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Codes of Ethics in Research and Experimentation in Man

A. W. Liley, Ph.D.

With increasing human social organization, individual curiosity has been channeled into the collective inquiry we call research. Now all curiosity, individual or collective, may be judged on both its motivation and methodology, and medical research has not escaped scrutiny on either score. Interestingly, but perhaps hardly surprisingly, much of the most serious and informed criticism and apprehension comes from the ranks of the medical profession, particularly from the investigators themselves.

Some of this concern stems from the modern enormous expansion of organized medical research with questions of the necessity, efficiency, quality, coordination and

economics of so much apparently competitive and at times redundant effort. More acute alarm is well justified by serious lapses of legal and ethical standards of conduct in countries purporting to be civilized whereby prisoners, handicapped children or the indigent have been used as experimental subjects. Finally some modern fields of medical endeavor may offend both layman and physician by striking directly at traditional concepts of just what constitutes a human body, a human personality, a human life, of just where legitimate investigation ends and unjustifiable and unethical meddling begins. In this latter regard, it is important to note that what is extraordinary med-

Professor Liley's most notable contribution to medicine was the introduction of intrauterine fetal blood transfusion in the management of Rh sensitization. His work has had worldwide recognition. He is Research Professor in Perinatal Physiology, Postgraduate School of Obstetrics and Gynecology, University of Auckland.

It would be illogical for the founder of fetology to accept the thesis that his intrauterine patients had no right to life. Dr. Liley is the first president of the Society for the Protection of the Unborn Child. Not a Catholic, his leadership is particularly effective in a pluralis-



tic society that sometimes regards abortion as merely a "Catholic issue."

icine in one generation has often become quite ordinary, accepted and mundane in another. In 1591, for instance, the citizens of Edinburgh turned out to see Eufame Macalyane and her midwife, Agnes Sampson, burned at the stake, the one for seeking, the other for providing pain relief in childbirth in brazen defiance of Holy Writ.

Along with these major sources of concern there exist, especially among laymen, a multitude of minor criticisms and misgivings whose persistence can only be attributed to the astonishing ineptitude of the medical profession in handling their public relations and information. Most of these criticisms stem from misconceptions that neither the profession nor publicity media have done anything to dispel. The first and most popular of these misconceptions is the stereotype of the medical scientist himself — a picture all too familiar from toothpaste advertisements and portraits of Nobel Prize winners — august and olympian figures with steel rimmed glasses, seated at microscopes in laboratories or libraries with never a patient in sight.

However, as news items also remind us, no matter how much basic chemistry or engineering has gone into a new drug or appliance, no matter how much animal work has gone into the development of a new operation, no matter how much thought and study has gone into a new technique, somewhere along the line the medical scientist must have contact with patients and his clinical colleagues. But put him in among these patients

or colleagues and the medical scientist looks like any other physician. I think the stereotype really illustrates the simple fact that the most elusive commodity for any professional man to secure is time to think.

Fear of Research

Another disconcerting attitude encountered is the fear that people may be used as "guinea pigs" and find themselves hapless victims in a research project. This fear is, or should be, irrational because for any physician to carry out any investigative or therapeutic procedure, whether new or well established, without the informed consent of a patient constitutes a legal assault. It is true, of course, that we all start off at a psychological disadvantage and may doubt the integrity of anyone possessed of arcane skills or knowledge when we are utterly dependent on them — whether they be physicians, lawyers, watchmakers, TV repairmen or motor mechanics. And "doctor's orders" are binding on all who hear — they may be used to coerce relatives, avoid unwelcome commitments, placate an employer or escape a subpoena. But strictly, doctors cannot "order" anyone — they can only advise, persuade and request; from a legal point of view there is no question that physicians are in the position of servants and patients are masters.

A third popular assertion is that the physician engaged in research does not have his patient's interests at heart, that he is really more interested in his problem. Unless we are very great or famous, none

of us when ill will have the undivided attention of our medical attendants. Indeed when we hear that a potent factor in the migration of rural physicians to the city is the educational needs of their children, we can argue that the physicians clearly did not have the interests of their flock at heart when they married and had children. They really should have remained childless or, better still, celibate — an argument that has been applied even more effectively to clergy. In fact, every physician must dilute his responsibility to individual patients with responsibilities to all his other patients, his students, colleagues, family, community, church, service organizations and country. The medical research worker adds just one more responsibility to this load — to try to throw some light in some dark corner of human ignorance.

Patient Risks

A fourth assertion is summarized succinctly by the surgeon in Shaw's play, *The Doctor's Dilemma*, who says, "Whenever a medical experiment is necessary it is always the patient who takes the risks." Now clearly if a medical experiment is necessary, it means that current methods are at best questionable and at worst useless or dangerous. In this situation, the patient is taking risks without the experiment. Indeed there are still many maladies in which the patient has taken a serious or fatal risk in getting ill in the first place because there isn't any effective therapy.

Now it is not my purpose to expand further on these and similar popular notions and assertions. My only justification for introducing them at all is to point out that by their very prevalence and shallowness they distract attention from much more fundamental issues. In particular, these notions perpetuate what I consider a major fallacy — that established medicine and new or investigative medicine are somehow different, or rather, have different codes of ethics. Essentially their codes of ethics are, or should be, the same. I shall return to this important point frequently.

First then, what do we understand or define as medical research? New knowledge is obtained by two methods, observation and experiment. It is erroneous to think that all research consists of experiment; many problems have been solved by careful observation and deduction, the noting of certain associations or repetitive patterns. This process has its precise counterpart in clinical care — when we listen to or look at or examine our patients, and the data obtained leads to at least a provisional conclusion or diagnosis when we mentally compare that data with what we have read or seen in some other patients.

Ethical Issues

Research by rigorous observation, documentation, classification and comparison of data might superficially appear an unimpeachable pursuit, but, it does raise ethical issues, especially with the teamwork

often involved in modern medicine. How far are medical confidence and medical records inviolable? This is a question that worries administrators and legal officers. Just as there are certain questions that are awkward or embarrassing to ask of individual patients, so there are questions that are awkward to seek to answer by collecting data. Few people would mind being asked about their physical pursuits before and after a myocardial infarction or their dietary tolerance before and after treatment of their ulcer, nor would they care much who saw their answers. But to get reliable information on many serious problems like illegitimacy or venereal disease is very difficult because physicians, do not like to ask searching questions in the first place or divulge information in the second.

This problem of confidentiality looms larger with computer techniques and with the news that our entire lives, health and affairs could be compressed into a few inches of magnetic tape — no doubt a great medical and administrative convenience and in many circumstances to our own benefit. But who shall have access to this information, with what qualifications and to what purpose? This question of individual privacy, of course, is not confined to medical data.

However, there are limitations to what can be achieved by observation and data collection alone. We may be looking at data the wrong way or more than one logical interpretation of data may be possible. It is when we deliberately

set out to discriminate between possible alternatives that we embark on the stormy seas of experiment. What do we consider an experiment? The Declaration of Helsinki, drawn up by the Ethical Committee of the World Medical Association, defines an experiment on a human being as an act "whereby the investigator changes the internal or external environment in order to observe the effects of such a change." I think this is a very logical definition, but clearly it covers both established and new medicine. Any physician who treats any patient by any method is concerned to observe the effects of his procedure, first as a check on the correctness of his diagnosis and second as a check on the appropriateness of that particular treatment for that particular patient. It is no play on words when we insist that all medical treatment, no matter how commonplace the diagnosis and how well established the method, is an experiment when applied to an individual. Note that the definition includes changes of external as well as internal environment and the mention of the purpose of the change — to observe the effects.

Other Experiments

Apparently if we are not interested in observing the effects but have some other motive, we are no longer conducting a medical experiment and the ethics no longer apply. Thus, had some inquiring orthopedic surgeon in bygone days proposed to equip each of some random volunteers with a fragile

metal box, four wheels and an internal combustion engine to study the effects of hypermobility on human subjects, I am sure such a proposal would have been discarded, first on the grounds of excessive cost and second as being ethically unacceptable in view of risk to the subjects. After all, the effects of abruptly decelerating a human body at 55 miles per hour or striking a pedestrian with a ton of moving machinery are readily foreseeable and rather serious. But physicians and medicine and ethics were not involved, but rather laymen and commerce and profit.

Had a pediatrician or hospital administrator proposed to dress infants for some purpose in inflammable synthetic night wear, the risk of mishap, of some children getting burned, would have condemned the proposal. But a manufacturer is not expected to show such forethought. Had a physiologist proposed to supply some households with 25 volts DC mains and some with 230 volts AC to see which had the most electrocutions, the experiment would have been considered outrageous. But the electricity department and power boards know that it is physically easier and cheaper to transmit and switch high voltage AC. What are a few deaths per annum to weigh against this advantage? The thalidomide experiment was a disaster; but the company that made thalidomide also makes whiskey. If the truth be known, whiskey has done more damage and caused more human misery than thalidomide ever did. But whiskey is business

and the treasury gains revenue from its importation and sale.

I could multiply these instances — how in the name of profit and economy, of administrative convenience, of cupidity and stupidity, our air and water are polluted, our food and clothes adulterated, our surroundings despoiled and our physical and social environment disrupted. These vast changes do not qualify as experiments and are not subject to ethical censure. Instead they are worshipped as progress.

Special Standards

Clearly the physician is expected to observe ethical standards of a very special kind. What then do medical ethics require of a physician? Simply that at all times he will do what is best for his patient. Now this is a rather idealistic standard because very often it is impossible to say what is best or the best is obviously not very good. In this situation, experiment would not only appear logically desirable but ethically mandatory. The law does not demand such idealism but, in considering questions of medical negligence or mishap, only requires that a physician will do what is reasonable.

Even this may be an impossible standard because if we are sufficiently ignorant of what is wrong with a patient or how to treat or cure his disease, it is ridiculous to maintain that anything is reasonable — except to try something else. The law does not even require that a majority of physicians would have done the same as the physician in

question but only that a responsible body of medical opinion would consider his conduct reasonable. This standard applies to both established and new methods although a responsible body of support may be easier to recruit for the conventional than the unorthodox. Thus when a court of appeal observed that success was the best justification for unusual treatment, they were not propounding a legal maxim but rather paraphrasing Napoleon's remark, "Victory has a thousand fathers but defeat is an orphan."

Unfortunately medical ethics, despite the idealism, may be no bar to colossal blunders. We shall never know how many people in Europe died over many centuries from phlebotomy. But had anyone suggested putting bleeding to a clinical trial, they would have been considered stupid or wicked. Everyone "knew" that bleeding was a good thing and once everyone "knows" something is true, it may be difficult to tell anyone whether it be true or false, as the climate in which you can even ask this question has disappeared. Purging and cautery are similar examples but modern medicine is not immune. Little more than a generation ago, a number of children had their thymus glands radiated for what we now consider a non-existent disease but what physicians then took seriously. As a result of this unnecessary radiation, a distressing proportion of these children developed thyroid cancer as adults. Thalidomide itself was introduced with the best intentions as the an-

swer to barbiturate poisonings and suicides.

Conflicting Theories

In the 1950's, as premature baby care improved and more pre-matures survived, a new eye disease appeared — retrolental fibroplasia, resulting in partial or total blindness. Quite early, there grew up the idea that oxygen had something to do with this condition. Pediatric units were divided into two camps, those who believed the disease was caused by too little oxygen and those who believed it was caused by too much. It was almost inconceivable that both these theories were correct; almost certainly one, possibly both, was wrong. But the physicians who believed that the blindness was caused by too little oxygen could not ethically restrict oxygen in some babies as an experiment, while those who believed that the blindness was caused by oxygen toxicity could not ethically give high levels of oxygen. Fortunately there were pediatricians who considered this controversy ethically intolerable and demanded experiment. In short order, it was easily demonstrated that the condition was caused by oxygen poisoning, and retrolental fibroplasia is now an avoidable disease.

I could multiply these examples many times — cancer therapy, especially, abounds in such stories — but the lessons should be obvious. Medical ethics should not be the coat of whitewash we apply to ignorance, inertia, habit or prej-

udice. There is little scope for belief in medical knowledge. We may accept certain propositions on the current balance of evidence but must always consider that perhaps the evidence is misleading or our interpretation in error. Pragmatically, given serious illnesses, we cannot just do nothing. We must do something while often well aware that we could be wrong. We cannot withhold action but we can reserve judgment; in many situations, honest doubt is as much an act of faith as uncritical acceptance. And if we have honest doubt and the qualification and facilities to resolve this doubt, we have an ethical duty to resolve it as effectively as possible.

Patient Safeguards

What safeguards, if any, are there for the patient? Foremost is the requirement that no examination, investigation or treatment, new or old, is ethically and legally permissible without the patient's (or his legal guardian's) consent. This consent must be informed and freely given, without duress or coercion and without dependence on any obligation of the subject toward the physician.

This principle, of course, is flouted daily in established medicine. Anyone who thinks this assertion is rash has never tried to travel overseas without a vaccination certificate, applied for employment with a body such as a hospital board, bought life insurance, been conscripted into the armed forces or asked patients what pills they are taking. However, accepting

that investigators have to be more conscientious, the principle and clauses in general are admirable.

In the matter of informed consent, it is true that some patients when asked if they know why they are in hospital or what is proposed reply, "No, but you just do what you think best, doctor." Such faith is touching but is hardly informed consent. The occasional physician who maintains that most patients are too stupid to understand or will get it all wrong is usually passing judgment on his own explanations and manner rather than on lay intelligence. The wording is clearly designed to protect anyone under restraint of any sort, children and the mentally handicapped. But if we take the words literally, there are difficulties. The words "without dependence on any obligation" are probably legitimately intended to protect students from calls for volunteers by their teachers and technicians from the enthusiasms of their chiefs. But ordinary people may be motivated by simple gratitude for past care or have genuine admiration for a unit in good repute.

"Without duress or coercion" covers concentration camps, prisons and P.O.W.'s nicely. But what of the acutely ill and their relatives, always under duress and coercion even though not primarily of the physician's application? In the early days of fetal transfusion, we often had to tell unsuspecting parents that their baby was going to die if nothing was done, then explain a possible solution and seek their consent. We bore the evil tidings, then offered a chance of escape.

Was this not duress and coercion? They wanted the baby and we wanted to help them. But did they really have any choice?

Investigating the Healthy

A special ethical problem arises where we seek to investigate healthy rather than ill people in so-called "experiments conducted solely for the acquisition of knowledge." In the first place, I think this phrase, coined by the Ethical Committee of the World Medical Association, is singularly ill chosen. It implies some abstract, sterile concept of knowledge or some idle curiosity of the investigator. We are really talking about knowledge that will probably be of no benefit to the subject but will be to others, for standards of normality are essential in clinical medicine. How can we aim to restore sick people to health and normal function if we do not know what health and normal function are? For want of standards of normality, a generation of gynecologists made a fortune out of hitching up retroverted uteri until the light dawned that retroversion frequently is a normal anatomical variant; for a generation of children, the mere possession of tonsils and adenoids was an indication to remove them; a generation of surgeons tacked up dropped kidneys until radiologists pointed out that the kidneys may roam up and down five cms. with every breath we take; and I sometimes wonder if psychiatrists even yet have any concept of normality at all.

Of course, some information on normality can be obtained as a by-

product of clinical medicine and some surveys can be attractively baited. Thus a thousand random chest X-rays or blood samples on healthy volunteers would produce enough unexpected early pathology to make some argument of potential benefit to the volunteers tenable. But what if the procedure is not so trivial, if some discomfort and hazard are involved and only much smaller numbers are needed? Certainly physicians can and do perform experiments on themselves and each other: Forssman first passed a catheter into his own heart and one spartan neurophysiologist studied sensory nerve endings in skin by stretching out his own prepuce on a microscope stage with fish-hooks. But such normal values are limited by age and sex. No physicians are children, few are octogenarians and normal pregnancies are scarce in male obstetricians. In this situation, students, technicians, physicians' wives and families may be tempting and tempted — and subject for concern.

Supposing we call for volunteers, either colleagues or laymen. What motivates a volunteer? The few psychological and psychiatric surveys of volunteers for medical experiments are not entirely reassuring. Quite apart from the fact that the enthusiasm of volunteers has wrecked more than one experiment, how far should we protect the volunteer from himself? If someone wishes to engage in a dangerous sport or occupation, or is willing to risk his life and health to give service in some troubled part of the world, or is prepared to accept pos-

sible hazard in an experiment, how far are we entitled to question his motivation, his psychiatric state and his sanity?

Problems Remain

Consent then, however informed and freely given, leaves us with some problems. What other safeguards can we seek? We can ask that anyone engaged in investigation — and established medicine — be well informed. But the world's medical literature grows a foot higher each day, and that does not include the advertisements. We can ask that new drugs and methods be tested in animals, but for numerous human diseases there are no animal counterparts — largely due to humans escaping the biological and commercial culling of animals. We can ask whether the physician himself would be prepared to take the first dose of a drug or vaccine or have a procedure done on himself. Physicians are so prepared and many and famous are the examples. But all that this gallant gesture usually proves is that at least the physician has the courage of his convictions and at most the measure in question is not 100 percent fatal.

I think a more vital safeguard lies in avoiding any artificial separation of new and experimental medicine from conventional medicine — that, as far as possible, research workers are not secluded in architectural, intellectual or administrative Siberias but physically and intellectually share the environ-

ment and problems of clinicians and patients. It is important that the investigator present his proposals, methods and results to his clinical colleagues for comment, criticism, advice and assistance. It is equally desirable that clinicians should present their attitudes, methods and results to their academic colleagues for *their* comment, criticism, advice and assistance. Research and clinical care, along with teaching, are inseparable components of medicine. The medical profession needs its faithful workhorses, but it also needs its scouts, gadgeteers and visionaries because they are all part of a team.

Layman's Role

What I consider most important in any code of ethics are the attitude, education and active participation of the laymen, ill or well, themselves. It is reassuring to both physicians and public to see laymen as chairmen of research councils and foundations. It would be even more gratifying if the medical profession handled its public relations and public education a little better. I do not mean more demonstrations or programs of the "Gee Whiz" variety — "Gee, isn't it great what the doctors can do now!" Rather, physicians should approach the public with a little less superiority and a little more humility, a little less mystery and a little more honesty, giving a little more credit for public intelligence and selflessness; they and the publicity media should dwell a little less on the achievements of medicine and a

little more on what has not been achieved; and if they publicize triumphs as a token of what can be done with lay cooperation, they should also publicize problems that cannot be solved without lay cooperation. In good clinical medicine and good research, the public are not patients or subjects of physicians but partners in a common endeavor.

It has long been an axiom of politics that people will get no better government than they deserve. I

believe it is true also that people will get no better medicine than they deserve because ultimately the goals of medicine and the goals of a community will coincide. Our codes of ethics, of how we regard and treat our fellow humans, must depend on some concern for the sanctity, integrity and dignity of a person and his environment. I think it very dangerous if ever such concern be regarded as solely the prerogative and responsibility of physicians.

A Patient's Psalm

The Lord is my Genetics Counselor; I shall not want for risks.

He maketh me to lie down in genealogies; he non-directs me beside karyotypes.

He restoreth my inborn errors; he leads me in the paths of reproduction for my name's sake.

Yea, though I walk through the valley of amniocentesis or under the shadow of fetoscopy, I will fear no evil; for thou, the Greatest Good of the Greatest Number, art with me; thy chromosome counts and thy enzyme assays they comfort me.

Thou preparest multiphasic screening before me in the presence of my illnesses: thou anointest my head with check-ups; my profile runneth over.

Surely mutations and heterozygosity shall follow me all the days of my life; and I shall dwell in the house of computerized biomedical information forever.

Paul Ramsey, Ph.D.

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