12 The ethics of human experimentation

Since the time of Hippocrates, Western physicians have taken an oath in which they swear to protect their patients 'from whatever is deleterious and mischievous'. As it turned out in much of the past, common treatments were neither specifically nor intentionally injurious: most were harmless palliatives. Even when doctors used highly lethal agents like mercury and arsenic as supposed remedies, injury and death occurred on a relatively small scale if for no other reason than the fact that few could afford professional services. Nevertheless, the long list of truly assaultive therapies that were available and the persistence of barbarous practices like copious blood-letting are quite incredible.

REACTION TO EXUBERANT TREATMENT

In 1835, Pierre Charles Alexandre Louis, of Paris, used the numerical method to bolster his argument that exsanguinations were of little value in the treatment of pneumonia. Louis' influence led his American pupil, the elder Oliver Wendell Holmes, to declare, in 1860, that nearly all drugs then in use should be thrown '... into the sea where it would be better for mankind and all the worse for the fishes'. In the latter part of the nineteenth century there was a trend away from exuberant therapies. The movement was led by the new Viennese school of 'therapeutic nihilism'. A leading exponent said, 'While we can diagnose and describe disease, we dare not expect by any manner of means to cure it.'

A break with the past

The development of the germ theory of disease only one hundred years ago was responsible for a qualitative break with the past. There was now hope for specific treatments. The search began for what Paul Ehrlich—the founder of the Institute for Experimental Therapy in 1899 at Frankfurt, Germany—called 'magic bullets' to eradicate the agents of disease without injuring the host. For the first time, an observer commented, 'an average

Seventeenth century treatment

At eight o'clock on Monday morning of February 2, 1685, King Charles II of England was being shaved in his bedroom. With a sudden cry he fell backward and had a violent convulsion. He became unconscious, rallied once or twice, and, after a few days, died. Doctor Scarburgh, one of the twelve or fourteen physicians called to treat the stricken king, recorded the efforts made to cure the patient.

As the first step in treatment the king was bled to the extent of a pint from a vein in his right arm. Next his shoulder was cut into and the incised area was 'cupped' to suck out an additional eight ounces of blood. After this, the drugging began. An emetic and purgative were administered, and soon after a second purgative. This was followed by an enema containing antimony, sacred bitters, rock salt, mallow leaves, violets, beetroot, camomile flowers, fennel seed, linseed, cinnamon, cardamom seed, saphron, cochineal, and aloes. The enema was repeated in two hours and a purgative given. The king's head was shaved and a blister raised on his scalp. A sneezing powder of hellebore root was administered, and also a powder of cowslip flowers 'to strengthen his brain'.

The cathartics were repeated at frequent intervals and interspersed with a soothing drink composed of barley water, liquorice, and sweet almond. Likewise white wine, absinthe, and anise were given, as also were extracts of thistle leaves, mint, rue, and angelica. For external treatment a plaster of Burgundy pitch and pigeon dung was applied to the king's feet. The bleeding and purging continued, and to the medicaments were added melon seeds, manna, slippery elm, black cherry water, an extract of flowers of lime, lily of the valley, peony, lavender, and dissolved pearls. Later came gentian root, nutmeg, quinine, and cloves.

The king's condition did not improve, indeed it grew worse, and in the emergency forty drops of extract of human skull were administered to allay convulsions. A rallying dose of Raleigh's antidote was forced down the king's throat; this antidote contained an enormous number of herbs and animal extracts. Finally bezoar stone was given. 'Then,' said Scarburgh, 'Alas! after an ill-fated night his serene majesty's strength seemed exhausted to such a degree that the whole assembly of physicians lost all hope and became despondent: still so as not to appear to fail in doing their duty in any detail, they brought into play the most active cordial.' As a sort of grand summary to this pharmaceutical debauch, a mixture of Raleigh's antidote, pearl julep, and ammonia was forced down the throat of the dying king.
(Noted by H.W. Haggard)

patient treated by an average practitioner could expect a better than fifty-fifty chance of improvement'.

Deep-seated suspicion

The recently developed formal methods to evaluate specific interventions are intended, as I have discussed, to increase these odds. But deeply rooted fears of medicine's ancient excesses persist, and suspicions are rekindled by unfortunate incidents that are a reminder of the misguided past.

The phrase 'human experimentation' is beset with some dreadful connotations. The expression conjures up the image of demented doctors working in a chamber of horrors, and the destructive myth is exploited in lurid novels and in horror films.

FORMAL CODES OF MEDICAL ETHICS

A model for these frightening representations was provided by the all too real criminal behavior of physicians in the concentration camps of Nazi Germany during World War II who committed murders, tortures, and other atrocities in the name of medical science. Twenty doctors were tried for these crimes following the war. In the decision at the end of the trial, the panel of judges set out ten principles that must be observed in the conduct of human experimentation in order to satisfy moral, ethical, and legal concepts. These principles became known as the Nuremberg Code of 1947.

An international code

The Declaration of Helsinki, a formal code of ethics for the guidance of doctors in clinical research, was adopted by the World Medical Association in 1964, and the recommendations were extended in 1975. The revised code ('Helsinki II') took into account various considerations that arose in the intervening years. The Council for International Organizations of Medical Sciences and the World Health Organization, which played an active part in the preparation of the statement, indicated that the text would be subject to periodic review in the light of criticisms and comments. In September 1981 the Council endorsed a set of guidelines to suggest how the general principles of Helsinki II might be applied in the special circumstances of many technologically developing countries.

Proliferation of codes

It is notable that a number of codes and guidelines have been drafted, over the years following World War II, by such organizations as the American Medical Association, the American Psychological Association, the American Academy of Pediatrics, the British Medical Research Council, the British Paediatric Association, the National Institutes of Health, and the Association of American Medical Colleges (and the list is not complete). Jay Katz of Yale Law School has pointed out that the proliferation of such declarations testifies to the difficulty of developing a set of rules that do not have what may be called 'open texture'. By necessity, the canons have had to be succinctly worded, and their meaning has been subject to a variety of interpretations. Significant discrepancies between the codes also have helped to sow confusion.

Limited usefulness of general exhortation Katz opined that as long as these precepts remain unelaborated tablets of exhortation to promote ideal practices, they will, at best, have limited usefulness in guiding daily behavior of investigators.

The international code of ethics for biomedical research

Helsinki II

Basic principles in the Declaration of Helsinki, revised and extended by the Twenty-Ninth World Medical Assembly in Tokyo, 1975.

1 Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2 The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3 Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research even though the subject has given his or her consent.

4 Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5 Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interest of the subject must always prevail over the interests of science and society.

6 The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7 Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8 In the publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports on experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9 In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

10 When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11 In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12 The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

Justice Holmes once warned, 'General propositions do not decide concrete cases. The decision will depend on a judgment or intuition more subtle than any articulated major premise.' Indeed, the attempts to develop statutes for regulating the activities of medical experimentalists have been unsatisfactory; the ethical declarations are not legal documents. A British bill dealing with some aspects of experimentation in children was described by one Queen's Counsel as demonstrating the 'clumsiness of the law as a means of fine control of human endeavor'.

Failure of self-regulation

The promulgation of various codes of ethics may be viewed as tacit recognition within the medical and behavioral science professions that self-regulation by investigators could not be relied on to control research practices. However, headline scandals played the major role in focusing public attention on the issues.

Scandals The most widely publicized incident occurred in 1963 when two respected scientists who were studying the immune response to cancer injected live malignant cells into a number of aged patients in a chronic disease hospital without first obtaining the patients' consent.

More recently, the press disclosed a study conducted by the Public Health Service (PHS) which had been underway since the 1930s. A group of black men with syphilis had been kept under observation to record the 'natural' course of the disease. During the early years of inaction the observational study—the longest of its kind in medical history—was rationalized by the investigators on grounds that the drugs then available were toxic and only marginally effective. Moreover, when the study was undertaken, the PHS officials were unable to obtain funds for the accepted treatment of the day in an impoverished rural county. Despite the fact that in 1945 penicillin became available as a safe, cheap, and dramatically effective cure for syphilis, the no-treatment observations continued. It has been presumed, with good reason, that some men died of the disease who could have been cured.

Prior review

Such disgraceful episodes and other less widely publicized examples of unrestrained investigative activities led to the development of procedures to implement the general principles stated in the codes of ethics. The move began in the United States with a memorandum from Surgeon-General William H. Steward, dated February 1966, that was sent to the heads of institutions conducting research with Public Health Service grants. The requirement of prior review had been in effect since 1953 for clinical research conducted within the Clinical Center in Bethesda, Maryland but the review was extended to all 'extra-mural' research supported by PHS grants and

awards (studies carried out by non-governmental employees and institutions). A review by 'a committee of the investigator's institutional associates' was mandated to assure an independent determination of the rights and welfare of the individual or individuals involved, the appropriateness of the methods used to secure informed consent, and the risks and potential medical benefits of the investigation.

Since that initial step, a series of guidelines for control of bedside studies have been formulated by the US Department of Health and Human Services and by the Food and Drug Administration; similar formats have been developed in other countries.

Review committees In these regulations, the primary responsibility for protection of research subjects is vested in institutional review committees composed of 'sufficient members with varying backgrounds to assure complete and adequate review'. Community representatives are included in many of these panels. The committees in local institutions undertake a formal evaluation of each proposed research project.

If an approved project is in need of US government financial support, it is reviewed again by a committee of experts in one of a number of specialized study sections convened by the National Institutes of Health.

GOALS OF HUMAN EXPERIMENTATION

Scientific research seems to thrive best when it is completely unrestricted and when it is not directed toward a specific practical goal. The oft quoted example of the success of a targeted research program in medicine is the crash development of a poliomyelitis vaccine, but this is outweighed by innumerable instances of unanticipated rewards from what appear to be purposeless searches for understanding about the natural world.

Freedom of inquiry in biomedical research

The issue of directed inquiry in biomedical research was examined several years ago. A review was made, by Julius H. Comroe Jr, University of California, and Robert Dripps, University of Pennsylvania, of the principal observations that led to the ten most important advances in cardiovascular and pulmonary medicine and surgery over a period of 30 years. Research efforts that had no foreseeable bearing on these problems of everyday importance in bedside medicine—the non-goal-directed investigations—paid off in terms of eventually useful discoveries almost twice as generously as other types of research and of development.

Although the 'active' observations of this after-the-fact survey provide only weak evidence of the advantages of freedom of inquiry in biomedical research, the proposition does not require a utilitarian justification. This

freedom is part of a generally accepted system of values in Western societies. Isidor I. Rabi, the Nobel laureate in physics at Columbia University, put it this way, 'Science simply operates on the faith that knowledge is good and ignorance is something to overcome. You can't really vindicate this faith empirically. It *is* a faith.' Holding that conviction, he advocated an unquenchable desire for knowledge and the search for it. Others have argued conversely and with equal sincerity that there are ethical limits to discovery.

Justification for clinical studies

The controversy about limits of research is irrelevant, I believe, to the issues that arise at the threshold of clinical applications of proposals originating in the findings of pre-human studies. At the application step we must concede that *all* medical actions have consequences that extend well beyond the immediate effects seen in individual patients. As a result, we are obliged to develop arguments of policy to justify the conduct of research involving human beings. Collective justifications that point to some overall benefit for the community as a whole are the minimal requirements in the development of policy; a world view adds even more burdens to be considered. I suggest that bedside studies, unlike pre-clinical research, should be sharply goal-directed, and the goals must not be defined solely by physicians.

The fundamental distinction between the freedom to pose questions, which is essential in the search for new knowledge, and the restrictions on questions, which are necessary at the point of implementation, is not a unique demarcation made by societies. The medical profession, however, has made entreaties for a privileged position: it appeals to the humanitarian impulses of society and points to the universal desire for relief, comfort, and longevity.

> In this very serious game between the doctor and the patient, it is the latter who plays for the highest stakes; he has to bear the consequences of the medical act and is therefore interested both in the profession and in the man who practises it.
>
> J.L. Sonderegger

PRINCIPLES AND RIGHTS

Until fairly recently, doctors have exercised unrestricted discretion to intervene in the lives of their patients for the sake of medical progress. An argument of principle can be made to support this sweeping prerogative, and, in fact, a resolution adopted by the Twenty-third World Health Assembly in 1970 affirmed that the 'right to health is a fundamental human right'.

The realistic limit to assertions about a fundamental right is made clear in the line of reasoning advanced by Ronald Dworkin of New York University School of Law. The force of an argument of principle, he asserts, lies in the acceptance by a community that a person or group is entitled to some advantage or protection regardless of whether or not the community as a whole actually loses thereby. Recognition of a right commits the community to the possibility of suffering some cost in the general interest, but not necessarily a very dramatic cost.

The qualification of cost is, of course, the crucial point. A responsible government, for instance, must be ready to justify anything it does, particularly when it limits the liberty of its citizens. It is a sufficient justification, even for an act that limits liberty, that the restrictive policy is calculated to increase general utility. But there is another very important justification for limiting a right: this invokes the idea of *competing* personal rights that would be jeopardized if the right in question were not limited.

Abstract versus concrete rights Abstract rights, like the right to health, take no account of a conflict. Concrete rights, however, reflect the impact of a competition among the rights of individual members of society. For example, we may proclaim that every infant has the right to be protected against the possibility of harmful side effects of a new treatment to prevent RLF, but this abstract right cannot be safeguarded in practice, since we can argue with equal conviction that no infant has the right to require others to undertake the unevaluated risk on his or her behalf. Thus, a strong case can be made for limiting the abstract right for a risk-free treatment by an appeal to the competing rights of those whose security will be sacrificed if the abstract right is made concrete.

Two definitions in a thesis of human rights

Policy: a kind of standard that sets out a goal to be reached, generally an improvement in some economic, political, or social feature of the community (though some goals are negative in that they stipulate that some present feature is to be protected from adverse change). Arguments of policy justify a political decision by showing that the decision advances or protects some collective goal of the community as a whole. The argument in favor of the use of public funds to conduct randomized clinical trials is an argument of policy: support will protect the populace against harmful new treatments.

Principle: a standard that is to be observed, not because it will advance or secure an economic, political, or social situation deemed desirable, but because it is a requirement of justice or fairness or some dimension of morality. Arguments of principle justify a political decision by showing that the decision respects or secures some individual or group right. The argument in favor of 'formal consent' is an argument of principle: an individual must be free to choose whether or not he or she will participate in a medical trial.

(Adapted from Dworkin)

Dworkin has proposed a human rights thesis that provides a basis for adjudicating difficult cases by confirming or denying concrete rights. But these rights, he asserts, must have two characteristics: they must be institutional rather than background rights, and they must be legal rather than some other form of institutional rights.

Institutional privileges may be found in social institutions of very different character. For example, we need some general agreement concerning the character of medicine if we are to define the prerogatives that are fixed by the distinctive rules of this institution. Needless to say, such agreement is hard to come by.

Spirit of human experimentation

In the wake of the syphilis study scandal, an ad hoc advisory panel was asked to examine the question of whether or not existing policies were adequate and effective to protect the rights of patients participating in health research supported by public funds. The panel concluded that it was the *spirit* in which an aware society undertakes to use human beings for research ends that will, ultimately, determine the protection these persons will receive.

Since the conduct of human experimentation raises important issues of social policy, greater participation is required in decision-making by representatives of non-medical professions and of the general public. But what is the 'spirit' and what is the over-arching 'social policy' that we look to for guidance?

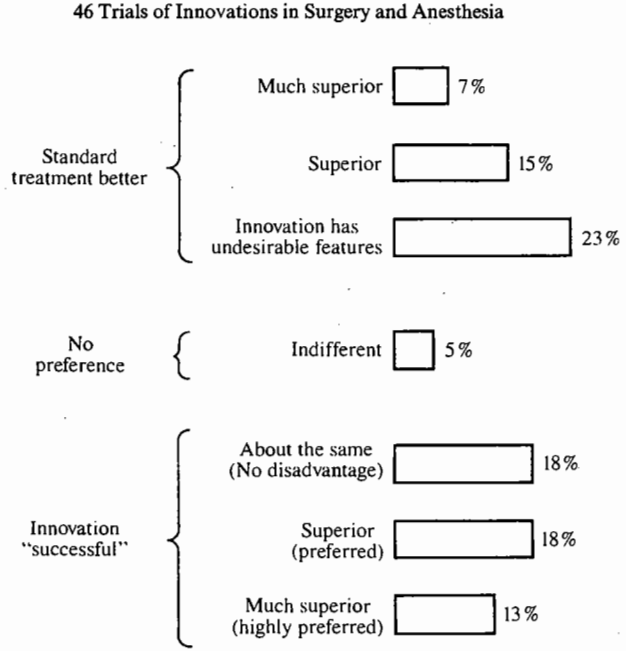
> The people's health ... is the concern of the people themselves. They must want health. They must struggle for it and plan for it. Physicians are merely experts whose advice is sought in drawing up plans and whose cooperation is needed in carrying them out. No plan, however well designed and well intentioned, will succeed if it is imposed on the people. The war against disease and for health cannot be fought by physicians alone. It is a people's war in which the entire population must be mobilized permanently.
>
> Henry E. Sigerist

A popular war Suppose, for the sake of argument, that we can gain general acceptance of an idea of medicine's character that sees this institution as an agency for waging a popular war. Now we can weigh some otherwise imponderable issues in realistic terms. Through this concept, we can frame questions and expect that fair-minded referees will make reasonable judgments about the rights of all concerned when new medical 'weapons' must be tested.

PATIENT RISK IN CLINICAL TRIALS

The first of the realistic issues that should be examined is the overall record of the formal approach to the testing of new treatments. Although the evidence on this point is fragmentary, there is little to support popular myth.

Outcomes in randomized clinical trials



John P. Gilbert and co-workers found that innovations brought to the stage of randomized trials were 'successful' only half of the time. Results indicating that the innovations were 'highly preferred' occurred one eighth of the time.

Forfeit associated with random allotment

Ethical arguments raised when patients are to be randomly allocated to compared treatments often take one of two mutually contradictory forms.

The first contends that the routine-management group is sacrificed because they are denied the benefit of a favorable new therapy. The second argument expresses the opposite concern: patients allotted to an untested new treatment are exposed to unwarranted risk.

John P. Gilbert and his associates of Harvard University have pointed out that to a large extent, both arguments imply that the investigators know in advance which is the favorable treatment. In order to obtain some evidence on this issue, they surveyed 46 randomized clinical trials that evaluated innovations in surgery and in anesthesia. The results suggested that, on balance, new treatments showed no net gain or loss when compared with standard management. The occasional marked gains found in the survey were almost offset by clear losses, indicating that innovative treatment was usually neither better nor worse than standard treatment. In most trials, it would appear, there is little basis for selecting between compared treatments prior to the trial.

Nature and magnitude of risks

In 1976, a task force of the National Institutes of Health reported the results of a first systematic attempt to obtain an estimate of the nature and magnitude of risks for human subjects who participate in research studies. A questionnaire survey polled 538 medical investigators who had studied 39 216 patients enrolled in therapeutic trials during the previous three years. The survey analysts stressed the limitations of this weak approach to the question, but they could detect no startling dangers: there was no indication that risks in these trials were any greater than are encountered when treatments are given in other medical settings. (Most of the research related deaths and injuries occurred in connection with the use of chemotherapy in cancer patients.)

Public attitudes

In the opening chapter, I noted that the public must be better informed about the experimental method as a risk-limiting alternative to the primitive trial and error approach that has been used in the past to evaluate innovations. I have argued throughout this volume that only critical, Galilean experiments provide the discriminatory power and efficiency we seek to safeguard the welfare of patients. (Demonstrative experiments, intended merely to illustrate 'revealed truth' and to convince others of its validity, belong in the stage presentations of faith healers.) The justification for the use of critical tests will only be accepted, Leon Eisenberg of Harvard Medical School has noted, when there is increased public awareness about the extent to which medical practice rests on custom rather than evidence, and when there is general agreement that the obligation to change this situation must be shared fairly.

Patients' attitudes Professionals in many fields have voiced opinions about the propriety of clinical trials, but little is known about the views of those most directly affected—the patients themselves. Barrie R. Cassileth and his co-workers at the University of Pennsylvania noticed this curious gap in knowledge and sought, in 1982, to document the attitudes of current and potential patients concerning investigative treatment and participation in clinical trials. They expected to find great diversity of opinion about such an emotionally charged issue. Instead they found surprisingly uniform belief in the importance and morality of contemporary clinical trials and approval of the altruistic rationale underlying their implementation.

A questionnaire filled out anonymously by 295 respondents (104 with cancer, 84 with heart disease, and 107 'members of the public') revealed that a large majority believed patients should serve as research subjects. The responses did not differ either by subgroup or by demographic characteristics of those surveyed. Asked why they might participate in medical research, over half selected the response 'to help me get the best medical care' as their first choice. A little more than one third thought patients receiving treatment recommended by a physician receive better care; a similar proportion thought that research patients receive better treatment or that treatment is equal whether received according to trial protocol or a doctor's plan. Only one in ten stated that they would not participate in experimental studies. If the largely favorable climate of opinion found in the Philadelphia survey is at all representative, the frequent attacks on the rightfulness of clinical trials may have less popular support than is commonly believed.

Cassileth and his colleagues suggested that when those surveyed chose 'best medical care' as their major reason for participating in a clinical trial, they may have been saying, in effect, the doctor's recommendation to enroll in a trial is equivalent to that doctor's best counsel with regard to patient care. The implication of trust places a heavy ethical burden on the research physician—where it properly belongs.

RECRUITMENT OF TRIAL PARTICIPANTS

Turning now to the matter of recruiting patients to participate in clinical trials, we come to the most sensitive aspect of the issue of competing rights. The self same quandaries have been resolved in conventional warfare with the use of a draft by lottery, but there is great reluctance to consider this democratic solution to the problem of apportioning risks and benefits in medical experimentation. For example, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, established by an act of Congress in 1974, has advised that children who participate in research projects should be *selected* so that the burdens of participation are distributed among all segments of our society, but the recommendation is painfully silent about how this standard is to be achieved in practice.

When the American public believed it was threatened by a frightening 'enemy' in the form of paralytic poliomyelitis, hundreds of thousands of children were volunteered by their parents for participation in a randomized trial of a preventive vaccine (p 66). In this experience there was broad representation; the requirements of a democratic ideal as well as those of the rules of scientific evidence were satisfied. Such dramatic episodes are unusual. In most trials involving relatively few patients, volunteering thwarts the basic principle of random sampling which is designed to *assure* unbiased representation, and it is almost impossible to avoid gross social inequities.

Hans Jonas, the philosopher at the New School for Social Research, considered the arguments for alternatives to the volunteering approach in medical studies and rejected conscription by lot on the grounds that it was threatening and utopian. He recoiled from the idea of such a demand in a free society. I suspect he expressed the initial reaction that most of us have. But if we view formal clinical study realistically as the only fair and practical means of controlling the risks and allocating the benefits in medical development, perhaps rejection may not be so final.

Identification with the research 'cause'

The topic of patient recruitment deserves a thorough public debate. It may be argued, for example, that a requirement for the broadest possible participation in clinical studies would exert a powerful influence in ensuring the authenticity of these exercises. The question of who should be called upon to participate in clinical studies, as Jonas noted, can only be made 'right' if the 'cause' of the study is the subject's as well as the researcher's 'cause'.

> It may be accepted as a maxim that a poorly or improperly designed study involving human subjects ... is by definition unethical. Moreover, when a study is in itself scientifically invalid, all other ethical considerations become irrelevant. There is no point in obtaining 'informed consent' to perform a useless study.
>
> David Rutstein

FREELY-GIVEN INFORMED CONSENT

Another thorny matter that must be faced in human experimentation revolves around the concept of consent. How can we fulfill the letter and spirit of the International Code of Ethics which specifies that each potential subject must be adequately informed and that he or she should grant freely-given consent? The stipulation that consent be obtained in writing

presents no difficulties, but it is virtually impossible to comply fully with the *intent* of the rule.

It has been pointed out that the very justification for a randomized trial is that there is insufficient information to permit a rational informed choice. Moreover, an explanation of the technical issues and an offer of choice of whether or not to enroll, give little assurance of compliance with the spirit of the ethics code. The quality of consent is often influenced by the social relationship of the principals; this quality is simply not the same when there is a wide social gap between doctor and patient as it is when they are more nearly social equals. It also cannot be denied that self-interest can make the research physician very persuasive.

Acquiescence of surrogates

Communal consent Carl E. Taylor of Johns Hopkins University has called attention to complications that arise when clinical trials are conducted in countries where health decisions are typically made by the family and the community. When most decisions about treatment are communal, is it only a facade, he asks, to insist on individual consent? The international guidelines endorsed in 1981 recognized the problem. When individual members of a rural community in developing countries do not have the necessary awareness of the implications of participation in an experiment, the guidelines advise that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader. The intermediary should make it clear that any eligible person is free to abstain or withdraw at any time.

Obsession with individual decision making in developed countries may obscure the general importance of distinguishing between situations that require personal consent and those which require community approval. The latter may be appropriate when a particular health measure has been sufficiently tested to be ready for a mass trial in a public health program.

'Permission' of guardians The concept of acquiescence when children and others not competent to understand the issues are involved in experimental trials has been considered at great length by many individuals and official groups. A review was undertaken by the President's National Commission which advised that the word 'consent' in this context be abandoned. The advisory group suggested that the 'permission' of parents or guardians be solicited to distinguish what a person may do autonomously (consent) from what one may do on behalf of another (grant permission). There is general agreement that, to the extent feasible, older children should be given the opportunity to make their own decisions with the additional permission of the parent or other legal guardian.

An additional suggestion made by the commission concerned the active involvement of traditional protectors. For example, it advised that small children should participate in certain investigations only if their parents or guardians agree to be present during some or all of the conduct of the research. In general, the parents should be sufficiently involved in the research to understand its effects on their children and be able to intervene, if necessary.

Informed surveillance I have proposed a plan for clinical trials which I have termed 'informed surveillance'. The objective is to enlist the active participation of personal physicians. In this format the investigator is charged with the responsibilities of informing the personal physician of a prospective enrollee about the details of the study protocol and answering questions that arise at all stages of the study. The personal physician, who must not be the investigator under this division of responsibilities, is charged with the task of *attempting* to inform the patient or guardian about the trial and requesting written permission in which the patient confirms only that he or she has *no objections* to proceeding.

This oblique form of assent, I have argued, makes no assumption that the patient *fully* understands the explanation provided. The more completely informed personal physician—as in day-to-day practice—acts as the intermediary who defends the rights and personal welfare of his or her patient. Moreover, both the patient and the personal physician retain veto options that may be exercised at any stage of the investigation. They should not be made to feel any obligation to adhere to the agreement made at the time of enrollment in a clinical trial; 'second thoughts' should be respected without coercion.

Discretionary informing

Conscientious doctors are in the habit of using discretion when they discuss illness and treatment with individual patients. In weighing the consequences of complete candor they usually wait for a clue from patients, some of whom make it clear that they wish to know every detail; others indicate they wish to be told very little when they say, 'I leave everything up to you, Doctor.' Arguments have been made that this usual practice of discretionary informing should be considered as an alternative to the rigid informed consent procedure in many clinical trials. The modification runs counter to the demand that all trial participants must be fully informed, but it is quite realistic. The discretionary approach received indirect support in a survey conducted by R.J. Simes and M.H.N. Tattersall of the University of Sydney; most of the patients surveyed believed that they alone should decide the extent of disclosure in randomized trials. Cassileth has shown that patients often avoid reading consent agreements which they have signed

because they regard the documents as legalistic, undesirable intrusions into the trust relationship with their doctors.

A balance sometimes needs to be struck between the fear that patients' rights will be violated if they are not fully informed and the fact that some patients will be made to suffer undue anxiety as the result of full disclosure. There is a special need for compromise when consent is obtained for treatment of disorders in patients who have no symptoms and regard themselves as completely well.

Disavowals in clinical trials

Human experimentation faces practical hindrances which frustrate investigators who chafe at the inefficiency of clinical trials. A basic impediment is erected by a free society's commitment to the principle of self-direction or autonomy, according to which an individual reaches practical decisions as the result of independent and rational reflection. Patients have the right of informed *dissent*. This source of 'inefficiency' is, I believe, an essential restraint that must not be set aside.

Uncooperative participants If the veto options of enrolled patients are exercised so frequently that a trial is 'ruined', the significance of this turn of events should not be overlooked. From a community oriented perspective, the rates of non-compliance and defection by patients (and by personal physicians in an informed surveillance plan) are basic pieces of information.

Since a major warrant for *human* experiments lies in the potential for projecting results to the community at large, bedside trials should be designed to generate useful information bearing on this fundamental objective. If patients and personal physicians are unable to identify with the goals of the trial and do not perceive themselves as active participants, there is little reason to expect that an outcome of interest to the investigator will be of any public interest. It makes no sense to develop potent weapons to fight an unpopular war.

Alienation of practitioners and communities As I proposed above, special efforts should be made to enlist the aid and to stimulate the interest of practicing physicians in formal clinical trials, for it is the practitioner who must translate the results of trials into everyday usage. The disturbing effect when personal physicians feel alienated from research efforts has been documented. Chalmers examined the extent to which the practice of medicine is a reflection of controlled clinical trials and found a number of examples in which there was a clear-cut dichotomy between the 'usual practice of the community' and the scientific data. Physicians seemed to be paying no attention to the results of carefully designed studies.

Community acceptance of research results also may founder when there

is little public representation in the planning of large-scale trials. The problem is seen most clearly when field trials conducted in developing countries are set up at the request of research workers in the developed world.

Obligation to freely consenting participants

What is the responsibility of the community to the recruits in medical studies? Schemes for compensating persons injured by immunizations, which are obligatory or recommended by health authorities, currently exist in a number of countries. An international conference on the role of the individual and the community in the development of biologicals (such as vaccines, toxoids, and antisera) has advised that governments enlarge the concept of support of medical research to include reparation for the inevitable casualties that occur. There is growing awareness of the need to assume this public obligation. It is inescapable that the benefits of well designed research are shared by society as a whole, whereas the risks are endured by the few who participate as experimental subjects.

No-fault reparation A system of obtaining payment from a centrally administered fund without proving fault has much to commend it as a satisfactory way of compensating for injuries received in the course of medical research. Under this arrangement, researchers and participants do not find themselves in the position of adversaries, and researchers may assist an injured recruit in assembling evidence for the claim. No-fault compensation schemes are already operating in at least three countries—Sweden, New Zealand, and the Federal Republic of Germany.

PUBLIC CHARACTER OF SCIENTIFIC MEDICINE

Medicine's ancient roots have left a lasting impression on the character of this healing art. Its early history is closely connected with the history of religion and this association goes a long way in explaining physicians' strange claims of righteousness when it comes to making value judgments and taking actions that affect the lives of others. For example, unbridled human experiments designed to 'save lives' are rationalized by an 'ends justify the means' principle which has its origin in religious doctrine. A seventeenth century Jesuit moralist, Busenbaum, defended the proposition *cum finis est lictus, etiam media sunt licita* (if the end is lawful, the means

> Human institutions are so imperfect by nature that in order to destroy them it is almost always enough to extend their underlying ideas to the extreme.
>
> Alexis de Tocqueville

are also lawful). This argument has since been renounced by Jesuits, but it has tended to linger on in medicine.

Role of medical knowledge in human affairs

What is the role of professional knowledge and action in human affairs? Sociologist Eliot Freidson of New York University has suggested that medicine offers the best test of the general question of whether the ends of established professions are so humanitarian that experts may be given the autonomy to lead all of society to them. Ideally, in medicine, actions are based on reliable objective evidence, and what the profession deems to be good, the public, on the surface, regards as good. However, there lies at the bottom of medicine's applied efforts a moral rather than an objective judgment. Further, the professionally defined 'good' is asserted to be worth the price the patient is asked to pay in relinquishing his independence. But unless the moral foundation of medicine is identical to that of the community, it will serve not the community but itself.

Limits of professional dominance Freidson examined the limits of professional authority and concluded that the professions, no matter how beneficent their intent, have neither the special qualifications nor the moral right to make choices for the individual or for society.

> What a man calls moral judgment is merely his desire to generalize, and so make available for others, those values he has come to choose.
>
> C. Wright Mills

Physicians often make the assumption that medical practice, especially when it is based on sound evidence, is a pure, moral, acultural activity. I believe that it is this issue—the conflict between value judgments of doctors and patients and their families—that is at the heart of the profession's well-founded fear that enlargement of the public role in all matters relating to human investigation will slow the rate of technical development. The medical profession is puzzled by a strange paradox: as medicine becomes more effective it receives more public criticism. I do not find this at all surprising and it is certainly not anti-scientific; sharp criticism is part and parcel of the scientific method.

Scientific medicine is not seen as having the property of closure or finality—a fixed body of undoubted knowledge and a limited set of unquestioned concepts. It is seen, rather, as an evolving, open-ended search and the uncertainties are very much the concern of everybody.

Social aspect of the scientific method

As medicine leaves religion and mysticism behind, abandons its secretive and authoritarian past, and becomes more scientific, it will move in the direction of openness. This means, I suggest, that it will become more responsive to human need than heretofore. What must be understood is that the scientific method has a public character. It flourishes only when there is free criticism that is not deterred by authorities.

Popper has emphasized this aspect of scientific objectivity: theories are expressed in a form that can be tested by anyone who has taken the time to learn the technique of understanding and evaluating scientific hypotheses.

The Robinson Crusoe parable In order to illustrate the social aspect of the scientific method, Popper asks us to suppose that Robinson Crusoe succeeded in building physical and chemical laboratories, an astronomical observatory, and so forth, during the period of isolation from the rest of the world on his remote island. Further, suppose that he wrote many papers, based on observation and experiment. We are also to assume that he succeeded in describing scientific systems that coincided with the results then currently accepted by mainland scientists.

Considering the character of Crusonian science, we may be inclined to regard it as authentic because the islander used the painstaking methodology of the natural sciences. But, Popper reminds us, a vital element of the scientific method is missing. There was nobody but himself to check his results, nobody but himself to correct those prejudices that are the unavoidable consequences of his unique mental history, nobody to help him get rid of that strange blindness concerning the inherent possibilities of his own results that is a consequence of the fact that most of them were reached through comparatively irrelevant approaches. Consequently, the fact that Crusoe arrived at conventional results, without the carping of critics, is nearly as accidental and miraculous as it would be if they were conjured by a clairvoyant.

Concerning Crusoe's papers, it is only in attempts to explain his work to somebody who has not done it that he can acquire the discipline of clear reasoned communication, which is also part of the scientific method. Thus, it may be said that what we call 'scientific objectivity' is not the product of the individual investigator's impartiality but a summation of the social or public character of the scientific method.

> Give me a good fruitful error anytime, full of seeds bursting with its own corrections. You can keep the sterile truth for yourself.
>
> *The Practical Cogitator*

It is openness to criticism rather than philosophical arguments, I submit, that constitutes the most substantial hope that scientific medicine will remain humane and responsive to human need. Even a society made wary of science, because of misapplication of technical developments, must know that the underlying logical machinery of the scientific method is in the public interest.

Science, Popper pointed out, is one of the very few human activities in which errors are systematically criticized and fairly often, in time, corrected.