evening.

After 11 PM, he began to sink rapidly, and I dared not to leave him. He did not speak much, but turned round at intervals to see if I were still by him. About 12 PM, I heard him muttering some prayers, but could not catch distinctly what they were. Shortly after this he turned round and held out his hand, which I took, and he said quite plainly, 'Oh thanks'. These were the last words the poor fellow spoke. From 12.30 he was unconscious, and at 1.25 AM passed away, without a groan or struggle. As the son of a clergyman and knowing well what it is to be 'a stranger in a strange land', I performed the last office of Christian friendship I could, and read the Commendatory Prayer at his departure. Such my dear sir, as briefly as I can give them are the facts relating to your son's death".

Thirty years later, when he went to Oxford as a Regius Professor of Medicine, the sister and mother of the young man after having heard his name enquired whether he possibly could be the same physician who wrote them that letter. He then visited the old mother and presented her the photograph of her son's grave which he specially obtained from Montreal before he called on the mother. Ladies and gentlemen, in this story there is no science, there is not even a diagnostic miracle. This is a moving story of deeper qualities of compassion, love and true feeling for the patients, which cannot be taught, but can only be demonstrated and felt.

It is amazing how he saw what would be coming with much greater intensity, i.e., our tendency to refer the patient by his disease or sometime by bed number rather than as a human being-*"But to care more particularly for the individual patient than for the special features of the diseases... Dealing, as we do, with poor suffering humanity, we see the man unmasked, exposed to all the frailties and weaknesses, and you have to keep your heart soft and tender lest you have too great a contempt for your fellow creatures. The best way is to keep a looking-glass in your own heart, and the more carefully you scan your own frailties the more tender you are for those of your fellow creatures".*

He had a great deal to say about the sense of cheerfulness, hope and optimism with which a physician should go round even among the seriously ill and even dying patients-*"Amidst an eternal heritage of sorrow and suffering our work is laid, and this eternal note of sadness would be insupportable if the daily tragedies were not relieved by the spectacle of the heroism and devotion displayed by the actors. Nothing will sustain you more potently than the power to recognize in your humdrum routine, as*

perhaps it may be thought, the true poetry of life-the poetry of the commonplace, of the ordinary man, of the plain, toil-worn woman, with their loves and their jobs, their sorrows and their griefs. The comedy, too, of life will be spread before you, and nobody laughs more often than the doctor at the pranks Puck plays upon the Titanias and the Bottoms among his patients. The humorous side is really almost as frequently turned towards him as the tragic. Lift up one hand to heaven and thank your stars if they have given you the proper sense to enable you to appreciate the inconceivably droll situations in which we catch our fellow creatures. Unhappily, this is one of the free gifts of the gods, unevenly distributed, not bestowed on all, or on all in equal proportions. In undue measure it is not without risk, and in any case in the doctor it is better appreciated by the eye than expressed on the tongue. Hilarity and good homour, a breezy cheerfulness, a nature, 'sloping towards the sunny side', as Lowell has it, help enormously both in the study and in the practice of medicine. To many of a sombre and sour disposition it is hard to maintain good spirits amid the trials and tribulations of the day, and yet it is an unpardonable mistake to go about among patients with a long face".

My dear friends, times have changed further. A scientific and technological explosion has taken place. In addition to the personal qualities and art of medicine, science has entered the practice of medicine in a big way. The traditional doctor-patient relation has been complicated or shall I say modified by- (i) the escalating cost of medicine; (ii) the role played by technology in the diagnosis and management of patients; (iii) multiple consultations with various specialists; (iv) movability of patients from place to place and hospital to hospital; (v) the increasing awareness of patients of their legal rights and the element of greed; and (vi) finally our hospital working on commercial basis and almost like a factory. The doctor-patient relation is, therefore, modified and changed greatly. However, I have no doubt that the basics and fundamentals would remain the same.

The basis of this relation remains the same as enunciated by Charak, Hippocrates and as practiced by Sir William Osler. These, however, need to be modified with the introduction of technology which has introduced new elements of diagnostic and therapeutic help as well being a source of error and commercialism. I don't think I should give a list of do's and don'ts in today's talk but based on my own experience would make mention of a few guiding principles and some areas of potential hazards.

Doctor-patient relation is a triangular relation with each having two way relation with the other two. This triangle consists of the doctor, the patient and the disease and enclosed in the triangle are the cultural, ethical, social and economic background both of the doctor and the patient. Sometime we forget that the doctor's own background greatly tempers his ability to deal with the patients and his capacity to handle various situations arising out of it, whether he comes from the urban background or the rural, originated from the middle

class, poor or the neo-rich convent educated class. You can see the difference of behaviour in these classes. The same is true of the patient. His expectations and needs will also vary according to these factors and anybody who does not recognise this is bound to falter. It is, therefore, imperative for the practising physician to know the full background of the patient. The personal history of the patient so much emphasized to a medical student is precisely for this reason. *"Know thy patient"* is thus the basic cardinal principle of a good doctor-patient relation. I wish we could also tell our patients to *"know thy doctor"*. That however could be a risky proposition. Many of us would be left with no patients!

Ethical behaviour (not the legal requirement) is, however, at the core of this relation. A lot has been written about this, as I referred to earlier. Only when something goes wrong here, the doctor-patient discord arises and the problems of the Consumer Protection Act start. A lot is available in the legal form as defined under Tort's law, Helsinki Code of the World Medical Association of 1964 and revised in 1975, the Nuremberg Code of 1945, Code of Medical Ethics of the Medical Council of India of 1970 in our own country, the Guidelines by the Counsel for the International Organisation of Medical Sciences of 1984 and so on. Recently the Indian Council for Medical Research have circulated elaborate ethical guidelines in our country.

One of the important and central considerations of these guidelines is the true and honest communication with the patient offering him all the information, advice and finally the choice. Informed consent has not been defined to every body's satisfaction. It is primarily a legal shape of a true and sincere communication between the doctor and the patient. Devoid of that sincerity and true desire to offer patient a choice, this consent has no meaning and that is why often does not hold water under close scrutiny. I am convinced, on the basis of my own experience and my observations of the practice of medicine in various places, that a sincere, sympathetic and compassionate advice to the patient describing both the potentialities and limitations of a particular therapy or procedure is the best antidote against any potential breakup of relation or legal maneuver. The modern practice of medicine does have limitations and constraints of time and attitude in establishing and maintaining this communication.

At the Postgraduate Institute of Medical Education and Research, Chandigarh we have been lucky that we have not had too many consumer-oriented legal cases. But whatever cases have arisen, I can say, almost all of the cases were because of basic lack of communication, lack of patience, respect for the family and sometime sheer pressure and stress of work. There would be vicious and misguided claimants, as a person demanding money for the failure of vasectomy operation claiming Rs. 10 lakh. But I have no doubt Courts and the concerned agencies can quickly sift through these cases and this case was thrown out promptly.

Let me mention the groups of patients, who, inspite of all your good intentions, would pose problems and anybody who has been practising medicine for some length of time can quickly recognise these patients. They include chronic demanding patients with vested interest in their ailments, one of the variants being the Munchausen syndrome, rich neurotics demanding attention for their money, highly educated but ignorant persons who will try to tell you that they know everything and would be most uncompliant, V.I.P. patients of all varieties, the hospital employees and finally let me admit, the doctors are most difficult of the patients. I would suggest that there is only one method of dealing with these types of patients. It needs utmost degree of patience, detailed communication, well kept record and polite but firm handling of their demands. One should neither yield to the oppression nor show any undue attention or repulsion. Collective consultations and bringing in an experienced colleague often helps in resolving the problems created by this category of patients. I hardly need to add here that the examination of a female patient needs all the precaution, care, dignity and grace. No person should run into any difficulty if he follows the ordinary social norms in this respect.

Conversely, let us not shy away from the poor, the unkempt, the demented, the helpless and the rogue. He perhaps truly tests the doctor's inner core, his professional commitment and human qualities. It is hard to emulate Mother Teresa or Bhagat Puran Singh of Pingalwara (Amritsar) but it is worth trying.

I do wish to mention another group of patients now being seen more and more in the modern tertiary care hospitals, intensive care units-acutely ill patients suffering from malignancies and other incurable diseases. Here again a good communication with the patients, their family and offering them the choices often resolves the conflicts which seemingly arise and often puts a young professional in dilemma. The cardinal principles of this relation are: never to abandon the patient and the family, not to withdraw, never to take the hope away (as Sir Osler said-*eternal hope which comes to us all*) and perhaps to make an attempt to put yourself in the position of the patient's family and offer them the advice as you would see from their side.

Ladies and gentlemen, the subject is such that one can go on perhaps indefinitely much longer, but I would like to end here and at the end, quote what I consider the best portrait of a doctor. This lyrical description from the first edition of the Textbook "Harrison's Principles of Internal Medicine" must have been quoted by me to my students, God knows how many times.

"No great opportunity, responsibility, or obligation can fall to the lot of a human being than to become a physician. In the care of the suffering he needs technical skill, scientific knowledge, and human unders-

tanding. He who uses these with courage, with humility, and with wisdom will provide a unique service for his fellow man, and will build an enduring edifice of character within himself. The physician should ask of his destiny no more than this; he should be content with no less.

Tact, sympathy and understanding are expected of the physician, for the patient is no mere collection of symptoms, signs, disordered functions, damaged organs, and disturbed emotions. He is human, fearful, and hopeful, seeking relief, help and reassurance. To the physician, as to the anthropologist, nothing human is strange or repulsive. The misanthrope may become a smart diagnostician of organic diseases, but he can scarcely hope to succeed as a physician. The true physician has a Shakespearean breadth of interest in the wise and the foolish, the proud and the humble, the stoic hero and the whining rogue. He cares for people".

Mr. Chairman, ladies and gentlemen, I thank you for your patience and indulgence.

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Neurosurgery Past, Present and Future–A Saga of Unceasing Effort and Wondrous Achievement

V. Balasubramaniam

SUMMARY

The history of neurosurgery is discussed in two parts the pre-Cushing era and the Cushing-Dandy era. The Cushing-Dandy era is described with the contributions of these two to neurosurgery. The development of neurosurgery and neurodiagnostic methods is traced upto 1972. The modern era of neurosurgery along with all the sophisticated equipments for diagnosis and neurosurgical procedures has brought improvement from many perspectives. The usefulness of modern neurosurgery and the various high cost equipments are analysed from various angles. Advances have taken place with increase in diagnostic accuracy, greater number of condtions diagnosed and also bolder surgery resulting in better quality of life. Judged from all these perspectives modern neurosurgery has justified the high cost and fulfilled the expectations of the scientists who have worked hard towards the improvement. The fear of displacement of clinical neurology is allayed indicating its continuing usefulness.

The future of neurosurgery is described in a limited way as a continuation of growth along the existing lines without allowing for sudden explosions of knowledge. Even at this predeterminated rate the future is bright.

Dedication

The citadel of neurosurgery as it is today is not the work of a few individuals. It is the culmination of the tireless efforts of many people. Some of them are well known and notable, yet for every single notable person there are at least ten whose efforts are not so well known. To all these well-known stalwarts and the unsung heroes, the saints without halos, this talk is dedicated.

The art of medicine is as old as mankind, but in this vast field of healing art, one of the youngest and unquestionably the queen of all specialities is neurosurgery.

The past is always the guide of the present to the future. A study of the history of any subject not only will induce a sense of humility in those who are apt to be proud of their achievements but it will also guide contemporary activity into useful channels for the sake of posterity.

The art and science of healing the sick arose when early man fell a victim to accident or disease. In most cases the parts so affected were easily seen and their repair attempted and achieved, as well as the existing conditions permitted. But, the brain enclosed as it was in the bony skull always remained an enigma. Moreover in the earlier part of the history

*General Amir Chand Oration, National Academy of Medical Sciences, 1991-92

of mankind the heart was always considered supreme and the brain was accorded only a secondary place. So knowledge about diseases of the brain and more so about their treatment did not make any headway. Because of the existence of neatly punched holes in the excavated skulls many would like to believe that these are evidences of earlier neurosurgery. However attractive this may sound, it is very likely that these were done with specific purposes of operating on the brain. However after these doubtful starts neurosurgery did not make an appearance till the latter half of the nineteenth century. The late start of neurosurgery was partly because of the need for solid ground work by giants like Galen, Willis and hosts of anatomists, physiologists and pathologists. This was also because the conventional surgical techniques that were available for abdominal surgery etc were not adequate for neurosurgery.

The history of neurosurgery can be divided into pre-Cushing era and the Cushing-Dandy era.

PRE-CUSHING ERA

Any attempt to assign chronological priority is always attended with risks of being misunderstood. And anyway it is not always a fruitful exercise where a large time gap exists. The generally accepted view will be presented here. It has been held that Sir William Macwean was the pioneer in neurosurgery. He had operated for many intracranial conditions including a meningioma. Borrowing his lines from Sir Issac Newton, Cushing (in the Macwean memorial Lecture delivered at the University of Glasgow in 1929) says *"We merely stand on the shoulders of our predecessors, and the study contemporary figures of Macwean on one side and of Horsely on the other side are what support the arch of modern neurological surgery."*

To Macwean belongs the distinction of having been the pioneer of craniocerebral surgery. As is well known Macewean was a superb surgeon and made a mark in other branches of surgery like orthopedics, thoracic surgery and otologic surgery. Many however hold that R.J. Godlee was the first to operate on a brain tumor. What is not so well known is that by the time Godlee presented his paper in 1885, Macwean had operated on many patients for 'tumorous' conditions. After Macewean and Godlee the next notable figure was Sir Victor Horsley. Horsley's contributions to neurosurgery were epoch making. He was the first to operate on a spinal tumour. Along with Henry Clarke, Horsley also introduced the Horsley-Clarke stereotactic apparatus for experimental purposes. There were also many early starters in other countries. In Denmark, in 1877 Carl Reinhold Struckmann removed the external portion of what was presumably the hyperostosis of a meningioma.

The reason why Horsley is generally considered as father of early neurosurgery is perhaps because he was entirely devoted to the speciality.

Horsley planted the seeds of neurosurgery but it was in the Cushing-Dandy era that this plant matured.

CUSHING-DANDY ERA

It can be said that neurosurgery as a distinct speciality began with Harvey Cushing (1869-1939). Before his days neurosurgery was performed by a few of the boldest but the techniques were not suited for the peculiarities of brain anatomy and physiology, hence it was no wonder that the outcome was unpredictable. A diagnosis of brain tumour was an exercise in clinical neurology but often a sentence of death. It was this that made Foster Kennedy exclaim, *"He who cares for patients suffering from brain tumours must bring to the problem much thought and stout action. There is need also of a formidable optimism as the dice of God are loaded."* Harvey Cushing's contributions to neurosurgery are unrivalled. He not only laid down the various techniques of neurosurgical procedures but also along with Percival Bailey gave out the first comprehensive classification of gliomas. This has been the launching pad for many of the later classifications like Kerhonahan's, Russel and Rubinstein's and others. Many objections have been raised against some of the terms and yet even after six decades no proper substitutes have been found for them like the terms meningioma and medulloblastoma-two of the most debated terms. Every step in a craniotomy was shaped by Cushing. Many of the younger neurosurgeons of today may not be aware that even the standard two later closure of the scalp was handed down from Cushing. He was responsible for introducing the Bovie electric cautery and this was described by him in his Macwean Memorial Lecture (alluded to earlier) of 1927. He described therein how he removed an olfactory meiningioma using this new instrument. Even today most neurosurgeons remove an olfactory groove meningioma in an identical fashion-an evidence of an outstanding and perennial contribution. But Cushing did not stop with laying a solid foundation. He soared to heights unheard of earlier and unlikely to be equalified in the future. By 1931 he was able to report on 2023 verified tumours.

Having been a student of John Halstead, Cushing's meticulous attention to details brought down the mortality of brain tumours. To take one examples prior to the days of cushing the mostality of *acoustic tumours* acoustic tumours was anywhere from 60 to 100%. Cushing brought down the mortality of this tumour steadily. In his earlier years the mortality was 18%, a feast in itself. Later he brought it to 4%-a stupendous achievement. His contributions to pituitary tumours are perhaps the best of his accomplishments.

It is difficult to imagine that there would be anyone equal in stature to Cushing. Yet there was another and what is more he was Cushing's contemporary. Never in the history of neurosurgery was the neurosurgical firmament lit by two suns shining at the same time. This person was Walter E. Dandy (1886-1946). While Cushing hewed and shaped neurosurgery, Dandy reinforced it, elevated it to the highest level imaginable through his innovative techniques and bold approaches into areas considered sacrosanct and dangerous. An obituary in Baltimore Sun wrote about Dandy as follows: *"The imaginative genius to conceive*

of new and startling techniques, courage to try them and skill-superb skill to make them successful." Dandy was not only a superb surgeon but also a researcher of great standard. His work on hydrocephalus, almost his first, stands unmatched even today. For the first time children with hydrocephalus could have relief and sometimes even cure. He practiced succussfully a series of bold operations like third ventriculostomy, catheterisation of the aqueduct and other procedures like excision of the choroid plexus. He was the first to excise the choroid plexus both by open method and by endoscope- a breathtaking achievement even today. Yet he realized the limitations of his method and did not promise a cure in every case. In his hands many apparently inoperable conditions became capable of solutions like arterio-venous malformations, pineal region turmours, intraventricular tumours and a host of others. His surgical successes are mind-boggling even today. To give one example in 1945 he had done 682 operations of eighth nerve section for Meniere's disease with 0.14% mortality! His observations as to a primary cause for trigeminal neuralgia and his anatomical observations on the entry zone of trigeminal root were greeted with skepticism, but now they have been corroborated by the operating microscope- thus reminding us the adage that cynicism is the reaction of ignorance to merit.

During Cushing-Dandy era surgeons had to operate on the basis of their neurological findings and because of this clinical neurology reached an acme. The only help available was from the plain x-rays, thanks to Roentgen. Anyone who reads Cushing's clinical notes cannot but be impressed by the astuteness of his observations and the exquisitely sharp clinical acumen. And yet this was not sufficient.

DANDY'S VENTRICULOGRAPHY

It fell to the lot of Walter E. Dandy to discover ventriculography. This straightway was able to pick out many tumours which had been elusive earlier. In the words of Horrax, a famous neurosurgeon, *"it brought immediately into operating field atleast a third more brain tumours than could be diagnosed and localised previously by the most refined neurologic method"*.

SOME MORE PIONEERS

The Cushing-Dandy era not only marked the beginning of the golden period of neurosurgery but was itself the most brilliant. To borrow the words of Churchill: *"Never in the field of human conflict was so much owed by so many to so few"*. Alongwith and after Cushing and Dandy came a galaxy of neurosurgeons who refined and polished the legacy of these pioneers. They included Sir Geoffrey Jefferson (1886-1961), Olivecrona (1891-1980), Norman McOmish Dott (1897-1973) and a host of others. Their skills were formidable and as if to suit this more diagnostic aids came in. They and others too numerous to mention, contributed enormously to the science and art of neurosurgery and worked hard to reduce the mortality following surgery. At this stage one is reminded of a statement attributed to Lord Rutherford : "It is not

in the nature of things for any one man to make a sudden, violent discovery; science goes step by step and every man depends on the work of his predecessors. When you hear of a sudden unexpected discovery, a bolt from the blue, as it were you can always be sure that it has grown up by the influence of one man on another, and it is the mutual influence which makes the enormous possibility of scientific advance. Scientists are not dependent on the ideas of a single man, but on the combined wisdom of thousands of men, all thinking of the same problem and each doing his little bit to add to the great structure of knowledge which is gradually being erected"

NEUROSURGERY IN INDIA

At this stage a few words must be said about neurosurgery in India. Before 1950 neurosurgical procedures were done by a few bold and dextrous general surgeons. Dr. Govindaswamy of Bangalore performed leucotomy for psychiatric indications and reported his experience as early as in 1944. Later came some more pioneers. Among them stand out Dr. Narasimha Iyer, Dr. Chintan Nambiar and Dr. C.P. Viswantha Menon. In 1950 neurosurgery was started in India almost simultaneously in two places separated by less than a hundred miles. The two pioneers were Prof. B. Ramamurthy (at Madras) and Prof. Jacob Chandy (at Vellore). After the start given by these two pioneers neurosurgery has grown rapidly and widely all over India and now there are as many as five hundred neurosurgeons.

CT SCAN AND BEYOND

The hard efforts of all the neurosurgeons and the profound skill of all the neurologists reduced the mortality to a considerable extent no doubt. But at times the morbidity following surgery was so severe as to question the wisdom and usefulness of some of the surgical procedures. For example a patient who has an acoustic tumour removed after 6-8 hours of gruelling surgical session might continue to be blind because the optic discs were already atrophic when the diagnosis was made. Angiography and ventriculography diagnosed these tumours only when their mass effect (or space-demanding size) was great.

Such was the state of affairs till 1972 when a great upheaval took place in neurodiagnostics. This was the discovery of Computerised Axial Tomography thanks to the work of Hounsfield and Cormack. Computerised Axial Tomography has become a household word now as CT scan. It is the forerunner of many other scanning techniques using computer technology. The diagnostic accuracy jumped from 60-65% to an astounding 90-95%.

The CT scan was followed by the Magnetic Resonance Imaging (MRI). There is a peculiar quirk of chronology here. The concept of MRI was envisaged as early as 1956 by the Dutch scientist Gorter. Ten years later Bloch and Purcell discovered its application. But only in 1976 (four years after the CT) MRI emerged as a diagnostic tool.

Both MRI and CT had pushed up the diagnostic accuracy to about 99%. Can we ask for more? No longer could neurosurgeons blame the delay in diagnosis and explain away the bad results. And they did not. It is a matter of pride that present-day neurosurgeons rose up to the occasion. Various other types of scanning machines began to appear. All of them were based on computers for the retrieval, deduction and display of the conditions. Some of them are the Single Photon Emission Computerised Tomography (SPECT), Positron Emission Tomography (PET Scan), Digital Substraction Angiography (DSA) etc.

ADJUNCTS TO SURGERY

Almost contemporaneous with these diagnostic paraphernalia many invaluable adjuncts to surgery were introduced. Of these the bipolar diathermy, operating microscope and intraoperative sonography are important. The bipolar diathermy, because of its ability to coagulate only the tissue between the tips of the forceps could be used safely in important areas. The part played by the operating microscope in neurosurgical operations is as significant as that of the CT in diagnosis. Through a small incision deep seated lesions could be easily tackled with absolute safety to overlying or neighbouring areas.

HISTORY OF MICROSURGERY IN BRIEF

Because of the significant role played by the operating microscope in neurosurgery it would be worthwhile to trace briefly the introduction of the operating microscope. The operating microscope was first used by the ophthalmic surgeons. What is surprising is that there was a gap of many decades before it was taken over by the neurosurgeons. To quote Donaghy *"it is not easy to understand why more than half a century elapsed between the introduction of magnification of surgery (in the field of opthamology) and its incorporation into neurosurgery, where the surgeon so often must deal with fine fragile structures at great depths-a situation for which the principle of magnification seems so admirably suited."* Kurze and House used the microscope during surgery of acoustic tumour. But the credit for establishing and popularising the use of the microscope in neurosurgery belongs to R.M.P. Donaghy and later to Robert Rand. Subsequently Gazi Yasargill brought it to the European continent. Today except for the simplest and most superficial of neurosurgical operation, no neurosurgeon would work without the microscope. Intraoperative sonography can be considered as an extension of the conventional B mode ultrasonography. Since the bony skull prevented the use of ultrasound, neurosurgeons got round this, by employing the ultrasound after bone was reflected. This method is extremely useful in reaching small lesions in the so-called eloquent areas or in deep recesses of the brain.

Besides these there are certain ancillaries which while not being indispensable, certainly make the operative procedures earlier. These are laser and cavitron ultrasonic aspirator.

Advances in physics are providing the neurosurgeon with more and more sophisticated forms of laser.

Besides these, a new approach has been evolved by borrowing a technique that was threatening to disappear after a short period of importance. This is the application of stereotactic principles to routine neurosurgical operations. With the manufacture of CT-compatible and even MRI-compatible stereotactic machines along with microdrivers, the diagnostic accuracy of these machines has been linked with the exquisitely pin-point localisation of stereotactic techniques. This has facilitated resection of deep seated tumour without a major craniotomy.

With all these gadgets the modern neurosurgidcal operation theatre would look like the control room of a spaceship.

The present day neurosurgeons are at the turn of the milennium. Those that took up neurosurgery after 1972 do not known what it is to do ventriculography in a patient with severe intracranial tension. Some of the older neurosurgeons will appreciate this.

PRESENT DAY NEUROSURGERY

Have all these advances done any good? Or are they mere gimmicks and gadgetry to befuddle the sick patients and their relatives? More than this, have the results been better than those of Cushing and Dandy? Can neuroscientists justify the enormous expenditure involved in the construction and maintenance of the various equipments. A CT machine costs about Rs. 1.25 crores, an MRI machine about 3-4 crores of rupees. The maintenance of some of these machines (like the MRI) would run upto 40-50 thousand rupees per month. Because of the high costs the various tests also are expensive. A doubt may arise at this stage. Are these tests essential? Are they cost effective? Can the public afford these tests?

There can be no two opinions that these diagnostic procedures are costly. This is particularly so in neurosurgical practice. To take an example of a patient suspected to have a tumour in the pineal region, the patient will need plain X-ray of skull, CT scan, and sometimes an MRI also as one must known its relationship to the brainstem and the extension in various directions to plan the approach. In most cases a vertebral angiogram (transfemoral or DSA) will be needed to know the displacement of the vessels. They will add upto Rs. 8000 at a very conservation estimate.

After this comes the fees for surgeon etc. How many people can afford this will be a question most of us would like to ask.

There is as yet another aspect to this. With increasing litigation in medical practice the concerned surgeon would not thinking long before ordering for these tests in spite of their cost. This is because he is justifiably scared that he may miss a small lesion or that he may be accused of negligence in not having asked for a test.

A big question that will arise is have all these tests improved the matters? This will be discussed from three angles.

1. Increase in Diagnostic Accuracy

Firstly while evaluating all these tests the diagnostic accuracy has to be balanced against the risks involved. In the evolution of these tests one can see that the tests are not only becoming less risky but also less, if not totally non-invasive. Dandy's ventriculography, which ushered in the era of diagnostic procedures, certainly carried a definite risk, at times serious enough to cause a fatality. Neurosurgeons of those era would remember nightmarish memories of patients, who after injection of a few c.c. of air, became decerebrate and unconscious and had to be resuscitated and even operated straight-away. Not all of them ended happily. Today the MRI is completely non-invasive, except when a para magnetic agent is administered. Simultaneous with reduction of risks there has been an increase in diagnostic accuracy. Because the earlier tests were not only invasive but carried a certain amount of risk there was a justifiable reluctance to resort to them until the indications were strong. The various tests, their risk and accuracy are shown in Table 1.

2. Increase in Number of Conditions Diagnosed

The second starts from the first. Since these tests can be ordered with absolute safety there has been an apparent increase in the incidence of some problems. As an outstanding example can be given the condition of chronic subdural haematoma. Prior to 1972 the number of chronic subdural haematomas diagnosed was very low. Any person above 50 or 60 years of age or more who developed a hemiplegia or so called 'mental' symptoms was diagnosed to be having a 'cerebrovascular accident' and treated accordingly. This was because cerebrovascular accidents were common at that age and for any other diagnosis an angiography was needed and this could not be asked for with impunity. When the symptoms were persistent and when the attending doctor was alert enough the lucky ones had angiography

Table 1 : Risk Justification and Safety of Modern Imaging Techniques in Neurosurgery

Test	Invasive/non invasive	Safety	Reliability
Air Studies	Invasive	Risk^{++}	50-60%
Angiography	Invasive	Risk^{+}	60-70%
EEG	Non invasive	Safe	30-40%
CT	Almost completely non invasive	Safe	90-95%
MRI	Almost completely non invasive	Safe	90-95%
DSA	Invasive	Risk^{+}	60-70%
PET San	Almost completely non invasive	Safe	80-90%
Ultrasound	Non invasive	Safe	30-40%

done and were cured by drainage of subdural haematoma. Today this impasse can be overcome by a CT scan. Every neurosurgeon can testify to the fact that suddenly chronic subdural haematomas have "increased" in incidence.

Thus CT has revealed that a diagnosis of hemiplegia which in earlier decades meant a cerebrovascular episode, is not always correct. Fortunately the modern surgical ancillaries have carried the improvement further and many of the cases could be treated satisfactorily. One such example is hemiplegia in children which was given the term 'infantile hemiplegia' and nothing more could be done. Not suprisingly many of them turned out to be correctable conditions. Another condition is the prompt evacuation of certain types of intracerebral haematomas.

In the pre-CT scan days the protocol for investigations of a focal seizure required an air study and/or an angiography. In neoplastic conditions which gave rise to such seizures these tests yielded positive results only if there was a mass effect. Consequently, such cases were missed in the early stages. This thing cannot happen today. With CT and MRI the diagnosis of a lesion even 1 cm in diameter is easy. Interestingly even in angiomatous malformations wherein one would expect angriography to have the last word, certain types of small lesions cannot be delineated. Only the CT and MRI can do this. A new term has been carried to describe these. These are known as 'angiographically occult AV malformations.

Yet there is another way CT and MRI have helped. As was already remarked angiography (except in cases of AV malformations) helps because the lesion displaces the various vessels. Tumours in the midline (like the anterior third ventricle, pineal region and foramen magnum) do not show up well in the angiogram. The CT can pickup such lesions. And even here the MRI has an edge over CT particularly in tumours of the clivus. Neoplasms of the brain stem do not produce mass effects early and hence only the CT or MRI can help. When we come to diseases of the spinal cord and spinal canal the MRI has no match. It is no slur on the earlier gneration of neurosurgeons that with all procedures more lesions of spinal cord are diagnosed and diagnosed much earlier.

Increase in diagnostic accuracy and increase in number of conditions detected are the two great benefits of modern neurodiagnostic armamentarium. The third improvement is the effect on the surgical techniques.

Before we discuss this we have to assess the effects of these diagnostic aids on contemporary neurology. Some of the older generations of neuroscientists might have a deep seated feeling that these tests are being ordered on flirmsy clinical findings. There is also (according to some) a more serious fallout from this. It is felt that these tests have already begun to toll the knell of clinical neurology. A vision of the clinical neurology so vigorously nourished by giants like Charot. Jackson, Gordon Holmes and a host of others, being pushed into the

background is in the minds of many scientists. According to this nightmare clinical neurological examination will become an academic pastime with no serious therapeutic application. The diagnosis will be given by the computer hooked on to the CT and MRI. To these Cassandras we can say that such a state of affairs will not occur to the extent they envisage. Neither the CT nor the MRI can give the diagnosis. It can list the probabilites. Without knowing the age, sex, state of patient and nature of evolution of the disease none of the tests can arrive at the diagnosis. Unless the whole clinical picture is taken into consideration the result will be disastrous. Many instances can be given of the CT diagnosis being forced to be changed when correlated with clinical findings. Clinical neurology will never be effaced. But it cannot be denied that some of the diseases can be detected a little earlier by these tests than by clinical examination. And that is after all for the good of the patient. Only one example need be given- of tumour of the clivus. There has been a sudden spurt in the number of cases of tumours of clivus being operated by individual surgeons. Is this a true increase in incidence? No. This is because these cases are easily diagnosed by MRI.

3. The Third Perspective-Bolder Surgery, Better Life

The third benefit from these newer tools is in the realm of surgical procedures. With adjuncts like the operating microscope and bipolar diathermy and others, better and/or more radical resections are being done. More difficult procedures are being performed. At the outset it must be pointed out (though it may be obvious) that these to not mean that we are better neurosurgeons than Cushing or Dandy. Even today, any discerning neurosurgeon would know that what Cushing and Dandy had achieved with the few facilities that were available, was indeed astonishing. And if Cushing or Dandy were to live today, what they would have accomplished with bipolar diathermy, microscope etc is beyond our comprehension. This statement is not just made for the sake of praising them. What is meant to be conveyed is that with the modern aids the standards of neurosurgery, judged from any angle has gone up.

As an example the management of craniopharyngioma stands out. Ironically this tumour offered the most formidable challenge even to Cushing who was a master of pituitary tumour surgery. Whereas with pituitary tumours his mortality figures for the last 79 cases was 3.9%, in craniographyngiomas he met his Waterloo. This is what he finally says about these tumours : *"But all in all these cases (cranioparyngiomas) offter the most baffling problem which confronts the neurosurgeon and the fact that the mortality which accompanied radical attempts to extirpate a large solidified tumour must approximate 100% probably accounts for the few reports of these lesions other than by pathologists. Even from the mere standpoint of preservation of vision the problem is a highly complicated and difficult one. Until some method is devised whereby the usually multilocular epithelial lesion can be destroyed or inactivited in situ, the mortality will remain high". This was in 1932.*

Dandy, the master surgeon, says of craniopharyngiomas : *"In proportion of their cystic element, their anterior position and their lack of adherence they are easy of removal. In proportion to the reverse of these factors the tumours are difficult, dangerous and at times impossible for complete extirpation". This was in 1935.*

With bipolar diathermy, operating microscope what is the position today? Certainly much better-let us go through two reports.

Yasargil reports that *"between 1980-1988, fifty nine patients had primary surgery for craniopharyngioma with complete removal of the tumour in each case. There was no operative mortality. One died after 6 months due to non compliance with medication for her diabetes. Two patients (2.5%) had severe morbidity and so far (in 1990) there has been no recurrence."*

Another report by Hoffmann et al in 1992 is as follows: *"Our experience indicates that over 60% of craniopharyngiomas in childhood can be totally resected with minimally significant mortality and morbidity."*

The conclusion is obvious. It cannot be denied that modern neurosurgery has justified the hi-tech diagnostic and operative aids. Yet another example is outstanding. As late as 1968, Matson, the doyen of paediatric neurosurgery while on the subject of brain stem tumours wrote, *"..... should any patient still be alive 18 months after diagnosis, reinvestigation and surgical exploration is indicated, as some other lesion is probably present. Regardless of their history brain stem gliomas must all be classified as malignant tumours since their location in itself renders them inoperable."* While this statement was justified then, the situation is certainly not so bleak now. With CT and MRI we know that there are different types of lesions and those that belong to the focal, cystic or exophytic varieties do carry a fairly good prognosis.

One of the most spectacular achievements of modern neurosurgery is the surgery of skull base tumours. Tumours arising from or involving the skull base usually meant relentless deterioration ending in death. Today a large number of these patients are being operated successfully by many surgeons. The clivus, the bony bridge between the sphenoid and occiput was long considered as absolutely inaccessible and today there are many excellent and innovative appraches to this region. The earlier inaccessibility of this area is exemplified by the title of a book published now in 1992, 'Approaches to the Clivus-Approaches to No Man's Land'.

Another striking innovative technique has resulted from combination of stereotactic surgery and radiotherapy. This is the radiosurgery of Leksell-commonly referred to as the gamma knife. The principle is to focus many beams of radiation (each in itself too mild to injure the brain) to deliver a heavy dose at the desired sites. This is done stereotactically, and since the skull offers no barrier to radiation there is no need for even burr holes. Many conditions like

AV malformation, tumours like acoustic tumours can be treated by this technique. The only disadvantage of this is the huge cost. The treatment charges alone come to round about $15,000 i.e. Rs. 4.5 lakhs.

The most significant point in present day surgery is the stress on the quality of life. It is not that our pioneers were not interested in this. But then their main concern was to save life at any cost. Later with increasing diagnostic accuracy and greater adjuncts for surgery, mere saving of life was not found sufficient. The stress was also on lowering the morbidity. There was no use in merely winning the battle and losing the war. Heroic attempts just to safe life however crippled the patient after the surgery, but could be accepted if the patients came late in the evolution of the disease; but not now. We saw how the absence of mortability was stressed in the surgery for craniopharyngiomas. Meticulous assessment of the quality of life is kept by various scores. One such is the Karnofsky's scale. To achieve this various steps are taken during surgery to avoid damage to uninvolved parts of the brain or spinal cord. One of the outstanding example of such attitudes that are emerging can be seen in the surgery of acoustic tumours. It was Cushing who brought down the mortality from over 60% to 4%, by his intracapsular excision wherein the capsule was left behind. This was advocated by Cushing to avoid damage to brain stem. At the same time Walter Dandy practised total excision with less mortality and less morbidity. In those days there was no question of saving the VIII never or even the VII nerve. In fact many of the surgeons who followed, concentrated on various methods of overcoming the facial paralysis by nerve grafting etc. From a superficial study it looked as if a facial palsy was a small price to pay for life. But the neurosurgeon of modern era would not rest on his laurels. With help from the enlarging field of otology, methods were evolved not only to remove the tumour completely but to save the facial nerve also. Today most patients need not fear this cosmetic disability. With more progress now attempts are being made to save the VIII nerve also. This has not been achieved completely. Recently a series of 6,982 cases was published where there was an emphasis on the preservation of hearing. To quote Moskowitz and Long, *".... cochlear nerve preservation was accomplished in 23.7% of patients, postoperative hearing preservation in 15.2% of patients, and serviceable or functional hearing in 9.7% of patients."* Surely a great progress from the days of Cushing who wrote: *"In the average case, if the pressure effects of the tumour can be so far overcome by an intracapsular excavation as to permit a subsidence of choked disc and thus to save vision, one may well be content; and should a secondary operation for recurrence ever be necessary it need not be particularly dreaded."*

Hitherto only the neurosurgical procedures have been outlined. It must not be forgotten that equally dynamic developments had taken place in many other branches under the umbrella of neurosurgery. One of them is in the field of radiology wherein a new branch of interventional radiology has come to stay and has taken over the management of

some problems like deep seated arteriovenous malformations.

It can be said without fear of contradiction that modern neurosurgery has justified all the amount of interest and time physicists, chemists and computer engineers have spent on this subject. At the same time it should be remembered that if this edifice is big and imposing today it is because it has been built on broad and sturdy foundation laid by the trail blazers.

The Future

Any discussion about the future can be considered only as an extension of the present at the same rate of growth. One can never predict sudden explosive innovations like what happened in 1972 when the CT scan was discovered. The future of neurosurgery will have to concern itself with many of the existing and till now unsolved problems in addition to adding newer methods and techniques.

Of the existing problems that need urgent attention some are

1. Severe head injuries
2. Spinal cord injuries
3. Vascular insufficiency
4. Management of gliomas
5. Congenital abnormalities
6. Neural transplantation

1. Severe Head Injuries

The management of minor head injuries and the evacuation of collections of blood in various compartments of the head have become common place. Today there can be no justification for loss of any life due to an extradural or subdural haematoma. But the patient with severe head injuries is an altogether different problem. Here we are dealing with massively injured brain tissue with a neurochemical explosion. As it is, our present day methods euphemistically called 'supportive and expectant' line of treatment have only enabled us to keep alive by artificial means a person who is deeply comatose and has stopped breathing. Quite properly some have even questioned the usefulness and the need for such aggressive treatment in these cases. If the direction of ongoing research is any indication perhaps the answer might come from neurochemistry. Many efforts are being made to avert the events after a head injury. These happen because of the unlimited formation of free radicals and chaotic movement of ions like calcium. This results in a vicious chain reaction in which more neural tissue is damaged resulting in oedema which produces further damage. Already some trial methods promise a breakthrough. These involve the use of chelating agents, administration of large doses of Vit C, Vit E and certain chemical agents like dimethylsulfoxide (DMSO). The use of methyl prednisolone with heightened anti-inflammatory effect and lessened minerolocorticoid effects promises to be of some use. At the same time we hope that our engineering colleagues will come up with better methods of preventing head injuries atleast in traffic accidents.

2. Spinal Cord Injuries

One of the most dismal chapters in neurosurgery is the management of spinal cord injuries. While we have garnered much information about the mechanisms involved, very little progress has been made in the management or cure of individual cases. Occasional cases of recovery after surgery are mostly anecdotal in nature. In this field again methyl prednisolone offers some hope. In the future, suture of the severed cord with assurance that the neural tissue will grow may come about if our knowledge of neural regrowth improves. But as it is, suture of the cord is useless, even if it is possible unless is regrowth. The place of drugs like naloxone and others is still undecided.

3. Vascular Insufficiency

In the management of vascular insufficiency, neurosurgeons have been overtaken by the cardiovascular sugeons. Of course the problems are not identical as the effects of hypoxia on the brain are more devastating to the specialised tissue of the brain. While it may be difficult to reverse the effects on tissue already damaged by anoxia, attempts to salvage the penumbra surrounding the dead area may be worthwhile. Again here methods to improve tissue perfusion might help as well as surgical procedures to augment the blood supply. The prophylaxis of this problem will consist in identifying the patients at risk and, to devise methods of reducing these factors. Attempts to revascularise the areas at risk would be useful at this stage. A small beginning has been made towards this.

4. Glioma Management

The management of glioma of the brain is still far from desirable. And this in spite of early diagnosis in at least 99% of cases. It must be said that nowadays radical surgery is practised with greater frequency. The problem now is one can never be sure that the entire tumor has been eradicated at time of surgery. It is necessary to know this as further management depends on as much cytoreduction as much as is feasible. Certain present day laboratory techniques may help to determine this.

The first is the determination of these dimensional size of tumor This is done by making use of the fact that the peripheral benzodiazepine receptors on the mitochondria are found to be increased by 20% in tumor tissues. When the appropriate ligand is used and the brain scanned with a PET scanner the tumor infiltration is seen fairly well. Better than this is to use peripheral benzodiazepine ligands with ferro-magnetic compounds and scan with MRI.

An intra operative estimation of tumor resection would be more useful. Here two avenues are being explored currently. The first is the extension of the conventional MRI into the operating theatre by making it portable and using ferrous magnetic ligands. This will also give rapid images during surgery.

The second is the betaprobe. Here the principle is simple. After the main excisional surgery a positron labelled material (like benzodiaepines, leucine or

fluorine—18 fluorodexyuridine) is injected and after sometime (depending on the time of uptake) the betaprobe is placed on different areas in the brain. When there is no uptake complete resection is proved. But unfortunately radical surgery is limited by the fear of producing neurological deficit particularly when the pathology involves the so-called eloquent areas. Radiation therapy, chemotherapy and immunotherapy are still to establish that they are really curative and not merely palliative. It is, at present impossible to predict in what forms a really useful form of therapy will come about.

5. Congenital Abnormalities

One of the unexplored territory is the management of congenital malformations. It is hoped that a cataclysmic breakthough will occur, as currently the picture is far from rosy. Identification of the causative factors and their elimination will be the ideal. Till then the detection of these abnormalities and their management in utero will have to be done. To a great extent the antenatal detection of these abnormalities either by ultrasound or aminocentesis or even blood examination has yielded commendable results. But then the treatment is not so successful. Ventriculoamniotic shunts are yet to be standardised and so also the antenatal repair of dysraphic anomalies.

6. Neural Transplantation

Neural transplant is one of the most exotic fields yet to be explored fully. The term neural transplant envisages a whole brain transplant like a kidney transplant. This is still in the realm of science fiction. At present transplant of small amounts of neural tissue seems to take very well both in the laboratory and at times is clinical practice. When established on a large scale it will be of great use in the management of injuries or replacement of neural tissue damaged by disease or at operation. When a small amount of foetal mesencephalic tissue from a foetus is transplanted the take is good. There are a few case reports of amelioration of Parkinsonism by this method. If these methods are developed perhaps much success will be obtained. There are however some problems in neural transplant not seen in kidney or heart transplant. The area transplanted must make physiological connexions with rest of the brain in addition to anatomical connexions. We do not know how tissue from parietal lobe will connect with tissue in midbrain. In addition, progress made in the preparation of neural growth factor has helped in neural transplantation. But all these problems will be solved one day. And one can never say that even whole brain transplant is not feasible because scientific progress always debunks existing theories and hypotheses.

The status of modern neurosurgery has certainly jusitfied the enormous effort and phenomenal amount of finance that has gone into research. At this same rate there is no doubt that the future of neuro surgery will continue to be equally bright and many of the problems which confront us today may be solved. One need not fear that the invasion of computers and

other modern marvels will ultimately displace the physician or the surgeon. Loss of work at one end will always mean increase of work at another end and at a different level. Neurorobotics wherein the entire neurosurgical procedure is done by a robot under a remote control is being practised in some centres. Still the master control is with the living brain of the neurosurgeon. This crest jewel of creation *"the human brain"* will always be in control directly or indirectly.

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Current Prospects in Diagnostic and Therapeutic Nuclear Medicine

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INTRODUCTION

Medicine is a rapidly changing science. Scientists are trying their best to develop newer, better and safer imaging and theraputic techniques to get the same or better information by cheaper and alternative means. The nuclear medicine is a amalgamation of basic science and clinical medicine and the strength of the modality is its ability to derive both functional and quantitative information about organ system. However, its weakness is the poor resolution i.e. poor quality images as compared to high-resolution images obtained from CT, MR and DSA etc.

Though, X-rays and gamma rays were discovered a century back, the pace of growth of nuclear medicine as a sub-speciality of medicine is disproportionately slow due to several reasons. First was the non-availability of suitable radiotracer till 1933. After discovery of artificial radioactivity and wide availability of tracer after World War II, this branch rapidly developed. The diagnostic use of radiotracer was handicapped due to non-availability of suitable imaging device. In 1951 and 1958 two remarskable discoveries, rectilinear scanner by Benidict Cassen and gamma camera by Hal Anger set a new pace for Nuclear Medicine. The rectilinear scanner decreased in popular due to slow mechanical movement of the detector, thus taking unusually long time for large organ imaging. Gamma camera was a good alternative but its potential could not be tapped till discovery of technetium in early 70s. Nuclear Medicine imaging became popular in late 70s and 80s. Tomographic techniques like US, CT and MR decreased its use further in late 80s. David Kuhl and Tor Pogossian developed Nuclear Medicine tomographic techniques such as SPECT and Position Emission Tomography, respectively. Now most of the Nuclear Medicine departments are equipped with SPECT and few with PET facility as well.

Diagnostic procedures in nuclear medicine are based on tracer kinetic principles. These can be broadly classified as follows :

1) In-vitro tests 2) In-vivo-Nonimaging procedures 3) In-vivo-Imaging

Procedures : a) Static imaging b) Dynamic imaging c) Gated imaging

1) In-vitro tests are mainly used in haematology practice. The most popular in-vitro test is the radioimmunoassay, which is universally practiced in medical profession. The other important tests are : (1) Autoradiography (2) Schillings test (3) Red cell mass estimation (4) Blood volume estimation (5) Red cell survival study (6) Platelet survival studies (7) Ferrokinetics (8) Radio respirometry (C-14 breath test) for malabsorbtion syndrome and widely used test for detection of H. Pylori in peptic ulcer disease. In the literature, there are many more procedures but few have survived over the years. The procedures are technically demanding and need certain degree of expertise for consistent results.

2) In-vivo non-imaging procedures : (i) The most popular and time tested procedure is Radio-active iodine uptake for the diagnosis of thyroid diseases. (ii) T4 Suppression test (iii) Perchlorate discharge Test (iv) Iodide perchlorate discharge test (v) GFR = (Glomerular Filtration Rate) and ERPF = (Effective Renal Plasma Flow) flow estimation (vi) Detection of hyperspleenism by spleen to cardiac uptake ratio estimation. The results are expressed as quantitative parameters and can be used in follow up for temporal comparisons. These are easy to perform with minimum laboratory equipments and technical expertise.

3) In-vivo imaging procedures : The modern day Nuclear Medicine is based on imaging procedures. The gamma camera is the work-horse of this speciality. This equipment can be used in planner or in tomographic mode. The number of detector head can vary from one to four. The widely available gamma camera is usually single headed, least expensive and highly versatile but time consuming and gives relatively poor quality image (due to inherent low sensitivity). As the number of detector heads increase the acquisition time decreases, count statistics improves thus giving better resolution and lower amount of tracer activity required thus, giving lower radiation dose to the patients. However, as the number of head increases arithmetically the cost of the equipment and the cost of the maintenance increase exponentially.

Apart from the detector heads in gamma camera, the other most important component is the computer (except the older generation analog cameras). Fortunately, over the years, the cost of the computers have decreased and the power to handle enormous data has increased indeed, it is the Nuclear medicine experts who started using computers for the first time in Medicine as early as 60s and paved the way for dedicated imaging computers in all branches of modern imaging.

The characteristics of an ideal radionuclide

There has been considerable discussion of the physical properties of an ideal radionuclide. Such an agent should be easily produced, readily available and inexpensive; and it should have high specific activity with no adverse reactions. Its physical half-life should be relatively short (i.e. only a few hours) and not longer than the time required for the agent to localize within the body and for imaging to be completed. The ideal gamma-emitting nuclide should decay by isomeric transition or electron capture without internal conversion. Those nuclides that decay with beta emission or significant conversion and those with longer physical half-lives are less desirable, since they result in a large radiation dose to the patient for the equivalent flux of externally detectable gamma photons. For most gamma cameras and scanning devices, the ideal nuclide should have a monoenergetic gamma emission of approximately 150 keV. At such an energy level, collimator septa may be extremely thin for higher counting efficiency, yet produce adequate attenuation. Furthermore, this energy level is high enough to permit demonstration of lesions at a considerable depth in tissues. The radionuclide that most closely approaches the characteristics of the ideal nuclide is technetium-99m, which will be discussed later.

In reality, no agent is ideal under all conditions. The agent of choice for the demonstration of a particular organ usually represents the best of several possible compromises. For example, ideal physical characteristics must often be sacrificed for biologic localizing properties. Some radionuclides, such as iodine-131, have been widely used in spite of their relatively poor physical properties because of their availability and chemical characteristics, which permit simple methods of labeling. Some compounds are so complex or difficult to label that the use of short-lived materials become impractical.

Imaging Procedures

a) The *static imaging* is performed either in spot views or in whole body mode depending on the need of the procedure. There is no count limitation however, the time limitation is the major factor. Pixel over saturation should be avoided and the acquisition time should be reasonably practical at the same time not compromising the quality of images. The best examples are bone scan, liver-spleen scan, renal cortical scan, thyroid scan, myocardiac infarct avid scan, ventilation/perfusion scans etc. These procedures need least expertise to acquire the images, but metionlousness is essential to get best results.

b) The *dynamic imaging* procedures are widely practiced in Nuclear Medicine. The dynamic word is in relation to temporal events i.e. the change of event in relation to time. From a routine renogram or to gall bladder ejection fraction calculation are all

based on dynamic imaging technique. The event is recorded over a period of time after introduction of tracer into biological system and to see how the body is handling it. The sequence of recording of temporal events can vary from milli-seconds to hours. For example first pass studies needs to be recorded in milli-seconds, where as HIDA scan can go upto 24 hrs. Thus, continued or interval recording as required, is done for dynamic studies. After recording the events, through a screen interactive device (track ball, light pen marker or mouse) You have to draw a region of interest (ROI) or just identify a boundary inside which the computer through an edge detection algorithm marks the ROI. All the digitised images are passed through the ROI and time-activity histogram/curve are plotted. Then all the required parameters are derived from the time-activity-curve. The pattern and the area under the curve are frequently used to compare against the contralateral organ or compared over the period of time with the same organ. As the pixels are digitized the differential calculus applied to pixel can give the functional or parametric images. For pattern recognition different statistical methods like factor analysis, cluster analysis or discriminant analysis are applied to dynamic imaging data and resolve the subtle changes that is practically impossible to identify by human naked-eye observation. The cross talk or background scattering is the major problems with dynamic studies. The second most important problem is the count limitations, thus producing noisy images. The later can be partially solved by high sensitive detection methods or increasing the administered activity albeit within the permissible limit of the recommended dose. The former problem is a very difficult one. Lot of research has gone down to improve the methods of background correction. But only a partial success has been achieved yet. A great deal of hope is now being placed on the stochastic resonance method to augment a poor signal to noise ratio. Thus hoping to get good quality pictures in future.

c) *Gated Imaging* : If an organ is oscillating, it is very difficult to get good quality dynamic images. Fortunately bioelectricity can be recorded easily and the pattern is used for diagnosing medical problems. For example, heart is an oscillatory organ and its bio-electricity in the recorded form is called ECG. In ECG the tallest wave is "R Wave" which can be sensed by computer and used as a signal to open the gate for recording counts from that moment till the end of one cardiac cycle i.e. R to R interval. The next cardiac cycle is recorded in the same fashion; thus at the end of the thousand cycles one can have only one gaint cardiac cycle in computer memory. This recorded cycle can be replayed in cine mode and the actual heart best can be visualised in the monitor. Then all

the techniques of dynamic image analyses can be applied and the time-activity curve can be derived. The functional images and the second derivatives parameter for the heart can be obtained easily. Principle of the same gating procedure can be applied for lungs as well, however its practical relevance is limited. The gating technique is efficient fully automated and operator friendly. However the atrio-ventricular overlaps and superimposition of great vessels create problems for proper analysis of the data. Gated-SPECT technique is being developed to overcome some of the problem of superimposition and background subtraction.

d) *Miscellaneous :* A score of new applications like radioimmunoscintigraphy, receptor imaging, absolute quantitation in metabolic imaging, perfusion imaging etc. are presently available, however, are beyond the scope of this discussion. The diagnostic Nuclear Medicine is becoming an exciting and challenging field with advent of receptor site visualization by modern PET and SPECT imaging.

THERAPEUTIC NUCLEAR MEDICINE

For more than 80 years, external beam radiotherapy, along with surgery and chemotherapy, has been a principal method in the triad of treatment modalities for cancer management. This treatment, however, results in irradiation of all tissue in the pathway of the radiation beam and thus normal tissues are also irradiated. Despite much improvement in linear accelerator collimation and multiple angles of irradiation (non-coplanar arc therapy), normal tissue toxicity in the local region limits treatment potential for many disease sites in the body. Sealed source or brachtherapy implants allow for targetting of target radiation in proximity to the lesions, but this form of radiotherapy is limited in practicalities of implant location (superficial or "cavity") and procedure invasiveness to normal tissues. In contrast to external beam radiotherapy, radiotherapy delivered via internal administration of radionuclides targeted via a tumor-seeking carrier has the allure of the "magic bullet." If a chemical form is found that specifically targets the undesired cell, specific therapy may be realized. Although the delivery method in practice, has been not without its problems. Treatment of diseases such as hyperthyroidism and thyroid cancer with radioiodine since the 1940s and polycythemia vera and leukemia with phosphorus (P-32) dating back to the 1930s (Saenger et al., 1979) exemplifies the history of routine treatment of some diseases via radionuclide therapy over several decades. As various small molecules and targeting proteins have been developed with specificity for malignant tissues, interest has been high in the development of an improved and broader base of targeted radiotherapy. Antibodies, in particular, by their nature have the potential of specific binding to

an antigen, and if the antigen is found only on a cancer cell, antibodies carrying a therapy radionuclide may deliver specific, targeted radiotherapy. More recently, the finding of receptors on breast tumors, neuroendocrine tumors, and melanoma has thrown open the possibility of delivery of radiotherapy via radiolabeled peptide ligands. Molecular targeting raises the possibility of treating metastasis that are too small to be detected by standard diagnostic imaging. Such small lesions play an important role in relapse and mortality from metastatic cancer. The ability of these molecular-targeting methods to localise to the small lesions offer the opportunity to treat metastatic disease effectively. Have been used for the treatment bony metastasis, peritoneal tumor metastasis, and for the treatment of myeloproliferative disorders including polycythemia vera, certain leukemias, and essential thromocytosis. More recently, ^{89}Sr-chloride, ^{186}Re HEDP, and ^{153}Sm-EDTMP have been used for the therapy of bony pain from metastatic breast and prostatic carcinoma. Radiotherapy with these injected radionuclides has been effective in treating tumors because of the localization of the β emitting radionuclide within the tumor cell or within near proximity of the tumor cell. The success of the treatment depends on a high target-to-non target ratio of the radioisotope and on the residence time of the radionuclide within the tumor. These radiopharmaceuticals have a selectivity for tumor cells or, for the eroded bone adjacent to the tumor cells. The target binding is due to specific chemical properties that allow the radiopharmaceutical to bind. Except intracavitary uses, the radionuclide therapy is based on sound physico-chemical principles of tracer localisation. For example thyrocytes take radioiodine as the raw material for thyroid hormone synthesis, thus dying in the process. Similarly Sr-89/P-32 is taken up by osteoblasts for hydroxy apatite crystal formation and P-32 by proliferating haemopoietic cells for DNA synthesis and causing their self destruction. The third important point is the amount of radiation absorbed dose delivered to the organ or metastatic deposit is enormous as compared to the conventional radiotherapy.

Radioiodine for treatment of Graves' disease or toxic nodule has been the best example of a radionuclide targeting agent with a high target-to-non target ratio, rapid clearance of the unbound radioisotope, and a long residence time in the target. The result has been an effective therapy with little or no toxicity. The other targeted radiotherapy agents for systemic treatment of tumors have not had as high a therapeutic ratio and, in many cases, have not been as effective because of lower target to preferentially at or near tumor cells as compared to the non target cells. The tumor uptake in most intravenously injected radiolabeled antibody studies has been 1% or significantly less. Carrier molecules such as metaiodobenzylguanidine (MIBG) and somatostatin analogues have the advantage of being much smaller, which allows better tumor penetration. Additionally, they lack the problem of

human anti-mouse or antihuman immune responses seen with the use of mouse-or human-derived monoclonal antibodies, potentially limiting the ability to repeat therapy. However, the slow rate of dose delivery over prolonged period, spares the healthy tissue surrounding the lesion, thus very little side effects by this mode of therapy.

PHYSICAL PROPERTIES OF THERAEUTIC RADIONUCLIDES

Several lists of rodionuclides suitable for therapy have been generated over the years (Fritzberg et al. 1988, Mausner and Srivstava 1984). A number of basic physical properties of these radionuclides are common to the group namely : A high non-penetrating to penetrating energy-abundance ratio (>0.5), particulate emissions, a physical half-life that the longer than the biological half-life, high specific activity of the final product and reasonable production methodology and availability. The basic theoretical considerations is presented in detail for beta-emitting radionuclides as they constitute main stay of therapeutic nuclear medicine. Humm et al (1986, 1987; Humm et al and Cobb, 1990), Howell et al. (1989), and Wheldon et al. (1991) have considered beta emitter potential with respect to energies, penetration or cell traversals, and appropriate size of tumor targets. A unique advantage of beta emitters over other therapeutic modalities (such as drugs and toxins) is that not every cell needs to be targeted to be killed. Thus, the transversals of cells by multiple beta particles results in enhanced killing by cross-fire. This result is efficient for lesions larger in diameter than the average path length. If the desired effect is eradication of micro-metastases in an adjuvant setting, a target cluster of tumor cells may range from several thousand cells (0.1mm) to 10^5 (1 mm) cells.

A medium-energy beta emmitter, such as ^{131}I, has 17% of its energy absorbed in a cluster of cells of 0.2 mm diameter, whereas only 1.5% of the high-energy beta emitter ^{90}Y is absorbed. For a 1mm cluster, the corresponding absorbed percentages are 54% for ^{131}I and 10% for ^{90}Y (Humm 1986). This results in escape of most of ^{90}Y from micro-metastasis to give potential non-target toxicity. Detailed analysis of these considerations by Wheldon and co-workers in 1991 suggest that ^{131}I or similar energy radionuclides be used for tumors of $10^{4.5}$ to $10^{7.5}$ cells and ^{90}Y for tumors of 10^8 to 10^{11} cells. It is of interest that detectability of tumors and metastasis with standard imaging modalities is on the order of 10^9 cells, or about 1 cm diameter.

Humm (1986) has classified beta emitting radionuclides as low-range (mean range <200 micrometer), medium-range (mean range, 200 micrometer to < 1mm) and high range (mean range>1mm). Some examples are as follows :

* Low range : europium (169 Eu), lutetium (177 Lu)

* Medium range : scandium (^{47}Sc), copper (^{67}Cu), iodine (^{131}I), samarium (^{153}Sm), rhenium (^{186}Re)

Physical properties of selected Therapeutic Radionuclides

Radionuclide	Half-life (hrs)	E_{max} Beta (meV)	Mean Range (mm)	Imaging Gamma energy in KeV (%Abundance)
^{32}P	342	1.71	1.85	---
^{67}Cu	62	0.57	0.27	185(49%)
^{90}Y	64	2.27	2.76	---
^{131}I	193	0.61	0.4	364(81%)
^{153}Sm	47	0.8	0.53	103(28%)
^{177}Lu	162	0.5	0.28	208(11%)
^{186}Re	89	1.07	0.92	137(9%)
^{188}Re	50	2.12	2.43	155(15%)

* Long range : phosphorus (^{32}P), rhenium (^{188}Re), yttrium (^{90}Y)

The physical properties of radionuclides of interest that vary from low means range of 0.28 mm for ^{177} Lu to 2.76 mm for (^{90}Y) are listed in the following table.

External Monitoring

Penetrating gamma radiation is emitted by many therapeutic radionuclides. This property enables imaging of the biodistribution of the radiotracer and facilitates pharmacokinetic studies. When the gamma emissions are of appropriate energies (between 100-200 KeV), the target activity and other normal tissue uptake and retention of radioactivity can be measured as a function of time after injection of the radiopharmaceutical. This allows dosimetry estimates to be made on the actual therapeutic dose rather than relying on similarities to the behaviour of diagnostic imaging agents. The radionuclides should emit a relatively low abundance of gamma photons so that the absorbed dose contributed to normal tissues is not significant. On the other hand, ^{32}P and ^{90}Y lack gamma emission. Although their high energy beta emissions result in penetrating *bremsstrahlung* radiation, the broad energy spectrum of high energy photons limits the spatial resolution that can be obtained and results in poor images of radiotracer distribution.

Preparation of the patient before therapy

A suitable tracer study should be performed to give an idea of the distribution and uptake pattern of the tracer and from this dosimetry can be obtained. The blood or marrow dose is most important dose limitting factor. Thus, special attention should be given to that while administering the radionuclide therapy. As it is expected after therapy these shall be tissue oedema, any critical organ must be adequately protected. For example in a patient with thyroid cancer and tracheal/laryngeal infiltration likely to go for respiratory distress. So a prophylate tracheostomy is advocated, similarly, patients with

impending paraplegia should be given local radiotherapy prior to 1-131 therapy in metastatic CA thyroid. In an elder thyrotoxic patient adequate control of hyperthyroidism is required before giving 1-131 therapy.

The route of administration : Intraoral, intravenous, Intraarterial or Intracavitary

Limitations of Radionuclide of Therapy : The major limitations of radionuclide therapy are as follows : i) The patient becomes a radioactive source and if the radionuclide produces energetic gamma rays alongwith particulate emission, needs strict isolation for many days. ii) Each type of tissue needs a unique radionuclide thus an array of radionuclides are needed to cover large number of diseases/organs. Whereas a Telecobalt unit can treat most of the tissues with the same source of radiation. iii) The radioactive waste disposal become problem. Needs special care to handle the wastes with due permission from the regulatory bodies of the nation as well as local authorities. iv) You have to have trained and dedicated staff to cater the need of large volume of patients with isolation rooms specially designed and ear marked exclusively for this therapy only. v) The limited availability of the common radionuclides like 1-131/P-32 and prohibitively expensive radionuclides like Sr-89 has really handicapped the Nuclear Physician to treat more number of patients by this therapeutic modality.

The vast therapeutic potential of nuclear medicine is as yet untapped. Exciting new applications include palli ative therapy of bone metastasis of neuroectodermal and somatostatin expressing tumors.

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The total therapeutic potential of nuclear medicine is in its untapped flexibility new applications include palliative therapy of bone metastases or immunoradiotherapy and chemotherapy modes.

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Evolving Concepts in Breast Cancer Management : A Review

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SUMMARY

The magnitude of the problem of breast cancer is on the rise in our country. The last century has witnessed several landmark changes in the approach to patients wih breast cancer. Till recently, women had to under go extirpation of the entire breast resulting in significant physical and psychological trauma. The current trend is to go for a figure-conserving procedure. Tumour biologists have unraveled many mysteries about cancer cell growth. Most notable among these is the identification of estrogen receptors and tamoxifen. Next breakthrough was the demonstration of the effectiveness of combination chemotherapy in premenopausal women and tamoxifen in the postmenopausal women. The current treatment policy is one of the spectacular examples of *"Evidence based medicine"* where sound scientific proof of effectiveness has been gathered through very large multicentric randomized trials and meta-analyses on well over 75,000 women across the globe.

Key words : Breast cancer, Treatment policy, Surgery, Hormone therapy, Chemotherapy.

INTRODUCTION

Breast cancer is the commonest cancer among middle aged women in developed [western] countries. Its incidence has been increasing in India and now it is the second most common cancer in Indian women as per the reports of National Cancer Registry Project (1, 2). It has been estimated that annually about 52,000 women develop breast cancer in India and as a result of increasing population and longevity alone, this figure would increase to 86,000 by the turn of this century (3). Most patients (90%) in India present to the physician with advanced disease (4). The reasons for this delay are poor awareness among women, illiteracy, socio-economic factors, inadequate distribution of health care system in rural and semi-urban areas and improper training of doctors to diagnose early cancer.

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Epidemiology

Almost one third (32%) of all new cases and 18% of cancer deaths in women are related to breast cancer. The cause of mammary cancer remains obscure but insight continues through epidemiologic, genetic and animal research. The patterns of risk are complex and suggest that both hereditary and environmental factors are influential. It has been estimated that approximately 25% of all breast cancers can be explained by currently recognized somatic risk factors viz., age above 40 years, nulliparity [Relative risk; RR 1.4], history of breast cancer [RR 1.2 to 1.5], family history [RR 1.7 to 2.5], early menarche and late menopause, irradiation, obesity [RR 1.8], alcoholism (RR 1.5) and estrogen pills (RR 1.7 - 4.1). Moreover patients with benign breast disease demonstrating histological atypia have a RR of 5 (5, 6). It has been hypothesized that psychological factors also play a role in the development of breast cancer (7). Recognition of these factors has helped define women at risk, on whom screening test could be applied to improve early detection and outcome. Patients with very early breast cancer have a ten-year survival of around 90%. Early detection can be easily accomplished by breast self-examination (BSE), physician examination and mammography (8).

Breast cancer has long been regarded as a local disease with an orderly sequence of progression from breast parenchyma to the regional nodes and eventually to the blood stream *(Halstedian concept).* The originator of this belief, William Stuart Halsted developed the first radical mastectomy in 1882 (9). Since then millions of women across the globe have undergone this procedure for breast cancer.

Despite local aggressive treatment with radical mastectomy and radiotherapy, many women with breast cancer still succumb to systemic metastases. Therefore, in early seventies a new concept was propounded which enunciated that breast cancer was a systemic disease soon after its inception (10). This paved way to the development of limited surgery and systemic therapy even for early disease. In the eighties European surgeons performed breast conservation surgery and demonstrated its effectiveness to be at par with the radical procedure. Incidentally, this coincided with the Women's Liberation movement, with consumers demanding a figure conserving operation. The next revolutionary step in the management of breast cancer was the introduction of anti-estrogen-tamoxifen. Almost at the same time, G. Bonadonna of Milan, Italy described the famous chemotherapy [CT] combination of cyclophosphamide, methotrexate and 5-fluorouracil [CMF] which is one of the most widely tested and effective regimens in Oncology (10).

The foundations of systemic adjuvant chemotherapy were derived from the facts that (10): [i] by the time tumor becomes clinically detectable, it is advanced and has many opportunities to establish micro-metastases; [ii] neoplastic cell dissemination is both by lymphatic and blood vascular system and is interrelated; and [iii] surgical 'cure' rates drop

as tumor size and axillary lymph node metastasis increase.

Modern Surgical Procedures for Invasive Breast Cancer

Both clinical presentation and surgical approach to breast cancer have changed dramatically over the last century. In 1882, Halsted performed the first radical mastectomy, and this was the standard for therapy about 75 years. Realization that 90% of treatment failures are systemic metastases has led the surgical oncologist to explore alternatives to radical mastec-tomy as an initial approach to operable breast cancer (11). The surgical practice changed in the mid seventies from radical mastectomy [RM] to modified radical mastectomy [MRM].

Radical and Extended Radical Mastectomy

The breast and the underlying pectoral muscles are sacrificed leaving a bare chest wall. Regional lymph nodes along the axillary vein up to the costoclavicular ligament are removed with the breast specimen. This procedure often requires a skin graft or a flap repair. Prosthetic reconstruction is difficult unless the muscle flaps are mobilized. The extended radical mastectomy is standard RM along with the removal of internal mammary nodes. Breast reconstruction in such women is difficult.

Modified Radical Mastectomy

David Patey of the Middlesex Hospital in London developed a procedure bearing his name that preserves pectoralis major and sacrifices pectoralis minor in order to remove level 1, 2 and 3. This is currently the most widely used procedure for locally advanced disease and refers to combining total mastectomy with removal of axillary lymph nodes. Since it leaves the pectoral muscle, the defect is well suited to prosthetic reconstruction. The 10-year survival among axillary node negative women was 82% and with positive nodes, it dropped to 48% (12). Thus, the long-term survival is similar to radical mastectomy but cosmetic and functional results are far superior to radical mastectomy.

Local excision and primary radiotherapy

Excision of the primary tumor with preservation of the breast has been referred to by many terms such as partial mastectomy, segmentectomy, tylectomy or lumpectomy. In essence, this procedure entails wide local excision of the primary tumor together with axillary node dissection followed by whole breast irradiation (13).

HORMONAL THERAPY

Estrogen and progesterone receptors

Constant effort by the tumor biologists to unravel the mysteries of cancer growth led to the understanding of estrogen receptors and other growth factors which influence the breast cancer metastasis. The number of estrogen receptors [ER] in the breast cancer cells can be high, intermediate or absent. This quantitative grading of ER is predictive of response to hormonal manipulations

viz., oophorectomy or tamoxifen. Seventy percent of the tumors with positive estrogen receptors regress after hormonal manipulation whereas only 5% of negative tumours respond to these procedures. The highest response rates are observed in patients with tumors containing both estrogen and progesterone receptors. On the whole, cancers with high levels of estrogen receptors have a better prognosis than those with intermediate levels or no receptors. Laboratory medicine continues to play an important role in the management of the patients with cancer breast. Investigations in the past decades have provided bio-chemical and clinical evidence that estrogen and progesterone receptors, EGF receptor, the protein product of the C-erb B-2 Oncogene and Cathepsin D represent a panel of bio-clinical markers that are useful for ascertaining the biological aggressiveness of a carcinoma (14).

Tamoxifen

Tamoxifen (15-18) is a non-steroidal anti-estrogen. It appears to exert its main anti-proliferative effect by competing with estrogen for binding to estrogen receptor proteins. Estrogen receptor complex inhibits gene transcription and protein synthesis of factors important to tumour growth. After binding to the ER tamoxifen antagonizes many of the cellular events affected by estrogen. The predominant effect of tamoxifen is cytostatic. Although tamoxifen behaves primarily as an estrogen antagonist, it may act as a partial agonist for some organs. The anti-estrogen properties of tamoxifen usually are not sufficient to suppress ovarian function. The long term use of tamoxifen continues to result in increased steroido-genesis in pre-menopausal women. The ovulation continues and there is a possibility of pregnancy. The standard therapeutic dose is 20mg orally daily. Very large world-wide randomized trials on women receiving tamoxifen as an adjunct to surgery and radiation therapy have demonstrated improved 5 year survival and reduced local recurrence. Moreover, it reduces the incidence of cancer in the opposite breast. Therefore, it is being tried for the chemoprevention of breast cancer in high-risk women. These benefits have been observed in both pre-menopausal as well as postmenopausal women. The drug is well tolerated by most women and the toxicity is minimal and transient. The frequency of nausea and vomiting, weight gain, vaginal bleeding, skin rash, edema and abnormal liver function is < 3%. Transient ocular disturbances of the eyes due to damage of retina and optic nerve are rare (< 1%) (19). Thrombocytopenia, tumour flare and hypercalcemia may ocur in 5% of cases. Other newer anti-estrogens are trioxifen, zindoxifen and torenifene. A randomized trial of 2 vs. 5 year of adjuvant tamoxifen showed that 5 years of tamoxifien is more beneficial than 2 years (20). Although tamoxifen has been used for periods longer than 5 years with some extra lives saved in some trials, the finding is not consistent across the studies. Moreover ther is an increased incidence of endometrial cancer in these patients.

Therefore, Richard Peto and others are trying to find the optimum duration of tamoxifen therapy through a large multi-national trial [ATLAS trial].

Surgical oophorectomy

Oophorectomy improves 10-year survival in women under 50 years. Oophorectomy is indicated in pre-menopausal women with slow growing metastatic disease, a long disease free interval, and age over thirty-five years. In a meta-analysis of 75,000 women, the Early Breast Cancer Trialists Collaborative group demonstrated a proportional reduction in annual mortality of 28% with ovarian ablation compared to no ablation (21).

Formestane - the new endocrine alternative

Formestane is a highly specific aromatase inhibitor, the key enzyme in estrogen biosynthesis which significantly suppresses estrogen levels in post menopausal women with advanced breast cancer. It has a long duration of response (13 to 33 months). The usual dosage is 250 mg administered intramuscularly at weekly intervals. It produces an objective response in 25% of women after relapse or failure of previous hormone therapy. It is relatively non-toxic and is used as a second line drug (22).

Modern Adjuvant Chemotherapy

The first randomized trials were performed by NSABP and National Cancer Institute, Italy using patients with positive axillary lymph nodes. NSABP used single agent chemotheraphy in the adjuvant situation and hence became the standard approach. The fifteen-year results of the CMF (12 cycles) trial showed a 10% survival benefit in the CMF treated women compared to the control (36% vs. 26%). The significant survival benefit observed in pre-menopausal women was not observed in post-menopausal women. A second trial compared the effectiveness of 6 vs. 12 cycles of CMF for node positive patients. At 14 years, both relapse free and total survival rates between the two groups remain similar. Henceforth only 6 cycles of CMF have been recommended in the adjuvant setting. All premenopausal women receive chemotherapy regardless of the nodal status. For a post-menopausal patient the hormone receptor status decides the approach. In the presence of positive ER, with unfavorable prognostic indicators [poor histological grading, aneuploidy, high tumor cell proliferative activity, more than 3 positive nodes etc] and negative receptor status adjuvant CT is beneficial (10).

The Treatment of Stage I Node Negative Breast Cancer

Approximately 20-25% women with stage 1 breast cancer eventually develop disseminated disease. A comprehensive meta-analysis of adjuvant chemotherapy was reported based on 133 randomized trials involving 75,000 women including both poly-chemotherapy and adjuvant hormonal manipulations. The results of this meta-analysis are depicted in Table 1

Table 1 : *Reduction in annual odds of recurrence and death. Data based on Meta-analysis of 11,000 women (see reference-21)*

Age group (years)	No. of cases & controls	Recurrence*	Death*
<50 (pre-menopausal)	3138	36 (5)	25 (6)
<50 (post-menopausal)	225	37 (19)	†
50-59 (pre-menopausal)	911	25 (9)	23 (9)
50-59 (post-menopausal)	3128	29 (5)	13 (7)
60-69	3774	20 (5)	10 (6)

Data based on meta-analysis of 11,000 women (reference 21)
* Data shown as % [SD]
† There are very few patients in this group; therefore, the estimate is imprecise.

(21). This data indicated that there was both reduced recurrence and improved survival for node positive and node negative patients. The greatest benefit was seen in younger patients with at least 6 months combined chemotherapy. Patients with tumours less than 1 cm have an excellent prognosis and do not require adjuvant systemic chemotherapy.

The Treatment of Stage II Node Positive Cancers

Prognosis is directly related to the number of nodes histologically involved with metastasis. After surgery, women with 1-3 positive nodes have a 10-year survival of 38% - 63% and with four or more nodes that are positive have a survival rate of 13% - 27% (23,24,25,26). Thus, a sizable proportion of women in stage II cancer succumb to systemic disease. Hence, adjuvant CT aims at killing any remaining breast cancer cells thereby increasing the disease free survival and cure.

The anthracycline derivative doxorubicin remains the single most effective drug in the treatment of advanced breast cancer. Initially the drug did not gain much popularity due to its potential for myocardial damage after prolonged treatment. Combination CT regimens with doxorubicin or its analogue eqirubicin have shown to induce a higher response rate in patients with more than three positive axillary lymph nodes in stage II cancer, locally advanced or clinically disseminated breast cancer than those that do not contain an anthracycline.

Primary Chemotherapy in Stage III Disease

Combination chemotherapy is necessary to improve survival of patients with Stage III disease (27). Advantages of anterior chemotherapy are :

[i] sub-clinical metastasis as well as primary disease can be treated and may facilitate later resection; [ii] drug delivery may be more consistent if tumor vasculature is unaltered by surgery or radiation; [iii] the sensitivity to the chemotherapy can be established and the tumor response can be observed.

Patients treated with combination chemotherapy with CAF followed by local therapy and then resuming chemotherapy had a five-year disease free survival of 40%. Because of the poor prognosis of stage III, recently high dose chemotherapy with bone marrow support is under trial.

Newer Chemotherapeutic Agents

Docetaxel (28) is a member of the toxoid class of antineoplastic agents. Its mechanism of action is primarily related to its ability to enhance microtuble assembly and to stabilize microtubules by preventing their depolymerisation thus disrupting normal cell division. It has been investigated in the treatment of patients with advanced and / or metastatic breast cancers. As first line treatment, monotherapy with docetaxel was associated with complete response rate of 5%-16% and partial response rate of 19%-53% with an overall response rate of 54% - 68%. It has also shown impressive activity as second line treatment. Vinorelbine, a new semisynthetic vinca alkaloid is also showing promise in advanced breast cancer.

Conclusion

The burden of breast cancer as a cause of morbidity and mortality in the Indian women is on the rise. In order to improve the present gloomy statistics we need to launch public health programmes for early detection through media and schoolgirl education, physician examination and mammographic screening. This, together with an improvement in the standard to surgical and radiation therapy across the country would brighten the picture.

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Low Prevalence of CHD Risk Factors in an Indian Tribal Population

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SUMMARY

High prevalence of coronary heart disease (CHD) in parallel with economic development is observed among South Asian Countries. It is interesting to note that a tribal population of Kerala (Kurichias), India are enjoying longevity relatively free from age-associated chronic problems. We therefore conducted a study to assess the prevalence of obesity, central obesity, hypertension, dyslipidemia and smoking habits in a random sample of 310 (175 male+135 female) subjects. The prevalence (age standardized to the world population of Segi 95% CI) was : obesity 2.87 (1.22-4.53), central obesity 3.71 (2.27-5.15), hypertension 2.70 (1.92-3.48), hypercholesterolemia 0.71 (0.66.0.76), hypertriglyceridemia 2.60 (1.18-4.02) and low high-density lipoprotein cholesterol 1.24 (1.07-1.42). The mean metabolic and anthropometric measurements in the study sample was lower as compared to other Indian and Western studies. The low prevalence of CHD risk factors in Kurichias could be attributed to the stress-free economic activities and intake of coarse variety of grain.

Key words : Obesity, Central obesity, Hypertension, Dyslipidemia

INTRODUCTION

Coronary heart disease (CHD) is one of the leading causes of death both in developed as well as in developing countries and is a major health problem associated with the adoption of atherogenic dietary habits in majority of the populations (1). Increasing number of developing nations acquire such life styles and experience an increase in the incidence of non-communicable diseases in parallel with economic development (2). The population most affected are those who have changed from traditional to western life style or have become rapidly industrialised over a short time span (3). Developing nations such as India are in state of epidemiological transition with increase in life expectancy, proportion of population above 35 yrs, as well as the proportion of deaths occuring at older ages which are attributable to

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non-communicable diseases. Industrialised countries have initiated programmes for preventing cancer, cardiovascular diseases and degenerative diseases, while developing countries concentrate on preventing communicable diseases due to their limited resources. This has led to a rise of non-communicable diseases like CHD in epidemic proportions in developing countries (1). The World Health Organisation estimates that 15% of deaths in developing countries are due to cardiovascular diseases (4).

The World Health Organisation has recommended the development of national programmes for prevention and control of cardiovascular diseases. Further, risk factor studies reveal (a) a higher prevalence of coronary risk factors in urban communities as compared to rural (with the notable exception of smoking) (b) higher levels of central obesity with associated dyslipdemia (low HDL-cholesterol, increased total cholesterol-HDL cholesterol ratio, elevated plasma triglycerides and (c) relatively leftward distribution of systolic and diastolic blood pressures (5-7). Appropriate exercise is clearly associated with a favourable risk factor profile, lower prevalence of dyslipidemia and reduction of upper-body obesity (7). Thus, control of obesity and greater physical activity are likely to be the most effective means of preventing CHD risk in South Asian populations (6). Knowledge about prevalence of CHD risk factors is an essential prerequisite to developing an effective programme for primary prevention. Though the rise in CHD mortality is plaguing the Asian Community, among Indian ethnicity, it is interesting to observe a tribal population of Kerala (Kurichias), India, who are enjoying longevity relatively free from age-associated chronic problems. Even so, the life style patterns of this tribal population are changing drastically due to a close association with the industrial population (8). With this background, it is of paramount importance to study and understand CHD risk factors and life-style related measures among Kurichias, which may be applicable to the other populations in reducing the burden of CHD.

MATERIALS AND METHODS

The study population was a healthy volunteer adult sample of 310 Kurichias of which 175 were males and 135 were females. Objectives of the study were clearly explained to all the subjects before taking their consent to participate in the study. Strict precautions were taken to avoid related individuals.

The participants were interviewed covering age, habits of smoking, alcohol usage and dietary intake. All the subjects were involved in heavy manual labour. Dietary information was collected, using a 7-day prospective survey. After examination, each person received a 7-d diary to record his daily food intake-its quality, quantity, origin and method of preparation. On the morning of the eighth day, a dietician interviewed each subject for more details and evaluated the quantity of food ingested per day. From the 7-day collection of data, daily intake of energy and other nutrients were

calculated from the food composition tables based on Gopalan et al (9).

Blood pressure (BP) was measured at the study site with a random-zero sphygmomanometer as per the procedure of Rose et al (10). Hypertension was diagnosed according to Kaplan criteria (11). The physical assessment included height, weight circumferences of the waist and hip according to the method specified by Shimokata et al (12). The body mass index (BMI) was calculated as BMI= weight in kg/(height in meters)^2 (kgm^{-2}). Obesity was defined as BMI>25. Waist hip ratio (WHR) was calculated from the circumferences of waist and hip. Central obesity was defined as WHR>0.85 (13).

Fasting venous blood (5 ml) was collected in the morning from all the subjects, and serum was separated from whole blood by centrifugation at 3000 rpm. Serum cholesterol, high density lipoprotein cholesterol (HDL-C) and triglycerides were estimated according to the procedure of Zlatkis et al (14), Burnstein et al(15), Foster and Dunn (16). Hypercholesterolemia was defined as total cholesterol greater than 244 mg% and hypertriglyceridemia as triglycerides greater than 128 mg%. Low HDL-C was defined as HDL cholesterol less than 35 mg% (17).

Data were processed for statistical analysis and p-values below 0.05 was regarded as having statistical significance. Age-specific rates were calculated and standardization performed by the direct method against the standard world population of Segi (18). Results were expressed as age-standardized rates with 95% confidence intervals.

RESULTS AND DISCUSSION

Serum cholesterol and HDL-cholesterol levels were higher in men while triglycerides were higher in women. A higher systolic BP and lower diastolic BP was observed in males. Both BMI and WHR (central obesity) was higher in men (table-1). Effects of age on metabolic and anthropometric measurements were tested by one-way analysis of variance for males and females (table-2). Metabolic and anthropometric measurements did not show significant variation within the age groups in both sexes. Lipid levels, body mass index and WHR were nearly constant in all the age groups in both sexes, while both systolic and diastolic BP showed an increase in older age groups. All the lipid levels, BP and anthropometric measurements were slightly higher in males than in females.

Though alcohol intake and smoking are not prohibited in this population, people were strictly non-alcoholic and only 5 men were smokers (2.86%). Almost all (98%) of the people were chewers of either tobacco or betelnut. Hypertension, central obesity and hypercholesterolemia was more frequent in men, whereas obesity, hypertriglyceridemia and low HDL-C status was more frequent in females (tables 3 & 4).

Women were found to be taking substantially more fibre, ascorbic acid, dietary fat and less protein, carbohydrate

Table 1 : *Metabolic and anthropometric measurements of Kurichia study population*

Parameter	Males n=175	Females n=135
Serum Cholesterol mg%	169.90 ± 39.90	155.93 ± 37.82
HDL-Cholesterol mg%	71.63 ± 17.52	63.64 ± 19.27
Triglycerides mg%	91.63 ± 27.61	97.43 ± 31.34
Systolic BP mmHg	125.44 ± 13.76	123.95 ± 17.74
Diastolic BP mmHg	73.60 ± 17.24	78.55 ± 10.46
Body Mass Index wtH^{-2}	19.44 ± 2.42	19.35 ± 1.90
Waist Hip Circumference Ratio	0.88 ± 0.04	0.82 ± 0.06

Data as Mean ± SD

and caloric intake than men in the study group (table 5).

The Kurichia population, known to be relatively free from coronary heart disease, displayed lower values of blood pressure, BMI, WHR, serum cholesterol, triglycerides and high levels of HDL-cholesterol when compared with Indian (7, 19-22) and western data (23-24). A positive correlation was characterised between serum cholesterol levels and the risk of CHD and negative correlation with high density lipoprotein cholesterol levels in earlier studies (24). People with a cholesterol level greater than 300 mg% have four times increased risk of coronary heart disease than people with <200 mg% (25). A WHO expert committee has stated that populations with a mean cholesterol of 175 mg% or less have no major effect on CHD risk (26). In the present study only 6 people (4 men, 2 women) were observed to have cholesterol greater than 200 mg% indicating that coronary risk was minimal in this population. Low levels of HDL-C are independent predictors of CHD and high levels of HDLC-C appear to be effective in preventing CHD (27). Only 5 (1 male + 4 females) had a HDL-C below 40 mg%, while 12 (7 males + 5 females) had HDL-C greater than 80 mg%. Nicholson et al (28) have documented a high life expectancy in families with elevated HDL-C levels. The results of the present study coincide with the findings in the quoted study.

The low prevalence of cigarette smoking and lack of alcohol intake among the Kurichias suggest that they may have been more health-consicious than the other populations. The prevalence of dyslipidemia, obesity, central obesity and hypertension in Kurichia population is lower than that of other populations (21, 29, 30). Fernando et al (30) observed that 15% of the subjects were hyper-cholesterolemic in their study. Similar percentages of hypercholesterolemia were observed elsewhere (18). Prevalence of

Table 2 : *Metabolic and anthropometric measurements by age in males and females*

Parameter	Males					Females				
	19-39 (n=35)	40-54 (n=70)	55-69 (n=42)	70 & above (n=28)	F-value	19-39 (n=28)	40-54 (n=42)	55-69 (n=35)	70 & above (n=30)	F-value
Serum Cholesterol (mg%)	160.98 ± 24.39	163.65 ± 31.59	168.74 ± 40.83	167.33 ± 42.72	0.78	147.35 ± 28.92	150.47 ± 26.27	158.96 ± 40.47	166.38 ± 48.67	1.02
HDL-Cholesterol (mg%)	64.69 ± 8.27	81.11 ± 16.96	68.04 ± 20.96	61.99 ± 7.51	0.59	58.09 ± 15.33	63.20 ± 20.01	67.17 ± 23.25	65.09 ± 15.42	0.95
Triglycerides (mg%)	86.86 ± 20.02	94.38 ± 23.67	97.93 ± 27.61	81.17 ± 38.66	0.71	91.41 ± 27.37	91.19 ± 30.44	102.10 ± 33.58	105.12 ± 30.57	0.62
Systolic BP (mmHg)	118.00 ± 6.79	125.60 ± 14.02	127.50 ± 11.45	131.25 ± 18.16	0.76	112.50 ± 8.29	122.50 ± 21.55	126.00 ± 13.92	132.80 ± 16.22	0.86
Diastolic BP (mmHg)	72.00 ± 6.78	76.30 ± 8.26	80.83 ± 10.17	80.50 ± 6.38	1.39	68.75 ± 5.45	80.20 ± 10.11	83.40 ± 10.60	0.48 ± 8.62	
Body Mass Index (WtH^{-2})	18.03 ± 1.45	19.55 ± 1.73	20.16 ± 3.75	18.64 ± 1.31	1.08	19.13 ± 0.75	21.13 ± 1.62	19.90 ± 1.86	18.47 ± 1.78	0.94
Waist Hip Circumference Ratio	0.85 ± 0.03	0.88 ± 0.03	0.91 ± 0.04	0.86 ± 0.04	1.07	0.78 ± 0.03	0.84 ± 0.05	0.83 ± 0.05	0.80 ± 0.06	0.55

Data as Mean ± SD

Table 3 : *Prevalence of obesity, central obesity, hypertension and dyslipidemia*

Age Groups	Obesity		Central Obesity		Hypertension		Hypercholesterolemia		Hypertriglyceridemia		Low HDLC	
	M	F	M	F	M	F	M	F	M	F	M	F
19-39	1(2.86)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(3.57)	0(0)	0(0)
40-54	1(1.43)	2(4.76)	3(4.28)	2(4.76)	2((2.86)	1(2.38)	0(0)	0(0)	1(1.43)	1(2.38)	0(0)	1(2.38)
55-69	2(4.76)	3(8.75)	4(9.52)	3(8.57)	4(9.52)	1(2.84)	1(2.38)	0(0)	2(4.76)	2(5.71)	1(2.38)	2(5.71)
70 & above	0(0)	1(3.33)	2(7.14)	1(3.33)	1(3.57)	2(6.67)	1(3.57)	1(3.33)	1(3.57)	1(3.33)	0(0)	1(3.33)
Total	4(2.29)	6(4.44)	9(5.14)	6(4.44)	7(4.00)	4(2.96)	2(1.14)	1(0.74)	4(2.29)	5(3.70)	1(0.57)	4(2.96)

Results expressed as number of subjects (with age and gender specific crude prevalence)

Table 4 : *Prevalence of obesity, central obesity, hypertension and dyslipidemia*

Variables	Crude prevalence	Age-standardized prevalence	95% confidence intervals
Obesity	3.23	2.87	1.22-4.53
Central Obesity	4.87	3.71	2.27-5.15
Hypertension	3.55	2.70	1.92-3.48
Hypercholesterolemia	0.97	0.71	0.66-0.76
Hypertriglyceridemia	2.90	2.60	1.18-4.02
Low HDLC	1.61	1.24	1.07-1.42

hypercholesterolemia in the present study is only 1%. The prevalence of low HDL-cholesterol is 9% in a European population (31), 13% in a Srilankan community (30) and only 2% in our study stample. The observed 3% of hypertriglyceridemia in Kurichias is lower as compared to Asian and Western studies (30, 31). Low HDLC and/or hypertriglyceridemia in the presence of normal cholesterol with central obesity are thought to be associated with Syndrome X. They have been implicated as a cause for high rate of CHD in South Asians (6), but elevated HDL-C levels and normal cholesterol and triglyceride levels observed in this population may offer protection against CHD.

Table 5 : *Results of analysis of 7-d weighed dietary records.*

Parameter		Males n = 70	Females n = 50
Total Energy	Kcal/d	2645.00 ± 275.50	2192.17 ± 356.22
Protein	g/d	66.49 ± 8.76	58.32 ± 10.29
Fat	g/d	15.97 ± 6.81	19.86 ± 8.83
Fibre	g/d	31.19 ± 10.22	37.63 ± 12.11
Carbohydrate	g/d	432.90 ± 89.30	398.71 ± 99.32
Ascorbic Acid	mg/d	69.24 ± 13.21	79.34 22.44

Data as Mean ± SD

Two Indian studies on rural and industrial workers observed a 24% and 42% prevalence of hypertension respectively (21). Couderc et al (32) found 22% of his study group were hypertensives and 13% were obese. While Fernando et al (30) found in his study that 16% were hypertensives, 10% obese and 17% centrally obese in a Srilankan community. In our study sample, 3% were hypertensives 3% obese and 4% had central obesity. Research reports from various communities show but an age related rise in blood pressure but hypertension is not an invariable accompaniment of aging, as lifestyle changes associated with develo-

pment may lead to increase in levels of blood pressure (21, 33). Although Hughes and Cruikshank (34) imply that hypertension does not make a significant contribution to CHD in South Asians, Fernando et al (35) reported an association between hypertension and CHD. The prevalence of hypertension and obesity in this study is lower than in other Indian populations (36).

The average intake of diet in Kurichias show that these people are meeting the requirements prescribed by ICMR (37). Though Kurichia is a tribal population, their energy intake, fibre, protein, vitamin C and carbohydrate is higher than that observed in other Indian populations (22). Research results emphasize the key role of obesity, hypertension, dyslipidemia and smoking as risk factors for coronary heart disease and diabetes. The causes for CHD in developing countries is same as in the developed world. It has been shown that preventive programmes can reduce coronary mortality in developed countries (38). But even in the absence of modern medicaments and preventive programmes, Kurichias have low CHD risk and enjoy healthier longevity than any other tribe or caste group of India. This could be attributed to the stress-free economic activities and intake of coarse variety of grain. The Kurichias' staple diet includes vegetables like *Nymphaea nouchali, Hydrocotyle, Roxburguia* and roots like *Ceropegia* and *Elaeocorpus*. The leafy and root vegetables they consume have beneficial influence on cardiac protection, aging process, and diabetes mellitus (39). Thus, balanced nutritional status of this community with centuries of interaction with the backdrop of rich forest ecosystem and undulating terrain may be serving this population to lead a healthy life.

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Prognostic Significance of Serum Beta-2 Microglobulin in Patients with HIV Infection and AIDS

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SUMMARY

Evaluation of beta-2 microglobulin [b_2M] levels was undertaken in 34 cases of full blown acquired immunodeficiency syndrome [AIDS], 20 apparently healthy human immunodeficiency virus (HIV) seropositive individuals and 20 normal controls to evaluate its usefulness as a surrogate marker to distinguish between full blown AIDS cases and HIV seropositive individuals. However, it had a poor predictive value in establishing a diagnosis of full blown AIDS in an individual patient. Further, the coefficient of correlation between CD4+ T-lymphocyte count and b_2M was low both in patients with full blown AIDS and HIV seropositive individuals.

INTRODUCTION

Human Immunodeficiency Virus (HIV) epidemic has taken deep roots in India ever since the first case was documented in a sex worker in Tamil Nadu (1). It is estimated that by the year 2000, India will have 5 million infected individuals. Stunning advances have been made in a short time spanning a decade regarding the pathogenesis of acquired immunodeficiency syndrome [AIDS]. It was recognized quite early that CD4+T-lymphocytes cells are the key targets (2) for the HIV virus and during the development of full blown AIDS a substantial reduction in the numbers of CD4+T-lymphocytes is an essential component (3). Enumeration of CD4 + T-lymphocytes has therefore been adjudged the best prognostic marker for the development of full blown AIDS and has been used regularly to monitor therapeutic regimes (4). Subsequently, however, it was revealed that the viral load assay was the most sensitive documentation of viral replication (5). Even when peripheral CD4+T-lymphocyte count is normal, there is a substantial replication of the virus in the tissues and blood (6-8). The draw back of these tests are that they are expensive and not available for routine use. While CD4+T-lymphocyte estimation requires sophisti-

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cated and expensive instrument i.e., flowcytometer and antibodies, the cost of viral assay is prohibitive. Most of the Indian patients belong to poor socio-economic background and they cannot afford these expensive tests. Surrogate markers thus have an important role in assessing prognosis of HIV infected patients. Beta-2 microglobulin [β_2M] is one such marker used in patients with HIV infection and AIDS.

β_2M is a small polypeptide that forms invariant chain with HLA class-I molecule and is present on all nucleated cells (9). Small amounts of β_2M occur in various body fluids (10). Increased [β_2M] levels in serum have been found in patients with malignancies including multiple myeloma where it is the most powerful prognostic and therapeutic marker (11). β_2M also reflects lymphoid activation, destruction and hence is indicative of HIV replication (12).

In the present study, we evaluated the usefulness of serum β_2M estimation in Indian patients with HIV infection and AIDS. We have attempted to address the question whether serum β_2M can be a reliable surrogate marker to diagnose full blown AIDS in patients with HIV infection.

MATERIAL AND METHODS

Cases reporting to the AIDS Surveillance Centre, Department of Postgraduate Institute of Medical Education and Research, Chandigarh were included in the study. The diagnosis of HIV infection was established by two different ELISA tests, i.e., Recombigen (Cambridge Biotech, Ireland), Detect (Biochem Immunosystem Inc., Canada) and a rapid test (Cambridge Biotech, Ireland) or Immunocomb (Orgenics, Israel). If all the three tests were frankly positive, the case was designated as HIV positive. In case of even a minor discord, Western blot test was performed (Newlav Blot-I/II, Sanofi Diagnostics, Pasteur, France). Clinical diagnosis of AIDS was established in 34 patients by the CDC clinical criteria or a CD4+T-lymphocyte count less than 200/mm^3. Twenty apparently healthy HIV-positive individuals and 20 healthy normal controls were also included in the study and subjected to similar investigations.

Serum β_2M estimation

β_2M was estimated using an enzyme immunoassay (United Biotech, Inc. USA) based on a sandwich enzyme-linked immunosorbent assay [ELISA] principle. Briefly, β_2M kit employs microwell coated with anti-β_2M antibodies. Patient sera diluted 1 : 1000 and standards were incubated in the microwell for 30 minutes at room temperature. After washing in phosphate buffer saline, 100 ml of the enzyme conjugated second antibody was added and the plate was incubated for another 30 minutes at room temperature. After several washings, the colour was developed using tetramethyl benzidine. After 10 minutes of incubation, the reaction was stopped by adding 100 ml of 1N H_2SO_4. The intensity of the colour was read at 450nm. This was quantitated by plotting standards vs O.D. on a double log graph paper according to the manufacturer's instructions.

Estimation of CD4+T-lymphocytes

In twenty randomly selected cases absolute CD4+T-lymphocyte count was measured in a Becton Dickinson flowcytometer using anti-CD4 + and anti-CD8+ antibodies and consort-30 programme. Briefly, 100 µl of EDTA blood was incubated with 20 µl of the Simulset reagent for 30 minutes. The mixture was subjected to red cell lysis using a 1 to 10 dilution of the lysing fluid (Becton Dickinson). After incubating for 10 minutes, the cells were washed thrice in phosphate buffer saline pH 7.2 and viewed in the flowcytometer. The percentage of CD4 + T-lymphocytes was enumerated and their absolute number was calculated from absolute number of total lymphocytes.

Statistical analysis : Unpaired 't' test was employed in different groups to evaluate significance of β_2M and CD4 + T-lymphocyte count. Correlation coefficients (r) were computed between CD4 + T-lymphocyte count and serum β_2M levels in patients with full blown AIDS and apparently healthy, HIV-seropositive individuals.

RESULTS

The mean age of full blown AIDS cases (n=34) was 35 [SD 12] years. There were 25 males. The mean age of apparently healthy HIV-seropositive individuals (n=20) was 26.7 [SD 7.5] years. The mean serum β_2M level in patients with full blown AIDS was 6.7 (SD 2.3) mg/ml. Considering a level of 7 µg/ml as the cutoff, 17 of the 34 patients with full blown AIDS (50%) had levels >7 µg/ml. Among the HIV-seropositive individuals the mean serum β_2M level was 4.15 (SD 2.2) µg/ml. Two cases (10%) had levels > 7 µg/ml. Mean serum β_2M levels in 20 healthy controls was 1.7 (SD 3.5) µg/ml. These details are shown in Table 1 and Figure 1.

Considering 4.15 µg/ml, 26 cases [76.5%] of full blown AIDS and 9 HIV-seropositive individuals [45%] had values > 4.15 µg/ml. However, when the cut off was taken as the mean normal value in

Table 1 : *Serum β_2 microglobulin levels in 30 patients with full blown AIDS, 20 HIV-seropositive individuals and 20 normal controls*

Cutoff value (mg/ml)	AIDS n (%)	HIV-seropositive individuals n (%)	Normal controls n (%)
> 7.0	17 (50.0)	2 (10.0)	0 (0)
< 7.0	17 (50.0)	18 (90.0)	20 (100)
> 4.15	26 (76.5)	9 (45.0)	0 (0)
< 4.15	8 (23.5)	11 (55.0)	20 (100)
> 2.4	33 (97.6)	16 (80.0)	0 (0)
< 2.4	1 (2.9)	4 (20.0)	20 (100)

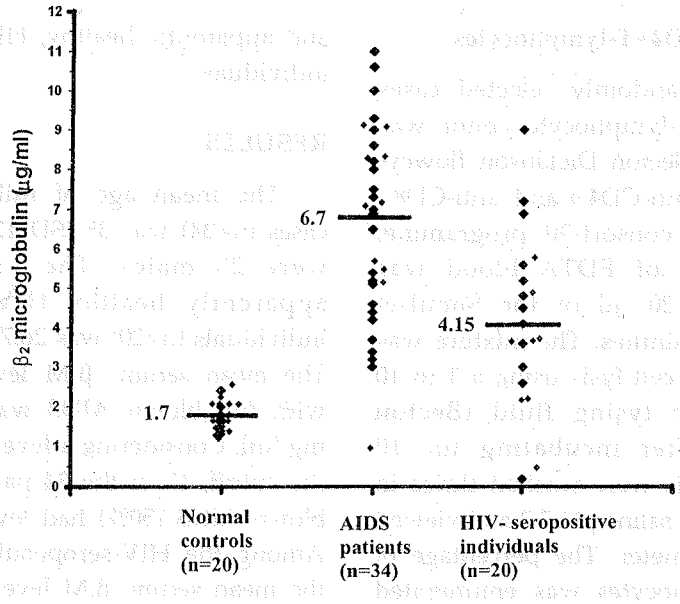

Figure 1. β_2 Microglobulin levels in control, HIV-postive individuals and AIDS patients.

controls ± 2SD i.e., 2.4 μg/ml., then 33 patients with full blown AIDS (97%) and 16 seropositive (80%) had values above 2.4 mg/ml. Thus this cut off was not able to distinguish AIDS patients from HIV seropositive individuals.

The serum β_2M values were significantly higher in patients with full blown AIDS compared to HIV-seropositive individuals ($p<0.04$) and normal controls ($p<0.001$). The serum β_2M values in HIV seropositive individuals was significantly higher than that observed in normal control ($p<0.001$). The sensitivity of β_2M for diagnosis of full blown AIDS was 76.5% considering a CD4+T-lymphocyte count of 200/mm^3 as the gold standard and serum β_2M level > 4.15 μg/ml as a cutoff value.

There was no significant correlation between CD4 + T-lymphocyte count and serum β_2M in patients with full blown AIDS ($r = 0.16$) and HIV seropositive individuals ($r = 0.26$).

DISCUSSION

The time interval between HIV infection and full blown AIDS is variable ranging from 2-10 years, depending upon the route of infection, dose of the virus, institution of the type of therapy, nutritional factors of the host and presence or absence of coreceptors (3,6,7,14). Assessment of the stage of the disease is crucial for initiation of appropriate therapy. Since it is not possible to study the extent of viral replication repeatedly in India, lot of stress has been laid on CD4 + T-lympocyte count and surrogate markers such as serum β_2M, p24 assays, neopterin levels etc (15). Assessing CD4 + T-lymphocyte count may be normal in the face of significant tissue viral replication

(7, 8). Therefore there is a need to have a set of adjunct markers which could be used to assess progression to AIDS as the cost of sequential viral load assay is prohibitive and will never be affordable.

In the present study there was a poor correlation between CD4 + T-lymphocyte count and β_2M serum in both HIV-seropositive individuals and patients with full blown AIDS. Thus serum β_2M levels cannot be used as a single marker to distinguish between full blown AIDS disease HIV-seropositivity.

In fact Fahey et al (16) also reiterated that although β_2M levels followed longitudinally had a strong predictive value, yet CD4+T-lymphocyte counts were the single most important parameters of activity (11). We conclude that although β_2M is a useful surrogate marker to differentiate a group of patients with full blown AIDS from HIV-seropositive individuals without AIDS, yet it cannot be used interchangeably with absolute CD4+T-lymphocyte count and results in a given case should be interpreted with caution.

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Disc Diffusion Sensitivity Testing of Candida Species

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SUMMARY

Fungal infections have become important in the modern era with many immunosuppressed patients and others who undergo many invasive procedures. Antifungal chemotherapy is selected primarily empirically. This study, a simple disc diffusion test for quick determination of susceptibility of Candida species to the four commonly used antifungal agents in our hospital was undertaken to determine the susceptibility or resistance of candida isolates. All the 155 strains were found to be sensitive to Fluconazole & Itraconazole respectively. C.tropicalis was the predominent species isolated (51.6%) followed by C.albicans (19.35%).

Key words : Candida species, disc diffusion sensitivity

INTRODUCTION

Fungal infections range from superficial infections to deep and systemic infections. These "systemic mycoses" occur primarily in patients with altered host defences usually due to underlying disease or due to various therapeutic interventions. Candida species is the most common organism causing fungal infections followed by Aspergillus species. Candida species is also the fourth most common nosocomial pathogen in most community and academic medical centers. The sensitivity of fungi are rarely tested on a routine basis in hospitals. However with reports of resistance to antifungal agents appearing in literature it was decided to carry out disc diffusion sensitivity tests on the candidal isolates encountered in our hospital.

MATERIALS AND METHODS

The culture medium used was Bacto Yeast Nitrogen Base as recommended by Casals (1979)[2] with slight modifications. It was prepared by taking

Bacto yeast Nitrogen Base (code 0392)	-	6.7 g
L. Asparagine	-	1.5 g
Glucose	-	10.0g
Distilled water [to make]	-	100 ml

After dissolution and sterilization by membrane filtration, a 10 x concentrate (Yeast Nitrogen Base conc. solution) remains. 1 litre of solid culture medium

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for sensitivity tests was prepared by taking

HaH_2PO4	0.33g
K_2HPO4	0.92g
Agarose	11.0g
D. water to make	900 ml

The phosphate, agarose and water are melted by heating to 90°C to 100°C for 10 minutes. pH is adjusted to 7. Medium is sterilized by autoclaving at 121°C for 15 minutes. After cooling, 100 ml of Yeast Nitrogen Base concentrated sterile solution is added and poured into petriplates.

Addition of glucose to media greatly enhances the growth of yeasts but may cause lowering pH. Nevertheless the phosphate buffer should avoid a drastic lowering of pH during incubation.

Innoculum Seeding and Incubation

Suspension of fungus is made in 0.1 M phosphate buffer (0.33g NaH_2 PO4 + 0.92 K^2HPO4 in 1 litre of distilled water along with 0.1% Triton X 100) The isolates were subcultured onto fresh SDA plates. Five to six colonies were then suspended in Triton broth (5m) and turbidity adjusted to match MacFarland's 0.5. A sterile swab was dipped into this and streaked evenly on to the freshly prepared Yeast Nitrogen Agar base plate. Discs of Amphotericin B 100 mg/ml, traconazole 25mg & Nystatin 100 units were placed on it. incubation was done at 35°C. Reading were taken at 24 & 48 hours.

When testing with Fluconazole and Itraconazole a zone of partially inhibited colonies appears. This should be disregarded and the zone measured to colonies of normal size. The smaller colonies within the zone are not resistant mutants and their presence is due to mode of action of imidazole blocking the synthesis of sterols in fungi, but not to 100%

Interpretation of Degree of Sensitivity

SENSITIVE - Infection may be expected to respond to normal dosage of drug.

INTERMEDIATE ; Infection may be treated in some cases by using a high dosage of drug and may respond to concentration attainable in areas such as urinary tract.

RESISTANT - Drug cannot be used for treatment.

Table 1 : Criteria for following the Zone Diameters[3, 4]

	Nystatin 100 units	Fluconazole 20 mg Itraconazole 25 mg	Ampho.B 100 mg
Sensitive	> 12 mm	> 16 mm	> 10 mm
Intermediate	8-11 mm	10-15 mm	8-10 mm
Resistant	< 7 mm (up to disc.)	< 9 mm	< mm

Range of Antifungal Drugs Used

1. Nystatin - 100 unit/disc.
2. Amphotericin B - 100 mg/disc. Commercially available. Himedia discs have been used.
3. Fluconazole - disc of 20 mg/discs prepared from Fluconazole IV (Syscan) formulation which is commercially available.
4. Itraconazole - 40 mg of Itraconazole weighed out from commercially available capsule was dissolved by vortexing with glass beads with 2ml of Dimethyl formamide to get 4000 mg/ml stock. Further dilutions are made using distilled water to prepare 25mg/disc.

RESULTS

The results are as indicated in Table 2 to 4 and figure 1.

Table 2 : Distribution of Candida isolates according to drug scientivity

Total no. of isolates of Candida studied	-	155
Total no. of isolates Resistant to Nystatin	-	0
Amphotericin B	-	0
Fluconazole	-	5 (3.2%)
Itraconazole	-	3 (1.9%)

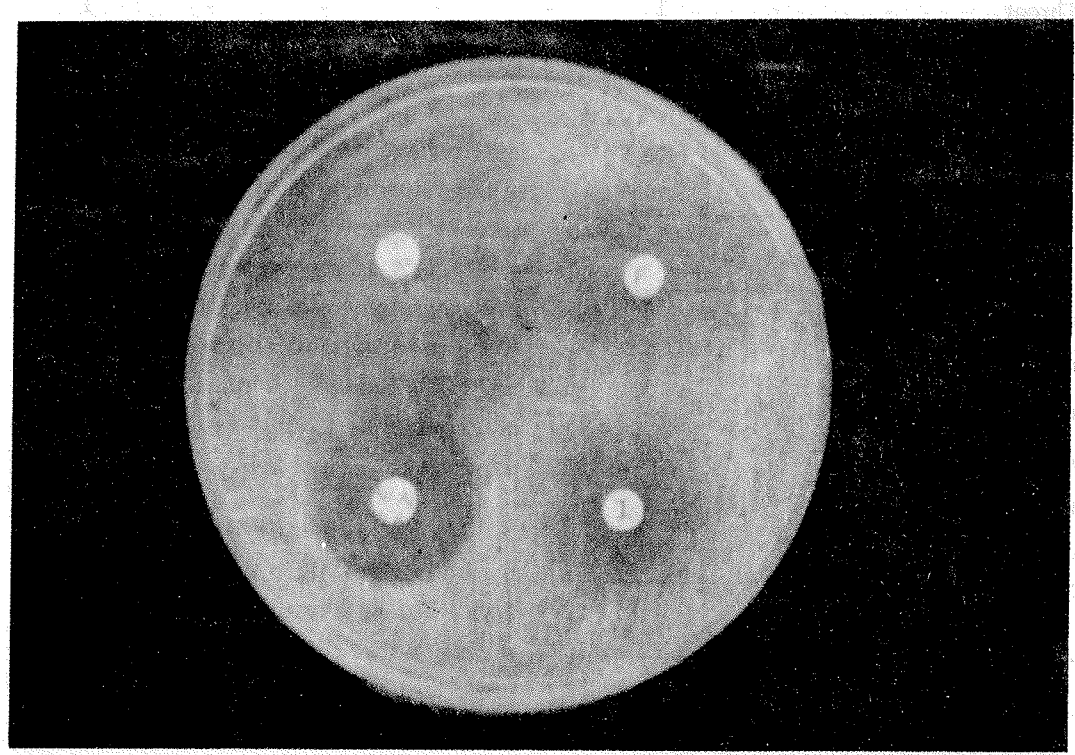

Fig. 1. Disc Sensitivity of Candida albicans to Nystatin, Amphotericin B, Fluconazole & Itraconazole.

Table 3 : Distribution of Candida isolates according to Prevalence (January-December 1997)

Specimens	C. tropi-	C. stell calis	C. albi- atoidea	C.parap cans	C. guill- silosis	C. krusei ermondii	Geotri -chum	Total
Blood	34	5	3	4	1	2	-	49
Tissue	2	-	-	1	4	1	1	9
Neckline	11	1	2	1	2	-	-	17
Pus	-	1	3	-	-	-	-	4
Urine	12	3	3	1	-	2	-	21
Fluids	3	-	1	-	-	-	-	4
Sputum	14	5	9	-	-	-	-	28
Suction	9	-	8	-	-	-	-	17
Faeces	1	-	-	2	-	2	-	5
Throat	-	-	1	-	-	-	-	1
Total	86	15	30	9	7	7	1	155

Table 4. Resistance of candida species to Fluconazole & Itraconazole.

	Fluconazole		Itraconazole	
	R	MS	MS	R
C.tropicalis	2	-	3	1
C.krusei	2	-	4	1
C.albicans	1	-	1	-
C.stellatoidea	-	-	-	1
Geotrichum candidum	-	1	-	1
Total	5 (3.2%)	1	8	3 (1.9%)

DISCUSSION

Methods of evaluating the susceptibility of yeasts to antifungal agents have been the subject of numerous studies during the last decade. A standard reference method described by NCCLS[5] which is a macro broth dilution assay is both cumbersome and time consuming to be used by clinical laboratories. The E test[6] (AB Biodisk, Solna, Sweden) which is capable of giving reliable results is expensive.

Macro and micro broth dilution methods give MIC'S which are extremely good. But in a routine clinical laboratory setting, a disc diffusion method has some important advantages. Multiple drugs can be tested and it is similar to the Kirby Baurer disc diffusion methods used to test antibacterial agents. It is important

to choose an appropriate medium, which is easy to prepare and dispense. The Bacto yeast nitrogen base agar used here has ammonia or asparagine as nitrogen sources and a pH of 7. Differences in pH may affect zone size or alter the activity of the drug itself. The medium is prepared in phosphate buffer which prevents drastic lowering of pH during incubation.

The routine candida isolates from the clinical laboratory were subjected to sensitivity testing. 155 clinical Candida strains isolated from blood, tissue urine, pus, sputum etc., were tested for sensitivity. All strains which showed resistant or moderately sensitive zones were retested twice and the average zone of inhibition was taken.

There were 86 C.tropicalis & 30 C.albicans isolates. The other species were C.stellatoidea (15), C.parapsilosis (9), C.guillermondii (7), C.krusei (7) and one species of Geotrichum candidum. In our hospital C.tropicalis was the predominant organism isolated from different clinical specimens. C.albicans is known to be the most common species isolated in different clinical specimens. C.albicans is known to be the most common species isolated in different studies. Perera et al reports on 40 isolations from 432 high vaginal swab cultures and C.albicans was the predominant species isolated forming 76% of the isolates.

All strains tested were found to be sensitive to Nystatin and Amphotericin B. Both these are polyenes, one a topical agent and the other an intravenous drug. Polyene drugs form complexes with ergosterol (the major sterol in fungal membranes) which opens channels in the membrane and causes leakage of critical intracellular constituents and causes subsequent cell death. Law et al (1994)[8] have reported that 96% of their isolates were sensitive to Amphotericin B and the rest were resistant to it.

Out of 155 strains tested by disc diffusion method in our study, five (3.2%) were resistant to Fluconazole, one (0.64%) was moderately sensitive and 149 (96.12%) of the strains were sensitive to Fluconazole. Resistance to Fluconazole has been reported to be increasing with 17.5%[8] to 11.8%[9] being reported in different studies. Resistance to Fluconazole is seen to be prevalent among patients with AIDS who have been treated with Fluconazole orally for prolonged periods.[8] Among our isolates two strains of *C.krusei*, two of *C.tropicalis* and one of *C.albicans* were found to be resistant to Fluconazole. One strain of Geotrichum candidum was moderately sensitive to Fluconazole.

Itraconazole[10], a newer triazole was also tested for sensitivity to all the Candida isolates. Four strains of C.krusei three of C.tropicalis and one of C.albicans showed moderate sensitivity to the drug.

Three strains (one each of Geotrichum, *C. tropicalis* & *C. stellatoidea*) were resistant to Itraconazole.

C.krusei is known for its relative resistance to azoles. Out of the seven isolates we had, two were found to be resistant to Fluconazole and four were moderatety sensitive to Itraconazole. Metzger et al[9] have also reported on four strains of *C.krusei* showing resistance to Fluconazole. Agar diffusion method[11,12] has been used by different authors for testing sensitivity of Candida isolates and Yeast nitrogen base medium has been found to be easy to prepare and easy to use in a routine clinical laboratory.

As a general recommendation, no topical or systemic antimycotic therapy should be started without reliable sensitivity tests and fungal reisolates during therapy should be tested for increasing resistance to the drug. As incidence of serious infections due to yeasts continue to escalate and reports of inherent or acquired resistance to antifungal agents emerge, invitro antifungal susceptibility testing of clinical isolates assumes increasingly significant role in over all therapeutic decision making.

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