*ETHICS OF TRANSPLANTATION AND HUMAN EXPERIMENTATION

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Mr. President, Councilors of the Singapore Medical Association, Ladies and Gentlemen.

I am sensible of the high honour and privilege you have bestowed on me by asking me to give this 7th Annual Lecture. It would be right for me at this moment to pay tribute to the renal and transplant teams and to doctors, nurses, pharmacists and technicians who have been behind the programme of dialysis and transplantation in the past 12 years and the public spirited laymen especially those in the National Kidney Foundation, the Rotary and Lion's Clubs who have contributed both time and money to support the programme.

The first two SMA Lectures which began in 1963 dealt directly with the problem of medical ethics. Dr. Gwee Ah Leng gave the first lecture on "Advertisement and the Medical Profession" and Dr. B. R. Sreenivasan the second Annual Lecture on "Infamous Conduct in a Professional Aspect" in 1964. Little did we suspect then that in the 7th Annual Lecture, I should inflict the subject of medical ethics on the profession again. However, there is good reason for the committee to propose this subject as one of two titles I might consider. I had no hesitation in choosing this subject "Ethics of Transplantation and Human Experimentation", not only because I had thought quite a good deal about it but because it has created a state of ethical crisis in which the medical profession has floundered and been caught napping. It is crucial at this time and age that our thinking should catch up with the implications of the rapid medical progress already manifesting itself in our midst. The alternative is to ask for a moratorium on medical progress until we have made up our minds. This would be a retrograde step and is tantamount to cutting the ground from under our own feet.

The medical profession is an honourable one and the doctor is bound by words so well put in the Declaration of Geneva. "The health of my patient will be my first consideration" and the International Code of Medical Ethics which states: "Any act or advice which would weaken physical or mental resistance of a human being may be used only in his interest." Because medicine and law serve the community they must walk in step. But when one progresses ahead of the other, as has Medicine after World War II, trouble arises as physicians must come under common law and the laws of the land. Lord Justice Edmund Davies[19] of the Royal Courts of Justice gives the reason. "Law it has been said does not search out as do science and medicine; it reacts to social needs and demands. . .The problem must arise before the law reacts to provide a solution." Here is where science and law differ.

INTRODUCTION

The Oxford Dictionary defines 'Ethic' as the science of morals and 'Ethics' as (1) the moral system of a particular school of thought or (2) the rules of conduct recognised in certain limited departments of human life. Ethics is therefore concerned with morals. We are not really concerned with etiquette or morality except to distinguish them from ethics. Etiquette is the code of conduct controlling relations between professional colleagues and morality is defined as the body of rules of conduct considered unconditionally valid. The codes of etiquette and morality cannot fully apply to the moral problems facing the doctor of today who has to make a choice between values that are not measurable e.g. between the physical and psychological risks incurred by the living donor of a renal graft and the value of the life of the recipient. Morality can only affirm that the value of human life is infinite both for the donor and for the recipient.[1]

As far back as 2000 B. C., the code of practice for physicians was very strict. In Egypt and Babylon, the physician could forfeit a considerable part of his own anatomy if he did an unnecessary operation or was careless in performing it.

The physicians in Cos devised the Hippocratic Oath which is attributed to Hippocrates about 4000 B.C. This code held sway until World War I. Prior to this, medical schools required graduates to subscribe to the oath on graduation. That it had been able to retain its position for so long

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is remarkable but it does indicate that the basic tenets of medical practice had remained unchanged throughout these past centuries.

What then has caused a re-thinking on the part of the physicians since World War I?

Perhaps we need only to point out two facts that have questioned the validity of the Hippocratic Oath in our modern situation.

First, the shocking revelations during the Nuremburg Trials showed that doctors had used drugs, physical methods of exposure and deprivation on human subjects without their consent and had callously caused suffering, bodily harm and death. The Nuremburg Code of 1947 lays down 10 standards to which physicians must conform when carrying out experiments on human subjects. Then swiftly in its wake, the World Medical Association reviewed the problem at its General Assembly in 1948 and adopted a modified oath known as the Declaration of Geneva (see Appendix I) which in effect modernised the Hippocratic Oath. This declaration was incorporated in the International Code of Ethics in 1949 (see Appendix II). The World Medical Association has requested that all medical schools should make students subscribe on graduation to the Declaration of Geneva. Most member nations of the United Nations have accepted the International Code of Ethics of 1949.

The second perhaps more important fact is the rapid progress of medicine in treatment and investigation as well as in the actual rate of medical discovery. These discoveries have created new problems not only for the individual physician but also for the community. With knowledge doubling every ten years, ninety per cent of what we know today will be out of date in ten years time. Certainly in the last 40 years, the world has seen many new drugs and treatments many of which have unintended and undesirable side effects in both medical and moral realms. An essential pre-requisite for medical progress in recent decades has been a very large and rapid increase in the use of human subjects in biomedical research. No one can gainsay the enormous benefits to the health and welfare of the many who enjoy modern medical care. The development of devices, which may support and even take over vital functions of the body, can effectively postpone death and patients can be kept alive in a way which was impossible only a few years ago. Since medical views and techniques develop faster than ethical concepts and current law, some procedures such as resuscitation and organ transplantation have created problems because the ethical and legal acceptability of the application of medical technology is generally only questioned after its use. Thus we can keep alive patients with no functioning brain tissue. We can profoundly alter personality by drugs and operations. In many countries, including Singapore, the new laws regarding abortion has made the operation legal when some would maintain still that it is not ethical. With elderly bedridden patients increasing faster than the beds to take them, some would like to make euthanasia a legal act. That would not necessarily make it ethical. In medical research using human subjects there is considerable concern that there has been the failure to achieve the highest or even adequate standards of control, thus usurping the rights and endangering the lives of patients and volunteers.

These developments have led the 18th World Medical Assembly in 1969 to adopt the Declaration of Helsinki (see Appendix III) which recommends certain guidelines to physicians in clinical research. Significantly the declaration begins with the statement, "It is the mission of the doctor to safeguard the health of the people.—His knowledge and conscience are dedicated to the fulfilment of the mission".

A LOOK INTO THE FUTURE

Prof. Salvador Luria, a Nobel prize winner in Medicine for work on the reproduction of viruses is Professor of Biology at the Massachussetts Institute of Technology. He warns mankind of the awesome consequences of the biological revolution of the past 20 years. Man is able to manipulate the genetic material which is the organic substrate of his evolution from one generation to the next and dictates what an organism is, how it responds and what kind of descendants it will in turn produce. In this new genetic technology, molecular biologists have purified the chemical code of life DNA (deoxyribo-nucleic acid) from bacteria, viruses and animal cells including human cells and clarified the chemical mechanism of gene mutation. In 1970 Prof. HarGobind Khorana of the Institute of Enzyme Research of the University of Wisconsin perfected the chemical synthesis of a gene in the test tube. Prof. Luria adds that the process of making gene messages and the use of these messages to produce the individual pieces of cell machinery have been duplicated and analysed in the test tube.[2]

In 1932, Aldous Huxley wrote "Brave New World" about an utopia of conditioned humanity for the year "600 After Ford" which incorporates a type of eugenics based on artificial fertilization, the possibility of twins induced in the test tube, chemical conditioning of growing embryos and

psychological conditioning of growing children. In principle Huxley's make-to-order human being "has become feasible sooner than he anticipated" and even more powerful embryological techniques are possible.

However, the promise of true genetic surgery is the artificial correction, replacement, removal or addition of genes based on the discoveries of molecular biology. Prof. Luria writes that "a coupling of genetic intervention with embryological surgery would open the way to truly awesome possibilities", when applied in four fields —medical, bioindustrial, social and military.

In medicine it may be possible to treat genétic defects e.g. insufficient production of a hormone as insulin by supplying the proper gene to certain cells from the outside or by implanting functional cells or by causing the corresponding gene to become activated in other cells of the body which fail to produce the hormone because of regulatory depression. Such manipulations could also alter immunological reaction to foreign tissue to improve the chances of organ transplants. In the bioindustrial field, direct genetic manipulation i.e. by implanting or removing specific genes may replace selective breeding in the manufacture of better strains of organisms from yeasts to cereals to cattle.

However the social implications of manipulation of human genes to achieve artificial fertilization and nuclear transplantation with human eggs, are truly terrifying. Who has the right to decide what the human race shall become? The removal of defective genes and replacing them with normal counterparts is fair enough. But when we introduce supposedly 'desirable' genes, it is one step away from the manufacture of a supposedly 'superior' race by introducing identical nuclei from the cells of a 'superior' individual into series of nucleated eggs and implanting them in the wombs of surrogate mothers. Enormous ethical and legal problems of an entirely new nature would arise at this point. Concerned scientists are urging their colleagues not to play with genétic manipulation because the effects could be irreversible. Among them are the 3 Nobel prize winners and discoverers of the double helix of DNA Francis Crick, James Watson, Maurice Wilkin and George Beadle, another Nobel prize winner for DNA work. Genetic means of controlling human heredity on a massive scale by genetic surgery is even more terrifying because its process is hereditary and irreversible. Prof. Luria mentions possible genetic weapons such as viruses that can spread in an enemy population, genes that produce sensitivity to poisons or susceptibility to tumour or even transmissable genetic defects—in other words genétic génocide! The fact is that the development of pathogenic germs resistant to certain antibiotics has been going on for years in the biological arsenals of so-called 'civilized' countries. Prof. Luria concluded 'Science, like the arts, has become an inseparable part of the intellectual adventure of man . . . What is needed rather, is a rational machinery, both national and international to determine sensible policies and priorities in the application of scientific knowledge. . . . We need to create a society in which technology is purposefully directed toward socially chosen goals'.

ON TRANSPLANTATION

The field of transplant biology collects a galaxy of scientific disciplines, which include the pathologist, microbiologist, biochemist, geneticist, zoologist, internist, physiologist, surgeon, pharmacologist, radiologist, virologist and veterinarian. Advances in any of these disciplines will influence the entire field. In the early 1900's sporadic skin grafting was attempted and in the late 1920's skin was successfully transplanted between monoxygotic twins thus revealing their identical nature. The barrier against transplantation between 2 persons of different genetic make-up seemed insurmountable until World War I when Gibson and Medawar[3] showed that skin allografts between genetically dissimilar members of the same species could immunize a recipient against the other tissues of the skin donor. It was then conceived that a rejection process was not unlike a potentially alterable disease process.

Experimental methods of crossing the immunological barriers were developed. Thus acquired immunological tolerance was produced by the injection of the foetus with allogeneic cells and radiation induced tolerance was produced by the injection of allogeneic bone marrow cells in a heavily X-irradiated recipient. These methods have failed in humans.

In 1954, the first successful kidney transplant was performed between identical twins, the success of which truly opened the way for kidney transplantation. In 1959, the first successful human transplant between other than identical twins was performed between a pair of fraternal twins using total body irradiation in sublethal dose to overcome the moderate immunological barriers.

About this time two groups of workers, Schwartz and Dameshak[4] and Calne[5] and Zukoski[6] independently used an antimetabolic drug, 6 mercaptopurine, the former to induce tolerance to foreign protein in the rabbit, the latter to prolong survival of dog kidney allografts.

However, the current state of kidney transplantation really began in 1961 with the use of Azathioprine in a patient who survived for 36 days but died of drug induced toxicity because the clinicians lacked knowledge at that time about the optimum use of the drugs.[7] It is true to say that without these early transplant experiences in man following animal work progress in organ transplantation would be highly improbable.

Up-to-date some 12,000 kidney transplantations have been performed throughout the world with 5000 survivors. The more recent 4 years experience however has shown that results could be as favourable in transplants between siblings who are genotypically identical for HL-A antigens as between monozygotic twins. Morris reports that of 141 transplants between HL-A identical siblings only 6 (4·2%) have failed and that rejection episodes have not recurred or generally have been mild and easily controlled.[8] Some centres, notably from Australia and New Zealand have reported a one year's survival of homografts of close to 70% using cadaveric donors' kidneys and a 5 years' survival of nearly 50%[9]—results that are much better than surgery for cancer of the gastrointestinal tract.

Properly organ transplantation involves a variety of tissues or organs. Thus autotransplants of the patient's own skin, cartilage, tendon and bone are widely used in plastic and orthopaedic surgery. Homotransplants from another person or animal of the same species will require a complete or a full house histocompatibility or immunosuppression of a single HL-A allele or at the most two allele incompatibility to ensure good results (absence of lymphocytoxic antibodies having been excluded by a direct cross match using the recipient's serum and donor's peripheral blood lymphocytes). Homotransplants include skin, bone marrow, leucocyte and platelet transfusion, organs such as kidney, liver, pancreas, lungs and heart. Homotransplants of liver, lung, and heart must necessarily come from cadavers. Heterotransplants from the higher primates have been attempted but the immunological barrier has been insurmountable.

The potential demand for organ transplantation in end-stage disease is very real with modern treatment keeping alive respiratory cripples, many patients with recurrent liver failure, terminal renal disease and chronic heart disease. Even in countries where medicine is highly developed it is only possible to treat a small fraction of patients. The overall total in Europe of renal patients treated by dialysis or transplantation is 10 per million of population. In a few countries where the community has provided an adequate supply of cadaveric kidneys and the policy of the government is to treat all patients with dialysis at home if not in an institution, the figure rises as high as over 80 per million in Denmark, 78 per million in Australia and 90 per million in New South Wales. Every year some 25 to 35 more per million are accepted for treatment in Australia.[9] In Singapore it has been difficult to treat more than 15 persons per million of population with end-stage kidney disease, the reason being the lack of kidney donors. The paradox is that theoretically we should have more than a sufficient supply of cadaveric kidneys and corneas from the 400 fatal road traffic accidents and 200 fatal industrial accidents that occur annually. Hence the community needs to be constantly informed and actively brought into the picture if they are to support the programme. The medical profession has been the first to search its conscience over the ethical problems inherent in organ transplantation during its early beginning when much of it was still experimental and the legal definition of death was inadequate for the speedy removal of kidneys from human bodies. To this end several nations have set up multidisciplinary committees on organ transplantation to make recommendation and give guidelines. The Ciba Foundation Symposium on Ethics in medical progress with special reference to transplantation in 1966 was one such platform where jurists and doctors freely shared views in transplantation practice.[10]

The efforts of at least one country deserve mention. In 1969 the Netherlands Red Cross[11] decided to make a study of organ transplantation especially of the problems surrounding organ donorship having been responsible for cornea and blood donation. After extensive preparation, its Ad Hoc Committee was formed of 46 representatives of various disciplines, divergent religions and philosophies, who discussed in interdisciplinary study groups, medical, legal, ethical and nursing problems. It also looked into the organisational problems of information and registration. After a total of 66 meetings over 3 years, an interim report was published in 1969, the Committee voting for the 'contracting-in-system' as against the 'contracting-out-system' (which will be explained later). Each study group had a physician and a lawyer as secretaries.

Since a precise diagnosis of death was regarded as a primary requisite of current medical conduct, each discipline had to define the death criteria. The medical group defined death as the irreversible cessation of all brain function, including function of the brainstem. The ethical group, legal group and nurses also agreed to these criteria, however, each on its own grounds. The medical

group based its decision on the fact that braindeath is 'the direct and irreversible cause of the disintegration of the biological unit, i.e. the living human being because by and at braindeath the integrity and stimulating function of the brain ceases completely and forever. The ethical group differentiated death from the diagnosis of irreversibility of serious brain damage or coma and from the decision to cease further effort to prolong human life. It held the view that 'once the biological oneness of the somatic organism has completely and irreversibly fallen apart the existence of a psychosomatic oneness 'living human person' has become impossible. The legal group understood that the Medical and Ethical Groups 'consider specific human life as qualitatively different from the life of cells or organs whether in situ or in vitro'. It was concluded that the symptom complex of the death criteria 'is exact and can be proved with certainty, is the same everywhere and for everybody, open to only one interpretation and is applicable in practice'. Legal regulations are desirable to protect the dying as well as the physicians.

Although it is very strongly recommended by the Netherlands Red Cross and (other working groups) that the donor and transplant teams should be separate, the medical group agreed that it might be impossible in practice because certain persons by virtue of their function and knowledge are members of both teams. It recommended an intermediary team to cope with personal problems which arise.

The Ad Hoc Committee of the Harvard Medical School was convened to establish when the physician must decide that indefinite artificial cardio-respiration is futile. Its report published in 1968[12] states the following criteria for establishing the presence of irreversible coma:—

1. Total unresponsiveness to all external stimuli even the most intense painful sort.
2. Absence of spontaneous respiration (if the patient is on a mechanical respirator, this should be turned off for 3 minutes).
3. Complete absence of elicitable reflexes and absence of any spontaneous muscular movements.

It recommended that examination over a period of at least 24 hours should be required in order to ascertain irreversibility. A flat EEG should be regarded only as a confirmatory adjunct in the determination of brain death. Dr. Henry Beecher, the Chairman of the Ad Hoc Committee, later extended the proposals to include the agreement by two physicians, one a neurologist or neurosurgeon that there is indeed braindeath and they in turn are to inform the family that the respirator is to be turned off thus sparing the family the agonising decision on this matter. However artificial respiration may be continued as long as necessary to preserve the organs. Beecher pointed out to one study in which autopsy showed absence of viable brain tissue in all 128 patients judged by the Committee's criteria to be in irreversible coma.[13]

The state of Kansas in U.S.A. made history in passing the first legislative definition of death in the history of the common law world.[14] Two separate and alternative criteria for determining death were adopted. The attending physician could use the classic criteria of 'an absence of spontaneous respiration and cardiac function'. Alternately he can base it on the absence of spontaneous brain function. In irreversible brain coma 'death is to be pronounced before artificial means of supporting respiratory and circulatory function are terminated and before any vital organ is removed for purposes of transplantation'. The Kansas law protects the attending physician from the accusation of causing death by turning off the respirator.

That the final criteria have yet to be universally agreed on is shown by the several techniques to verify absence of cerebral circulation and brain death that are listed by the Netherland Red Cross Committee on Organ Transplantation:—

1. Fluorescine—retinography
2. Cerebral scintigraphy
3. Carotid and vertebral angiography
4. An EEG recording of brain stem structure using cerebral depth electrodes.

The 22nd World Medical Assembly met in Sydney in August 1968 and made a statement on death called the Declaration of Sydney which is in effect a definition of death especially for purposes of transplantation (see Appendix IV).

Until now the policy of the Renal Unit in Singapore has been to use only cadavers for kidney transplant and the new Medical, Therapy, Research and Education Act of 1972 deals in respect of cadaveric donors. However this policy may be changed in view of excellent results of transplant between HL-A identical siblings reported by Morris and the difficulty of procuring organs from cadávers. Common Law decrees that no man has any right to his body after death and his directions as to disposal can be ignored.[16] However Common Law rule has been modified by Statute in U.K. firstly by the Corneal Grafting Act 1952 and far more extensively by the Human

Tissue Act 1961 and in Singapore by the Medical (Therapy, Education and Research) Act Chapter 160 of the Revised Edition 1966 and the new Act of 1972.

In Singapore the Medical (Therapy, Education and Research) Act of 1972 replaced the older act of 1966 which resembled the U.K. Human Tissues Act of 1961. Under the new Act any person over the age of 18 could expressly state the desire that his body or organs after death be used for any purposes of the Act. In the absence of any stated wishes, the relatives could give the necessary consent. The donor's wish cannot be overriden by the surviving relative who is defined by the new Act. Where no specific statement has been made by the deceased before death 'the person in lawful possession of the deceased' can give consent. This person is listed so that a prior class can donate the body or organ without deferring to the wishes of other classes. Thus the spouse of the deceased is ranked before the children or the parents. If there is a conflict between relatives belonging to the same order of priority the authority to examine or remove part of the body will not be given.[15] In Singapore, we have thus opted for what is in fact a 'contracting-in-system' as against the 'contracting-out-system' in which an adult has to inform the authorities before death if he does not wish to donate his organ. In the absence of this formal wish, the Medical Superintendent of the hospital would have the right to order the removal of organs after death for medical therapy or research. Few countries have opted for this system in its entirety.

In Singapore under the 1972 Act death is not defined. However in 1973 the Ministry of Health issued a Code of Practice on Medical Research and Human Experimentation which is an excellent publication that deserves to be better known by the profession. In it is set out the definition of death for purposes of organ transplantation as 'the increasing loss of organisation of the body starting from the higher brain centres and progressing down irreversibly through the tissues and cells' and death is certified at the moment in which the brain has irreversibly lost control of the spinal cord. Six criteria are given including an isoelectric EEG in the absence of hypothemia, anaesthetic agent and drug intoxication. Apart from falling blood pressure and absence of spontaneous breathing all the criteria should be present for 2 hours before death is certified by two senior doctors one of whom must be a clinical consultant and both must not be involved in transplantation.

In our current practice, consent is sought from the relatives by a senior physician, who is not involved in the resuscitation or the transplant team. Once consent is given by the relatives, the care of the patient is placed in the hands of a senior anaesthetist and death is independently assessed by two physicians one of whom is of senior consultant status. It has been difficult to have completely separate 'donor' and 'transplant' surgical teams but apart from one or two key persons, the teams are practically separate.

THE LIVING DONOR

Under English law no man may lawfully consent to his body being maimed. Thus in a case where a man had himself sterilized to spite his wife Lord Denning said in 1954 that the operation was plainly illegal even though performed at his request since it was without cause or excuse.[17] Could the living donor avoid this primafacie case of maiming if he allows one organ to be transplanted to another? However Lord Kilbrandon regards the 'maiming' doctrine as 'intended to strike at actions which are socially wrong, or at least inexpedient, such as brutal sports, the gratification of lust or the evasion of public duties'.[18] Lord Justice Edmund Davies did not think a surgeon could be "successfully sued for trespass to the person or convicted of causing bodily harm to one of full age and intelligence who freely consented to act as donor—always provided that the operation did not present unreasonable risk to that donor's life or health. That proviso is essential. A man may declare himself ready to die for another, but the surgeon must not take him at his word. . . . . The surgeon must not operate if, on balance, the risk involved to the donor cannot reasonably be regarded as justified in the public interest by the good likely to enure to the donee".[19]

We have mentioned that in Singapore the new Medical, Therapy, Education and Research Act of 1972 provides a contracting-in-system of organ donation after death of the donor. What about the position of the living donor? How can we ensure that his consent is both free and informed. Prof. Hamburger of the Paris Faculty of Medicine has laid down certain conditions which should be quite acceptable to both lawyers and scientists according to Lord Justice Edmund Davies.[19] They are:—

(a) The donor must be made fully aware of the exact dangers he is running.

(b) He must have a reasonable motive for wishing to donate part of his body. Hamburger adds 'At Paris we have adopted the habit of considering a volunteer acceptable if he is a relative of the patient to be saved and unacceptable if he is not.

(c) Adequate steps must be taken to verify whether there has been pressure from the family or elsewhere.

(d) There should be a psychological (if not a psychiatric) examination to verify that the volunteer is in full possession of his mental faculties. Hamburger concludes: This psychological examination seems to us to be mandatory.

The living donor must be of mature years and mentally sensible. The position of prisoners acting as living donors was discussed at the Ciba Symposium. It was pointed out that prisoners are subject to influences that do not afford complete freedom of choice and therefore it is questioned whether their undertaking as living donors is a result of balanced judgement. This led to the discontinuance of the use of prisoners as living donors in Colorado in 1966.

Likewise the use of minors as donors is not acceptable to Lord Justice Davies since neither parent nor guardian can lawfully consent to his child to so act. However in 1956 the Massachussetts Supreme Judicial Court declared it lawful to transplant a kidney from a healthy boy of 14 to his identical twin dying from renal disease.[19] The court accepted the psychiatric evidence that if the operation were not performed and the sick twin died there would be 'a grave emotional impact' on the survivor and it therefore held that the transplant was necessary for the emotional good health of the donor and that the operation should accordingly benefit both him and the donee. Yet in another case the United States Supreme Court ruled that 'Parents may be free to become martyrs themselves. But it does not follow that they are free to make martyrs of their children![20]

Should tests such as ángiography be conducted on a dying patient without his knowledge or acceptable consént in order to determine the suitability of his organ for transplant purposes after death? Technically such kinds of test amount to assaults but it is a different and acceptable matter to tissue type terminal patients as potential donors especially after consent has been given by relatives.

It is in the category of single organ donation that must necessarily involve the inevitable death of the donor that specially causes ethical problems and misunderstanding. The removal of a heart from a donor can really be effective only when that heart is capable of resuscitation and either continues beating or can be immediately restored to beating.[21]

In their article, "Human subjects in clinical research", Martin *et al* state forcibly: "The heart transplant requires the participation of two human experimental subjects. One subject must give up his heart. The other accepts the donated heart and its potential risks. The once abstract, philosophical and academic considerations of 'life' and 'death' have become real. The person who becomes the donor of a heart faces not a risk but a certainty—death, if this has not already occurred"[22].

Thus the definition of the moment of death rather than the fact of death in this situation is crucial if the heart or liver can be of any use in a transplant.

In concluding this section on the ethics of transplantation I can do no better than to quote the words of the Professor of Civil Law at Oxford, Dr. Daube[23] at the Ciba Foundation Sympodium of 1966 chaired by Lord Kilbrandon: "Progress in transplantation is a matter for wonder and dread; and no tribute to the courage and humanity of the pioneers can be too high. The jurists certainly must adapt their rigid, over-conceptualized thinking to the noble conditions; and the doctors in their turn should perhaps acknowledge in increasing measure their accountability outside their closed circle of peers before a wider forum of society, ethics and law .... we are becoming more and more answerable to a wider and wider public. If we take care to preserve the principal traditional values in the process, we may yet achieve a civilized result".

HUMAN EXPERIMENTATION

The history of medicine has shown that the controlled experiments in animals and man have marked the progress in many fields ranging from physiology, nutrition, anaesthesia, radiology, therapeutics to surgery. It is accepted that the concept of the controlled clinical trial may have done more to make modern medicine a reality than any single factor.[24] However attitudes towards human experimentation have changed over the years. Perhaps two examples from the development of medicine in one subject of beri beri in our own region would suffice.

In December 1905 William Fletcher took lunatics from an asylum in Kuala Lumpur and numbered them off. The odd numbered patients were given the regular hospital diet of polished rice and the even numbered received unpolished rice containing sufficient vitamin B^1 to prevent beri beri. Some 34 of the 120 patients on the polished rice developed beri beri and 18 of them died. No patient of the 123 on the unpolished rice died and only 2 developed beri beri having had it on admission.[27]

In 1913 Vedder [28] commenting on experiments on beri beri by Fraser and Stanton said, "Finally I have been authoritatively informed that Fraser and Stanton in the course of their work on beri beri, performed a large number of human experiments in which they tried every conceivable method including insect transmission to infect healthy individuals from beri beri patients. The experiments were all negative but were unfortunately suppressed by the Government for political reasons".[27]

In more recent times, experiments have been done without the knowledge or consent of the patient and not for his benefit. For example, live cancer cells were injected into 22 specific, sick and elderly patients without their knowledge and penicillin was withheld from young airmen with streptococcal sore throat infections resulting in more than a score of rheumatic fever cases.[24]

As a measure of the tremendous increase since World War II in experimentation on man, one could compare the research expenditure of a hospital such as the Massachussetts General Hospital and the National Institutes of Health. In a 20-year-period from 1945 to 1965, the former annual expenditure increased 17 fold from ½ to 8·3 million, the latter a gigantic 624 fold from 0·8 to 436 million.

That ethical violations in human experimentation occur not infrequently can be seen from several studies. Beecher[25] mentioned 100 consecutive human studies published in 1964 in an excellent journal; 12 of these seemed to be unethical. In England, Pappworth[26] collected more than 500 papers based upon unethical experimentation.

The biomedical research community have themselves paid increasing attention to the subject of abuse of the subjects of human experimentation. They have jointly organised symposia with professors of law and social scientists to view the problem.

The Research Group on Human Experimentation[29] supported by the Russell Sage Foundation of USA analysed a mailed questionnaire survey of 293 biomedical institutions which represented a national sample of all American institutions of this kind. The questionnaire which was filled by active researchers and members of their institutions' peer-review committee covered a wide field including the structure, processes and efficiency of the peer-review committee and such key ethical concerns in the use of human subjects as the importance of informed voluntary consent and the proper balance between risk and benefit in experiments done with human subjects.

They also interviewed researchers in two types of institutions, one called University Hospital and Research Centre which fulfilled the criteria of the typical biomedical research institution such as a large number of researchers, a large research budget, highly productive researchers, a medical school with a teaching hospital connected to it, strongly encouraging research particularly at the scientific frontiers and involving risk for human subjects and receiving a high proportion of its research funds from the National Institutes of Health. The other institution called the Community and Teaching Hospital would be a teaching hospital loosely affiliated to a medical school and with less emphasis on research. Thus the authors were able to obtain 352 interviews with researchers using human subjects, 298 at University Hospital and Research Centre, 54 at Community and Teaching Hospital. From those who refused interview 35 completed short questionnaires. Altogether a response rate of 72% was obtained. To get at expressed standards of research, the researchers had to respond to a battery of 6 extremely detailed hypothetical research protocols which measured their concern with the patients voluntary consent and their willingness to do more and less risky studies. The research protocols which had been constructed out of research literature and pretested with a dozen chiefs of research included the following: a study of the relation between hallucinogenic drug use and chromosome break, a test of alternate treatments for congenital heart defect in children, a test of new antidepressant drugs in a psychiatric hospital doing unnecessary thymectomies in children to ascertain effects on tissue transplant survival, a study of the effects of radioactive calcium on bone metabolism in children and a study of pulmonary function in adults under anaesthesia for routine hernia repair and requiring the prolongation of anaesthesia.

The results found that the majority followed the strict pattern of voluntary consent, concern over the risk-benefit ratio and avoidance of studies in which the risk exceeded the benefit.

However there was a permissive minority who were less strict on one or more of the issues raised or more permissive being not concerned over consent and would do studies where the risk exceeded the benefit. For example some 25% saw nothing wrong in doing the chromosome break study without asking consent of the students involved, 6% would approve the high risk on thymectomy study, 14% would approve the high risk use of radioactive calcium in the bone metabolism study in children. Only 11% of the actual

work of biomedical researchers involved more than 'very little' risk for the subjects, whilst 20% entailed greater risks than benefits to the subjects.

Researchers who do not get sufficient reward for equally productive work would tend to push harder and are willing to take greater risks and work with the more permissive group. Of the institutions covered, about 15% do not review all research. The permissive minority are thus characterised by (i) relative failure in competition for scientific success and sacrifice of the value of humane therapy to the value of scientific achievement, (ii) attempt to overcome effects of ethnic and other forms of discrimination by over-emphasis on scientific striving, (iii) inadequate training on 'socialization' into the norms of humane therapy and (iv) ineffective peer review control. Barber and his colleagues[29] concluded that the 'patterns of ethical standards and practice are not entirely satisfactory in the light of the high aspirations and claims of the biomedical research community'.

CLINICAL TRIAL

In discussing the position of controlled clinical trial especially double blind trials, Dr. Tyrrell, Head of the Division for Communicable Diseases and Common Cold Research Unit of the Medical Research Council, U.K. maintains that 'any other sort of study is unethical since it means performing an experiment which cannot answer the question in doubt'.[31] When the issue is not in doubt any trial such as a placebo-controlled trial of pneumonia, is not ethical. The profession is only entitled to compare the best available treatment with a new and potentially better one.

The doctor has always to practise constant vigilance, always "putting himself in the patient's place" as Lister advised, always trying to help all patients equally whether they are terminal cancer patients, volunteers for human experimentation or private patients, always searching his conscience lest ambition, idleness, pride or personal failing affect his clinical judgement and ethical standards so that the patient suffers.

What then can our profession in Singapore do? I believe these annual lectures have helped to bring to the notice of the profession the need to be concerned with high standards of ethics. In the past it was considered essential for the doctor to accept the sanctity of human life and the mandate to ease suffering and maintain life. There is ever greater need to do so in our day and age. More should be done for example by (i) teaching medical students these concepts in the context of our accelerating medical progress, (ii) the implementation of peer-review committees in all medical institutions, (iii) the definition of a policy that absolutely all research be screened, approved, modified or rejected on unethical grounds, (iv) the setting up of teaching programmes in research ethics by the biomedical research community, which should also exert much of the social control through both experts and outsiders.

We should now return to the primary relationship between the patient and his doctor which undergirds the basis of principles of ethical behaviour. This relationship is based on an implicit agreement that the doctor will care for him according to the best of his abilities declaring, "The health of my patient will be my first consideration".[30] The agreement is broken only if the doctor does not treat to help the patient or he fails to do it as well as he can. It would occur to anyone that if the doctor does what seems to be right and fails to cure the patient he is still ethical e.g. if he performs an emergency tracheostomy which would be better done by an ENT surgeon. However the standards of practice change with progress and what would be ethical in the past such as venesection for pneumonia and high concentration of oxygen for premature babies would now be definitely unethical. The doctor's part is therefore to act for the patient in such a way that although he may take risks with the patient's limb and life, he 'judges that these risks are kept as low as possible and the chances of benefit as high as possible' . . . Doctors thus take risks with their patient's health quite ethically".[31]

In conceptualizing and designing experiments the decisions have been hitherto strictly that of the medical profession and in particular of the biomedical research community. Since future subjects for clinical research must come from the general public, some would strongly recommend that the discussion of human participation in medical research be taken to the public so that the decision on the use of human subjects reflect the sentiments of the total community.[22] There is a growing public reluctance to see the sick and dying used as subjects in medical research, suggesting that greater efforts should be directed towards the development of experimental models in normal man.

CONCLUSION

We cannot deny the fact that we are living today in a crisis of values. A surgeon, Douglas Jackson,[33] declared "It is arrogant and contrary to recent history to think that a doctor's conscience is always right, especially as he is often untrained ethically. . . . The strongest incentive to serve our patients is to see their worth in God's sight".[33]

Lord Denning brings us back to the subject of our discussion. I quote, "The person is primary not the society: the State exists for the citizen, not the citizen for the State" and adds "Without religion, there can be no morality and without morality, there can be no law".[33] Religion particularly personal religion therefore has much to do with a doctor's ethics in practice and experimentation.

At the close of this presentation, one may perhaps feel that I am about to call for a moratorium in human experimentation. Yet nothing can be farther from the truth. With the present accelerating of scientific progress, man can look forward not so much to the total abolition of disease as the enjoyment of good health in all aspects. We cannot halt now. Beecher[25] has rightly said, "It has become evident that the physician has a duty to go beyond the patient's immediate complaint—a duty not only to relieve or cure but to prevent disease. With this concept . . . .the need for searching out causes, for treating, for testing, for comparing and for experimenting is no longer a privilege; it has become a duty. This is to say that the medical profession must accept its responsibility not only for the prevention of disease and the care of the sick, but also the advancement of knowledge on which both depend". McCance's views[34] would not only agree with the last statement but would also emphasize the importance of impressing patients with the fact that the very best hospitals carry out experimental work not only for the benefit of the ill, but also for the benefit of mankind and that the patients owe a great debt to such work that has already been done on others. One hopes that eventually the public will understand that if they are to have the privilege of entering these leading hospitals they can be expected to collaborate knowingly and willingly in medical research.

APPENDIX I

DECLARATION OF GENEVA

"At the time of being admitted as a member of the Medical Profession:

I solemnly pledge myself to consecrate my life to the service of humanity.

I will give to my teachers the respect and gratitude which is their due;

I will practise my profession with conscience and dignity;

The health of my patient will be my first consideration;

I will respect the secrets which are confided to me;

I will maintain by all the means in my power, the honour and the noble traditions of the medical profession;

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient;

I will maintain the utmost respect for human life, from the time of conception; even under threat, I will not use my medical knowledge contrary to the laws of humanity.

I make these promises solemnly, freely and upon my honour".

APPENDIX II

INTERNATIONAL CODE OF MEDICAL ETHICS

Duties of Doctors in General

"A doctor must always maintain the highest standards of professional conduct.

A doctor must practise his profession uninfluenced by motives of profit.

The following practices are deemed unethical:

(a) Any self-advertisement except such as is expressly authorised by the national code of medical ethics.

(b) Collaborating in any form of medical service in which the doctor does not have professional independence.

(c) Receiving any money in connection with services rendered to a patient other than a proper professional fee, even with the knowledge of the patient.

Any act or advice, which could weaken physical or mental resistance of a human being, may be used only in his interest.

The doctor is advised to use great caution in divulging discoveries or new techniques of treatment.

A doctor should certify or testify only to that which he has personally verified.

Duties of Doctors to the Sick

A doctor must always bear in mind the obligation of preserving human life.

A doctor owes to his patient complete loyalty and all the resources of his science. Whenever an examination or treatment is beyond his capacity he should summon another doctor who has the necessary ability.

A doctor shall preserve absolute secrecy on all he knows about his patient because of the confidence entrusted to him.

A doctor must give emergency care as a humanitarian duty unless he is assured that others are willing and able to give such care.

Duties of Doctors to Each Other

A doctor ought to behave to his colleagues as he would have them behave to him.

A doctor must not entice patients from his colleagues.

A doctor must observe the principles of 'The Declaration of Geneva' approved by the World Medical Association.'

APPENDIX III

DECLARATION OF HELSINKI

Recommendations Guiding Doctors in Clinical Research

(Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964)

INTRODUCTION

It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of The World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics which declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest".

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subjects or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgement it offers hope of saving life, reestablishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

2. The doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

III. Non-Therapeutic Clinical Research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.

2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally competent, the consent of the legal guardian should be procured.

3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued.

The investigator or the investigating team should discontinue the research if in his or their judgement, it may, if continued, be harmful to the individual.

APPENDIX IV

DECLARATION OF SYDNEY

A Statement on Death

(Adopted by the 22nd World Medical Assembly, Sydney, Australia August 1968).

The determination of the time of death is in most countries the legal responsibility of the physician and should remain so. Usually he will be able without special assistance to decide that a person is dead, employing the classical criteria known to all physicians.

Two modern practices in medicine, however, have made it necessary to study the question of the time of death further:—

1. the ability to maintain by artificial means the circulation of oxygenated blood through tissues of the body which may have been irreversibly injured and
2. the use of cadaver organs such as heart or kidneys for transplantation.

A complication is that death is a gradual process at the cellular level with tissues varying in their ability to withstand deprivation of oxygen. But clinical interest lies not in the state of preservation of isolated cells but in the fate of a person. Here the point of death of the different cells and organs is not so important as the certainty that the process has become irreversible by whatever techniques of resuscitation that may be employed. This determination will be based on clinical judgement supplemented if necessary by a number of diagnostic aids of which the electroencephalograph is currently the most helpful. However, no single technological criterion is entirely satisfactory in the present state of medicine nor can any one technological procedure be substituted for the overall judgement of the physician. If transplantation of an organ is involved, the decision that death exists should be made by two or more physicians and the physicians determining the moment of death should in no way be immediately concerned with the performance of the transplantation.

Determination of the point of death of the person makes it ethically permissible to cease attempts at resuscitation and in countries where the law permits, to remove organs from the cadaver provided that prevailing legal requirements of consent have been fulfilled.

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