JENNER EXPERIMENTANT LE VACCIN SUR SON FILS
Therapeutic Innovation: Ethical Boundaries in the Initial Clinical Trials of New Drugs and Surgical Procedures

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I define “human experimentation” as either the intentional employment of normal human subjects as volunteers for physiologic experiments, or the study of patients (in a way that would not directly benefit them) to gather information on a disease or its treatment. While both of these ethical problems are worthy of consideration, they do not appear to me to present any severe ongoing ethical or technical difficulty in American medicine today. There are far more severe ethical problems in the Armed Forces, where chemical and biological warfare systems are studied on normal human volunteers who suffer the coercion intrinsic in military activity, or in the Space Program with its high lethality-potential in failed missions.

Nonetheless, public discussion of the purely medical problems such as they are has led to efforts at regulation and standardization; public attention to the climate of clinical investigation has helped to rectify ethical irregularities.

A far more important biomedical-ethical problem arises daily in thousands of hospitals concerning the ini-
tial use of drugs, treatments or operations and the initial employment of untrained personnel in the care of patients. Here, the subject-patient stands to benefit from the "experiment" if it is properly done; the line between experiment and therapy is never clearly drawn. Every new operation, for example, is an experiment; indeed every operation of any type contains certain aspects of experimental work. Likewise the employment of a familiar drug on a new patient for the first time constitutes an experiment in the precise determination of the proper dose, and there is an inevitable period of uncertainty about unusual reactions that the patient may exhibit.

Medical education in America aims to inspire in every physician a sense of inquiry, an intuition for biological variables, and an innate desire to evaluate evidence realistically. Each doctor should employ some of the essential features of the scientific and experimental method in the daily treatment of every patient. Without such an approach, the patient would suffer through the application of blind dogma and arbitrary rule-of-thumb; without the experimental method, medicine would become traditional, since it could not move ahead on the basis of established observations and experience.

Despite these clear advantages of the scientific and experimental approach, severe and pressing problems remain when new treatments are applied to man and when new personnel carry out standard operations for the first time. This latter problem—that of educating and gradually transferring responsibility to young men without, at the same time jeopardizing the patient's safety—is the central focus of clinical education. It is most especially pressing and obvious in surgery. The young surgeon passes from the status of a "greenhorn" intern at the age of twenty-six to a phase of technical perfection at about the age of thirty-two, when, frequently, his sheer operative skill is unequaled by an older generation. But he has yet to acquire judgment, wisdom, forbearance, and human insight—qualities that require the passage of time in any physician's education. Nevertheless, during those seven or eight years the young man has operated on many patients, and in many instances has carried out an operation for the first time on some patient. The clear recognition of the joint responsibility of the professor and the intern in such a setting is one of the most fascinating ethical problems in all of American education, but this is not our concern here.

Instead, we are concerned with a few of the ethical questions of therapeutic innovation raised by the application of new treatment to sick people. These are initial trials, carried out in human patients, of drugs or operations that may benefit the subject. This is the largest single category of medical experimentation—if that is a suitable term for therapeutic innovation—currently practiced at the clinical level.

The problems posed in such innovations are legion, and public reactions to their accomplishment range from malpractice suits to the Nobel Prize. Our problem here is to distinguish degrees of acceptability within this spectrum. Why do some of these activities most ennable the biomedical sciences, while others elicit more adverse comment among scientists than any other category of clinical experiment?

An Historic Example of Mass Human Experimentation

A familiar though remarkable historic example of therapeutic innovation which took place in Brookline, Massachusetts, about 250 years ago raises questions as appropriate for review in 1970 as they originally were in 1721.
An epidemic of smallpox had carried away many of the colonists in Boston and eastern New England in 1702. Accounts vary as to what brought word of smallpox inoculation to the keen ear of the Reverend Cotton Mather. But to this enterprising clergyman belongs the full credit of stimulating physicians to activity. Whether he saw accounts of the Turkish experiments or learned from talks with his own Negro slave that the practice of inoculation had been tried among primitive African populations (the latter being the more dramatic version which he himself preferred), the fact remains that he stimulated others to action with such promptness that the inoculation in Britain carried out by Lady Montagu took place only a few weeks prior to his, and the much larger New England experience became the prototype for widespread application both in this country and abroad.

The practice of inoculation against smallpox in the early eighteenth century consisted in the intentional infection of a normal person with virulent unattenuated smallpox virus obtained from a patient who himself might later die of the disease. This inoculation was done with the hope that the recipient would be afflicted with a mild case of smallpox—a "distinct case" as it was then called—and that the resultant "nonsusceptibility" would last the rest of his life. By contrast, the practice of vaccination introduced seventy-five years later by Jenner in England and, following his lead, by Waterhouse in the United States consisted in inoculating the recipient with the virus of the cowpox. This mild and rarely lethal disease confers immunity to smallpox by virtue of an antigen shared by the two viruses.

Cotton Mather could find none of his Boston medical cronies interested in such a heterodox undertaking. So he turned to the nearby town of Brookline where he discussed the matter with Zabdiel Boylston, then thirty-seven years of age. Boylston was the son of a doctor who had studied at Oxford, yet he himself had no medical degree. He was still a young man who had not emerged as a medical figure in a society that was already teeming with strong medical characters. Among these were the men who, a few years later, were to found the Harvard Medical School and the Massachusetts Medical Society. This large conservative wing of practitioners would have no part of the Reverend Mather's suggestion. But Zabdiel Boylston saw it for what it was—a chance to reduce the mortality from smallpox epidemics.

Accordingly, Zabdiel fetched some pus from a pock and proceeded to inoculate his thirteen-year-old son by rubbing this material on a scarification on the boy's arm. This epic experiment occurred on June 26 or 27, 1721. It is generally conceded that Boylston did not select himself for this experiment because he had already suffered the disease and was immune. In any event, the deed was successfully accomplished—at least the son did not die of the disease—and Boylston inoculated 247 persons in the next few months. Of these, six died. There was a clamorous and riotous opposition to the procedure both among fellow practitioners and among the laity who were aroused by their friends the doctors. Not long thereafter, out of a group of 5,759 cases of the naturally occurring disease, 844 died, according to Boylston's own account. Other figures from contemporary literature state that Boylston inoculated 242 persons of whom six died, and that there were 5,889 cases in the epidemic of whom 844 died. Whichever figures are correct, it was evident that the mortality was lower in the inoculated form of the disease, and that those who had
been successfully inoculated rarely, if ever, contracted the naturally occurring epidemic form of smallpox.

After a time of persecution, Boylston won out. He was acclaimed and honored here and in England. The practice spread to the other colonies. Benjamin Franklin, who had been a severe critic, later became a strong proponent. It is alleged that this stimulated an interest in medical science which resulted in his founding of the School of Medicine at Philadelphia in 1765. Although never really systematized, inoculation against smallpox was carried out in the colonies, often in hospitals built expressly for that purpose—such as that built at Salem for Dr. Holyoke in 1773. This practice of inoculation unquestionably led to the understanding and rapid widespread acceptance of vaccination, once it became available following Jenner's lead in 1796.

This was a lethal experiment. It carried a mortality of over two percent. It was undertaken to protect the individual, and through him the larger group, from the ravages of an epidemic disease. It was undertaken by people who had little idea of the nature either of the disease or the infectious agent, although Mather wrote of the "animalculi" that were involved. The basis for any confidence that this experiment would be successful was in large part hearsay from the Middle and Far East. There was no animal trial or laboratory work. A cloud of fantasy and petty controversy surrounded the actual details of inoculation techniques. Little effort was made to isolate those who had been inoculated with the disease, and they could become carriers of a virulent virus. Curiously enough, opponents of the procedure based their claims on the assertion that inoculation would not protect against the epidemic disease; they were not so interested in its public hazards or mortality, although this hazard to society was quite evident at the time. (Princess Caroline, for example, following the lead of Lady Montagu, inoculated convicted criminals and pauper children before she did her own family. She evidently hesitated to inflict an experiment that she considered hazardous on people whom she considered to be of great importance.) Finally, and most remarkably, the entire mass experiment carried out in Boston and Brookline was proposed and urged by a man of the church and was opposed almost to a man by the medical profession.

Could this experiment be conducted in 1970? Certainly not. The mortality was prohibitive. There was no scientific basis or preliminary laboratory work. It is quite evident that both Cotton Mather and Zabdiel Boylston perceived a potential social benefit that was greater in their minds than the immediate sacrifice of six lives. From this experiment was born the initial awareness of active immunization as a means of protecting society against the scourge of epidemic disease. The first mass trials of the Salk polio vaccine and all the other inoculations from Pasteur to Enders went through moments when they shared precisely the same ethical problems faced by Mather and Boylston.

Although Dr. Boylston (and the many others who have worked with preventive inoculations) were dealing with the prevention of disease rather than with its treatment, the subjects of the experiment stood to benefit. For this reason, the ethical problem raised here falls into that general family of ethical issues involved in therapeutic innovation.

Other Examples of Initial Therapeutic Trial

The first use of ether anesthesia, the first injection of insulin, the first use of liver extract, and the first application to a patient of any one of a host of
new drugs are all part of the same ethical family. At the present time, we are engaged in one of the largest mass human experiments of this type ever considered: the widespread use of oral contraceptives. It has been estimated that more than twenty-five million women have taken these tablets and that at any one time fifteen million women are taking them. Their effects after prolonged administration are entirely unknown. There is virtually no animal work reporting the continuous administration of these drugs for more than three years, and their impact—either on the psyche, ovaries, endometrium, or breast—on women after twenty years of continuous administration remains entirely unknown. Although their administration seems to be a matter of great social and human urgency, urged by many national and international groups, the ethical problem is real and the unknowns are serious. Oral contraception has certain features that set it apart from ordinary therapeutic innovation because it is a medicinal treatment given to a healthy person to prevent a normal occurrence, rather than an inoculation given to prevent fatal epidemic disease or a drug (or operation) employed to treat human illness. Oral contraception must, therefore, be even more free of taint than innovations involved with the treatment of disease.

New surgical operations pose problems similar to those raised by other therapeutic innovations. At the present time, they are assuming a new order of magnitude in ethical implication. There was a time when new surgical operations depended for their success only on the drainage of pus, the removal of some gangrenous or diseased part known to be dispensable, or the rearrangement of musculo-skeletal anatomy. So long as the surgeon could rely on the un failing tendency of wounds to heal, of blood to clot, and of bacteria to be overcome by immune defenses, his success was virtually assured. Fortunately, the natural process of evolution had already provided these solutions. The body perceives no essential difference between injury incurred accidentally in the traumatic life of a higher vertebrate and an injury inflicted by the surgeon. Wound-healing, blood-clotting, and immunology are the first line of defense that enables the survival of the fittest; these Darwinian mechanisms are used every day by the surgeon—or, strictly speaking, by his patient.

This simple state of affairs no longer obtains in surgical innovation. For the last twenty-five years and with increasing frequency, new operations are being employed that depend for their success on complicated physiologic or pharmacologic interactions. At the simplest, these may involve such a thing as the removal of an entire lung—a procedure that depends for its success on the fact that, in man, cardiac output and normal respiration can both be accomplished in a single lung. Other recent examples of this type of physiologic readjustment involve operations on the autonomic nervous system, interference with tracts in the brain, or the rearrangement of the anatomy of the bowel or of the heart. In all of these, the surgeon must depend upon a physiologic readjustment to assure recovery. These physiologic adaptations are complex, often specific to man, and the initial period of human trial of such new operations is much more difficult and demanding. Furthermore, unlike the basic recovery-drive after simple surgical injury, these complex physiologic adjustments are often paradoxical or unpredictable. Although the surgeon may be removing cancer, curing pain, or helping high blood pressure, he is silently depending upon an adaptation that was unheard of in the evolutionary process.
Vagotomy does not occur in nature.

In the past ten years, surgery has invaded an entirely different area of fundamental biology—one in which it must rely for success not on an evolutionary response or a physiologic adjustment, but on the outright abolition of a normal response established in the species during epochs of evolution. A specific example of this is to be found in transplantation, where success depends upon the abolition of normal immunologic defenses. In fact, in transplantation we have for the first time a surgical procedure that was "tried out" on patients (after a long laboratory trial) and depends for its success on a state of immunologic nonreactivity produced by drug treatment which, if applied generally, would result in illness and death. The transplant procedure involves the simultaneous application of dangerous drugs and a new operation; the success of both depends upon the interaction of each.

To complicate the ethics of transplantation further, there is always another individual involved. Either he is quite healthy and undergoes a major surgical injury to help another, or he is so recently deceased that bystanders sometimes wonder if he indeed is dead since so many organs and tissues of his body are still obviously alive.

As the constellation of biological variables around new surgical operations becomes more complicated, as in transplantation, so also does the ethical problem become more pressing. Many of us concerned in the development of tissue transplantation have felt that the questions which it has raised have been responsible in great measure for the renewed interest in the ethical standards of biological research.

The Need for Guidelines

These problems are urgent and press for solution; if a teaching hospital or university medical school is doing its job and carrying out its responsibility to the public, it must be involved with initial trials and therapeutic innovations that raise ethical problems.

Is it possible to design a set of principles that protect the patient under conditions of therapeutic innovation and yet maintain some atmosphere of permissiveness? We must always insist that these guidelines protect society by enabling a continuous advance of biomedical science in the clinical areas. By establishing arbitrary ethical standards, one might be surprised to find that while he is protecting the individual patient, he is exposing society to the hazard of a static rather than a dynamic medicine. The power to restrict becomes the power to stifle the enthusiasm that has brought forth the advance of modern medicine and public health.

Can Consent Be Informed?

In this context, the principle of informed consent has two special limitations. The first unique feature of informed consent in therapeutic innovation is that the patient actively seeks the untried therapy with an earnest plea to become the willing subject. To those who have never dealt with such desperate patients, it may come as a surprise to witness the enthusiasm with which the patient with late cancer or the family of children with severe heart disease approach an entirely new and untried procedure. This willingness is especially notable if the family knows or suspects, with or without suggestions by the doctor, that the new procedure is the only source of hope for survival. The cancer patient himself seeks out the new drug or the new treatment; people of education and considerable scientific sophistication become blinded and will transgress the boundaries of the simplest common sense not only in accepting new drugs, but in seeking quackery in
the hope of a cure. The posture of "informed consent" in therapeutic innovation is, therefore, not a matter of trying safely and sanely to explain to a volunteer what is going to be done, but rather the much more difficult task of explaining alternatives to a worried patient who wishes, above all else, to have the experiment carried out on him.

The second aspect of "informed consent" that is so limiting in its application to therapeutic innovation (as indeed it is also in experimental investigation of any sort) is the obvious fact that there is no means of becoming informed other than by the experiment itself, even if there is a desire to give consent. The very fact that the procedure has not previously been carried out in man indicates that the scientist himself lacks the critical information required for informed consent. If the doctor knew the most likely outcome of the procedure, such information could only have come from previous experience, and in that event the patient would hardly be at risk.

An intrinsic feature of consent lies in the presentation of sound alternatives to the patient. If I were to identify any one feature of the doctor-patient relationship that is most frequently colored by unconscious subjective factors on the part of the doctor, it is this question of clinical alternatives. One or two examples will illustrate. A colostomy or ileostomy is a form of diversion of the gastrointestinal tract made so that the fecal contents are emptied onto the abdominal skin. Here the discharge is received in some sort of a bag or receptacle that the patient empties from time to time. While unpleasant and unhygienic, most intelligent persons accept this as the price that they pay for the treatment of severe disease—usually malignancy. The more intelligent the patient and the more fastidious his care of his own physical person, the less difficulty he has with colostomy or ileostomy, since he takes special time each day to care for himself in a way that is acceptable to his own high standards. On many occasions I have borne witness to conversations between physicians and patients in which the picture painted of this colostomy or ileostomy was entirely the product of a physician's imagination, based on the fear that he himself might one day have to have such a procedure. A patient suffering from ulcerative colitis or cancer of the rectum who is given an offensive or frightening verbal description of colostomy or ileostomy would be so biased in his approach to the operation that he may actually refuse a procedure that offers him the greatest likelihood of survival. By contrast, the over-enthusiastic description of the state of well-being which may result from the surgical treatment of ruptured intervertebral disc, bursitis of the elbow, or hypertrophy of the prostate (considering only three of many examples) will sometimes result in a patient entering into an operation for benign disease, not life-threatening, with an optimism born of the surgeon's tone of voice rather than a realistic estimate of his own response to the projected treatment.

When we move from these rather familiar examples in the explanation of alternatives to such desperate measures as kidney or liver transplantation for fatal disease, it is evident that the hopes of the surgeon, the fears of the patient, and the inborn optimism of youthful science combine to push the patient onward. Ethics in clinical care bring a sense of balance between these two extremes.

**Preliminary Laboratory Trial**

There is no way of trying out a surgical operation in small doses, and, as with oral contraception, there is no
quick way to reproduce in the laboratory the passage of years. In addition, many surgical operations remove structures or rearrange anatomy in an irreversible or irreparable manner; there is no turning back. Even in the case of therapeutic innovation with drugs, hormones, or vaccines, the human experiment always carries a few surprises when contrasted with preliminary laboratory work.

Despite these limitations, preliminary laboratory trial occupies a position of unique importance. In the opinion of most scientists, physicians, and surgeons, laboratory study puts the stamp of human and ethical acceptability on therapeutic innovation more than does any other characteristic. Preliminary laboratory trial is the only way to provide information, however incomplete or inadequate, that might lead to an acceptable informed consent. Preliminary trial in animals is not always easy and is frequently expensive. For example, it is almost impossible to produce in a dog the type of chronic renal failure that has been the setting for most kidney transplantations carried out in man. It is entirely impossible to reproduce in the dog either the type of chronic valvular disease of the heart that has been the basis for open-heart surgery, or congenital heart disease that will provide an important indication for transplantation. Despite these limitations, preliminary laboratory work must be carried out with the greatest care and in an effort to reproduce as many features of the situation as possible. New drugs or operations should be employed in the dog or in some other large animal, as well as in the small laboratory rodent. The larger mammals are truer models for human application, and they permit repeated clinical observation and blood chemical sampling, together with physiologic monitoring, in a way that is not possible in the rat, mouse, or hamster.

But before leaving this matter, we should mention the present crisis in laboratory finance in the biomedical sphere. While the current cutback is considered by the Congress in terms of budget savings, and by the scientific public as one of the highly undesirable consequences of our military involvement in Southeast Asia, the sudden withdrawal of large amounts of federal support for biomedical research is going to have an inevitable ethical consequence: the necessary preliminary laboratory work is going to be severely curtailed in the instance of many forthcoming therapeutic innovations.

During the past ten years, the expense of conducting laboratory experimental work has doubled as a result of inflationary spirals in all the goods and services concerned. Prior to 1967, the National Institutes of Health budget increases had barely kept pace with laboratory inflation, but these had been sufficiently large so that other sources of laboratory support (such as certain philanthropic foundations and industry) had tended to withdraw from the field. With the withdrawal of laboratory financial support due to the congressional policy of pursuing military action in Southeast Asia, we are greeted with an almost unsupportable situation in biological research. An ironic example will illustrate. A certain young man of excellent medical background had just completed two years of service as a military surgeon in Vietnam. Here he had been handsomely supported in one of the largest and most wasteful of military encounters, and had worked himself without stint and without succor to assist in the care of the wounded. Returning to civilian life, he was to become a Research Fellow in our laboratories to study the transplantation of the liver (liver transplant being a potential help to babies born with bile duct anomalies, to individuals with liver tumors,
and to soldiers with severe bullet wounds of the liver. On returning to civilian life, he was told by the government that although his name had been accorded one of the highest places in the priority list for Senior Research Fellowships, funds were not available to support him. In the Sunday supplements that week, there was an account of new research being done to make a lunar module perform in a high vacuum simulating the surface of the moon, a research expending more money each month than has ever been spent on any aspect of tissue transplantation. It is clear, then, that ethical considerations in preliminary laboratory trial go to the roots of our society and to the question of what we regard as suitable priorities for human effort at this time.

The Ethical Nature of Clinical Science: An Historic Example of Its Violation

The subtitle to this section might easily have been “The Ethical Nature of Clinical Investigation,” and as such it would have been a perfectly proper heading. The term “clinical investigation” has unfortunately become almost a term of opprobrium, and many people regard the term as meaning exclusively research that is carried out on normal subjects or on patients who do not stand to benefit thereby. Actually, the terms “clinical research” and “clinical investigation” are synonymous and apply to any sort of research or investigation that is carried on in relation to patients. The term “clinical” is an ancient word which means “reclining in bed”; as an adjective applied to investigation, it merely refers to the human patient. Modern medical care cannot be pursued without an element of clinical research or clinical investigation. Careful study of the patient, careful recording of the results, and careful consideration of variables with statistical accuracy are essential to any sort of clinical research or investigation, just as they are essential to the ethical climate in the initial trial of new drugs or operations. In this way, the normal hospital environment of a high-grade university hospital becomes a cloak of protection that surrounds the patient. The history and physical examination, the complete workup, the inquiring though sometimes bothersome medical students, the interns and residents, the full view of the event by the rest of the staff—all protect the patient from premature, willful, ill-advised, or secret therapeutic innovations. The ethical content of science itself lies in careful observations, honest reporting, and an unbiased review of the results.

This essentially ethical nature of the scientific process provides protection when the scientific process is applied to the medical act. By the same token, when a new operation is attended by the most perfect pre- and postoperative management, skillful anesthesia, and expert surgical technique, these hospital surroundings enable the surgeon to carry out a new procedure with a minimum of hazard to the patient. Such safeguards cannot rescue a poorly conceived operation from failure, but they can surround a well-conceived procedure with the greatest likelihood of success and the least chance of accidental ill effects. The same is true in the therapeutic innovation of drugs, hormones, vaccines, and antibiotics.

The borderline between acceptable clinical science and unacceptable human experimentation is most frequently violated through breach of scientific method. Outright quackery posing as therapeutic innovation includes such nostrums as goat-gland grafts for virility, or electronic devices that tune sinusitis to the wave-length of the planets. Such absurd examples, though surprisingly common, do not illuminate our problem because they are patently
ridiculous, and those persons who seek such release from the realities of illness, infections, and aging might almost be considered as fair game.

Much closer to home are those recent examples of breach of scientific method that have brought down the reputations of outstanding scientists and have led to the fraudulent marketing of cancer cures with the apparent support of renowned institutions. In such examples, some sort of psychiatric insight is required to understand the scientist as he slowly swings from the dignity of recorded public knowledge to a frantic search for notoriety as the great discoverer of a cancer cure. A recent example of this process involves a substance called “Krebiozen,” a name coming from the Greek and meaning “that which regulates growth.” The Krebiozen episode illustrates how a highly sophisticated scientist, in mid-twentieth century, can go astray despite the protective surroundings of modern science and a self-conscious approach to ethics. (In my account, I am drawing heavily on the Boylston Society Essay of Dr. William D. Morain, entitled “Krebiozen: Nineteen Years of Controversy,” which gathers together many loose ends of this still controversial case.)

The story began in 1947 when Dr. Andrew C. Ivy of Chicago published an article in Science entitled “The Biology of Cancer.” In this piece he advanced the concept that a unified method would be found to deal with all cancer. In 1949, two brothers named Durovic came to Chicago, bringing with them a drug called “Kositerin,” allegedly extracted from cattle and alleged to cure 98 percent of the people with high blood pressure. The Durovics refused to disclose the nature of this drug. They were referred to Dr. Ivy, who was at that time at the peak of his authority and brilliance, the author of many scientific publications, a representative of American medicine at the Nuremberg trials, and Executive Director of the National Advisory Council of the United States Public Health Service. Evidently the Durovics then told Dr. Ivy of another substance called Krebiozen which was extracted in milligram quantities from blood pooled from hundreds of horses. Again, the Durovics refused to state what the material was or how it was actually produced. It is probably only a coincidence that Dr. Ivy had advanced in his article in Science the thought that the normal body contains tiny traces of an anti-cancer substance.

Dr. Ivy administered the drug to a dog, then to himself (as per the Nuremberg Code), and within three weeks to a patient. Even at this time, one can perceive the seeds of disaster. Dr. Ivy claimed that Durovic was a widely known former Professor of Medicine at the University of Belgrade who had gone to Argentina after being expatriated during the war and had published extensively in the scientific literature. No such publication could be found. An investigation of his activities in Buenos Aires revealed that most of them centered around a private office where he injected hypertensive patients with Kositerin at the price of 5,000 pesos per treatment. Fifteen bulls, but no horses, were found to have been bought by his sponsoring company. It is stated that South American officials of the company involved with Kositerin were quite astonished when public press reports began to arrive of Durovic’s success with a second drug unknown to them and made from horses.

Many friends and associates tried to dissuade Dr. Ivy from involvement in the study of a material the nature of which was held secret; but nothing could move him to resolve.

The Journal of the American Medical Association published a “Status Report on Krebiozen” which stated that the
commission appointed to study it ordinarily "would not attempt to evaluate the clinical benefits, if any, of a substance whose character and method of manufacture were not known." It was stated that 98 of the 100 patients reviewed had not shown any improvement and 44 of them had expired.

Battle had thus been joined between an eminent scientist and an established organization of the medical profession, one regarded by many as reactionary to all advance or change. Dr. George D. Stoddard, then President of the University of Illinois, was given the role of referee. He appointed a committee of eminent clinicians and scientists. Within a year, a report was published indicating that the material had no curative value in the treatment of cancer, and again indicating total dissatisfaction with research on a material of unknown origin or composition. The door was left slightly open in that the committee could not state categorically that the material was entirely free of biological effect.

There is not space here to detail the rest of this unhappy story save to point out the subterfuge of the Durovics in stating, as increasing pressure arose to identify the material, that all the existing Krebiozen powder had been dissolved in the 200,000 ampules of mineral oil. A chemist had evidently been unable to find anything in the mineral oil. Countercharges of conspiracy were leveled against Dr. Ivy and the Durovics; a legislative committee was appointed; certain officials of the University ultimately sided with the harassed Durovics and Ivy; and Dr. Stoddard was forced to resign. Dr. Stoddard's book, due to be published in Boston in the middle-1950's, was banned by injunction prior to publication; when it was finally published, it was met by a libel suit by Dr. Ivy. As recently as 1963, Krebiozen was still being distributed for "clinical testing."

The Food and Drug Administration entered the controversy in 1963, the Thalidomide scandal having forced it to take a much closer look at all new drugs. Discussion in the United States Senate and a picket line in front of the White House both became features of the controversy.

Finally on August 14, 1963, the riddle of almost fifteen years' duration as to the exact chemical nature of the substance was solved. A chemistry student at the University of Pennsylvania had found an infrared tracing in an atlas of 20,000 tracings of known chemical compounds which exactly corresponded to a substance found in tiny quantities in Krebiozen. This powder was creatine monohydrate. It was administered to the cancer patients in tiny quantities, a miniscule fraction of the amount of this normal chemical constituent that the human body normally metabolizes each day. To make it soluble in mineral oil, it had been heated with other compounds, yet even this was difficult; evidently the ampules dispensed after 1963 contained absolutely nothing other than mineral oil.

The trial that followed is of historical importance in indicating the way in which popular lines are drawn between anything that smacks of the Scientific Establishment, on the one hand, and intuitive public sympathy with the Underdog Innovator, on the other. The defendants were not found guilty of fraud or conspiracy. Dr. Durovic left the country, and the conflict still rages.

"The main question left standing in the Krebiozen controversy," wrote Elinor Langer in an article in Science in 1966, "is how so many people could spend so much time on a problem so limited and come up with so little."

The breach in scientific method was clear in one important regard—that the actual nature of the material was unknown, not disclosed, and kept secret.
But more important than this was the consistent breach in the search for scientific evidence; the evidence had to be sought in the clinical results of the administration of the drug to cancer patients. Here was the flaw. Clinical investigation (as opposed to laboratory work) had not been a part of Dr. Ivy's long and brilliant career. Dr. Ivy became entrapped by the difficulties of clinical investigation in cancer patients, well-known to all clinical scientists, but new to him as a laboratory man.

The cancer patient has a tremendous investment in anything done to help him; he wants to see helpful results to give him new hope and relieve his pain. The most junior surgical intern daily sees cancer patients arousing from operations with hope and confidence, even though nothing whatsoever could be done; it takes many days or weeks for this reality to become evident. To gather scientific evidence under such circumstances requires special techniques and special disciplines. Although clinical research is seemingly simple when compared with some of the more rigorous or expensive laboratory techniques, clinical research places the investigator in a position of self-discipline that is almost unknown to the laboratory investigator who is surrounded by the conventional safeguards of the laboratory and shielded from the uncertainty of frail human patients who wish to bear witness to a favorable result.

To the outside world, and particularly to that segment of our society that is irrational, anti-intellectual, and antiscientific, the conventional trappings of science appear to be but an expression of the establishment. Individuals—often unknown to science—who are fighting against the establishment become heroes to those same persons who would restrict the activity of the universities, do away with professors and a free press. The public espousal of the cause of the lonely warrior fighting the great and powerful medical establishment provides strong popular support for the claim of either the quack or the misled scientist that he has "never received a fair trial." In the case of Krebiozen, this claim would have aroused greater sympathy had the protagonist sought the active collaboration of other scientists who might have borne witness to the chemical nature of the secret drug and the validity of the clinical trials.

**Checks and Balances: The Collaborative Enterprise**

A new policy was recently formulated by the National Institutes of Health requiring a review of projected new drugs or procedures in man by a local panel of peers. To our view, this formality confers little security on the patient and is far less important than the active collaboration of scientists from a variety of disciplines and backgrounds. Such workers provide a balance for one another's ideas; they act as a damper on ill-advised enthusiasm; and they become a check on personal ambition.

There can be little question that personal ambition, usually for career advancement or public acclaim, underlies much intense motivation in research work and in the trial of new ideas, drugs, operations, or treatment. Such personal ambition is usually well hidden under the sophisticated affect of the dedicated clinical scientist and, far from being remiss, is the sign of a healthy society. While social convention requires its disguise in the masquerade of scientific intercourse, this ambition is not a thing to be ashamed of. Personal ambition for advance and recognition is a far better motive for the work of difficult or protracted clinical investigation than is the seeking of political advancement or financial reward. No matter how deep the urge for
pure knowledge, few scientists have not derived some excitement from a general acceptance of their ideas or procedures, particularly if these were of potential social benefit. The possibility of such acceptance provides a more stimulating environment for scientific work than the even temper of an aphantetic society where, because of the heavy system of penalties placed upon failure, there is neither a channel for innovation nor an interest in departure from tradition.

But ambition, no matter how praiseworthy, can certainly lead individuals astray. A common example is found in the premature publication of scientific results. Personal ambition for recognition has clearly outstripped the cooler judgment of awaiting more definitive data. The active collaboration of scientists provides the best way of harnessing these fine qualities of excitement and ambition so as to maintain their force for forward motion and yet prevent them from running wild. For this reason, a collaborative group with open discussion, avoidance of secrecy, and frequent review of plans and policies seems far more important than the short-term arbitrary review of some one drug or operation by a formal panel with a strictly ad hoc mission. Such formal panels are usually composed of individuals who know little of the work contemplated, and they may even come to include individuals who for reasons of jealousy or ignorance would rather not see the old order challenged anyway. The ethical acceptability of therapeutic innovation documented in a research application, for example, is far better attested by the nature of the scientific consultants working on the project than it is by the nature of the hospital panel that is to review each case.

**Ethical Climate of the Institution**

Nearly all these remarks can be included under the general heading of "the intellectual and ethical climate of the institution." Such a climate is difficult to regulate or standardize, difficult at times even to recognize or describe. Yet it is more important than any other single consideration in protecting the willing patient from unwise, inexpert, or ill-advised therapeutic innovation. As one reads Zabdiel Boylston's own account of his inoculation experiments, one is impressed by his misgivings, the care with which he nursed each patient through the illness, the careful records he kept, and his plea to others to avoid secrecy and proceed with these innovations freely and openly. In these qualities, one senses his intellectual and ethical approach, and feels that although none of the other more familiar modern safeguards were present, all was right in Brookline in 1721.

In terms of the modern hospital, this ethical climate must be appreciated by direct personal participation. It has been said that no one knows whether a football game is rough unless he plays in it; the sideline spectator cannot really tell whether the kick in the ribs is necessary, accidental, or intentional. The same applies to a hospital. One cannot really see the inner workings of men's minds by reading the article or even visiting for a day. One must join the hospital staff for weeks or months as observer, visitor, research fellow, physician, or surgeon before he can decide that the ethical climate is suitable for the site of therapeutic innovation.

Only by visiting a hospital does one gain an impression as to whether or not the choice of subjects for therapeutic innovation indicates a fundamental unease on the part of the investigators. We have already alluded to the practice of selecting poor people, criminals, native populations, under-educated or backward people, or even the feebleminded for certain types of hazardous innovation. When one discovers that doctors are selecting patients in this
way, then one has identified a major flaw in the ethical climate and a severe chink in the scientific armor. It means that those carrying out the therapeutic innovation are ill at ease with it, would not wish to have it carried out on their own person or families, and are looking for some "easy game" to get over the first few barrier cases. If, by contrast, the therapeutic innovation has been researched and studied with such care that it is regarded by those carrying it out as a blessing to a properly selected patient, one then finds that these initial patients represent a true cross section of the hospital population rather than a hand-picked selection of underdogs. In this area, the Golden Rule finds its expression. The mere statement that somebody would like to have it "done on himself if needed" is meager comfort. What is significant is the demonstration that those selected for therapeutic innovation represent the full spectrum of the hospital population and not just a group for whom recourse would be scanty. When a new vaccine is first given trial in a primitive African tribe, one needs to go no further; the investigator feels insecure and unsafe with the material and wants to get his quick answer from a group in whom consent is impossible, information is totally lacking, and the backlash is insignificant.

Protection of Science and the Scientist

Finally, restrictions and guidelines can become so rigid that society risks a static science in which the scientist (biologist, clinician, physician, surgeon) is constantly bombarded by criticisms, suits, and penalties.

This problem, more than any other feature of our topic, is a matter of public relations, the public image, and the willingness of those in the scientific establishment to stand up and be counted on the side of intelligent therapeutic innovation carried out in an ethically acceptable setting. A large segment of the public, possibly lacking educational opportunity, may always be biased by bitter experiences with biomedical science, and perhaps biased without such experiences. These people will cry "guinea pig" when they hear of anything new being tried by doctors. It is but a step from this antirationalism to congressional unease with "what's going on in our hospitals and laboratories," restrictive legislation, inspection of laboratories and hospitals, the establishment of external review boards and finally stifling of effort.

To offset this danger, we need repeated public statement of the meaning of and the need for therapeutic innovation, the teaching of scientific history in a realistic way to emphasize the hazards and sacrifices as well as the rewards involved, defense in congressional hearings of the "open scientific society," and publications to define those elements that can make therapeutic innovation an ennobling and absolutely essential feature of modern scientific and medical growth, one more essential to our society than the man on the moon and far less expensive.

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