

Chapter 18

Research and Experimentation

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HISTORICAL BACKGROUND

Few subjects in the medicolegal field have raised as much widespread controversy since World War II as the question of human experimentation and clinical investigation. Exposés of activities by the Central Intelligence Agency (CIA), the Department of Defense, and other federal agencies involving the deaths of innocent victims, who were unknowing, involuntary guinea pigs, have raised many moral and ethical questions for the entire country. Ever since the Nuremberg trials after World War II, medical researchers and other professional scientific personnel involved in clinical investigation have been made aware of the medicolegal hazards and pitfalls of improper, illegal human experimentation. The Declaration of Helsinki and Codes and Guidelines adopted by the American Medical Association and other national professional organizations, as well as by the Department of Health and Human Services (DHHS), have emphasized the importance and necessity of having well-defined principles for all medical experimenters and researchers using human subjects in their studies.

The World Medical Association (WMA) addressed this controversial subject in 1949 at its meeting in London, at which time a rather strict International Code of Medical Ethics was adopted. It said in part: "Under no circumstances is a doctor permitted to do anything that would weaken the physical or mental resistance of a human being except from strictly therapeutic or prophylactic indications imposed in the interest of the patient." However, by 1954, the WMA had become uncomfortable with its commitment exclusively to the individual patient. That year, the organization adopted its "Principles for Those in Research and Experimentation," which, while warning that there must be "strict adherence to the general rules of respect of the individual," also explicitly recognized that experiments may be conducted on healthy subjects.

By 1964 the WMA had clearly abandoned the individual patient-centered commitment of 1949 in a new set of recommendations, "because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity." Today, not only the regulations of the WMA, but also those of the Nuremberg Code and the U.S. government, justify a human experiment if the risks compare favorably with the foreseeable benefits to the subject or to others.

Hence the Hippocratic tradition regarding human experimentation has been amended to include a concern for suffering humanity and, of course, for scientific progress.

Yet this same commitment to benefit society may also have opened the door for the type of experimentation that includes the injection of hepatitis virus into mentally retarded children, as occurred at Willowbrook State Hospital (see below). Thus a "Willowbrook" becomes possible once experimenters can convince themselves that the risks are outweighed by the possible benefits, including the potential benefits to people who were not included in the experiment.

Some scientific researchers have been irritated by the institution of codes and guidelines and continue to insist that they should be permitted to use their own best moral and ethical judgment as professional people. Although the majority of these persons would, of course, apply a high level of moral and ethical judgment, experience has demonstrated all too frequently that even highly experienced researchers can be carried away with a particular project and engage in activities that not only are in violation of the existing civil common law and criminal codes, but are in opposition to traditional medical morals and ethics. For all these reasons, it is essential that physicians and other scientists who directly or indirectly engage in any kind of experimentation or clinical investigation involving human beings be fully aware of all the legal ramifications and potential problems associated with this area of professional activity.

The late eminent Harvard Medical School anesthesiologist and medical ethicist, Dr. H. K. Beecher, claimed that human experimentation beyond the boundaries of medical ethics was being carried out to an alarming and dangerous degree by clinical investigators in the United States. He claimed that these investigators were more concerned with furthering the interests of science than with the good of the patient. He found 12 of 100 consecutively reported studies involving experimentation with human subjects, appearing in a highly respected medical journal in 1964, to be seemingly "unethical." Beecher concluded: "If only one fourth of them is truly unethical, this still indicates the existence of a serious situation." In the prestigious *New England Journal of Medicine*, he found 50 examples of unethical experimentation described or referred to in various articles.¹

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Government-Sponsored Experimentation

Medical experimentation on humans has a long history, but public concern over it is a comparatively recent development. One of the more spectacular recent examples of unethical human experimentation was partially revealed in June 1975 by the Commission on CIA Activities within the United States, the so-called Rockefeller Commission. In its chapter on domestic activities of the CIA's Directorate of Science and Technology, the Commission's report described some of the CIA projects involving drug experimentation on humans, noting that most of the records of such experiments had been destroyed. The report minimized the consequences of the experiments to the subjects involved, many of whom had not even been informed that they were subjects of an experiment. One of the CIA experiments was described more specifically, although still in casual, almost indifferent terms:

The Commission did learn, however, that on one occasion during the early phases of this program [in 1953], LSD was administered to an employee of the Department of the Army without his knowledge while he was attending a meeting with CIA personnel working on the drug project.

Before receiving the LSD, the subject had participated in discussions where the testing of such substances on unsuspecting subjects was agreed to in principle. However, this individual was not made aware that he had been given LSD until about 20 minutes after it had been administered. He developed serious side effects and was sent to New York with a CIA escort for psychiatric treatment. Several days later, he jumped from a tenth floor window of his room and died as a result.

The General Counsel ruled that the death resulted from circumstances arising out of an experiment undertaken in the course of his official duties for the U.S. Government, thus ensuring his survivors of receiving certain death benefits. The Director of Central Intelligence issued reprimands to two CIA employees responsible for the incident.²

As if to suggest that the experiment perhaps had nothing to do with the death, the report added a gratuitous footnote: "There are indications in the few remaining Agency records that this individual may have had a history of emotional instability." The individual was not identified in the Commission's report. The report went on to conclude that "it was clearly illegal to test potentially dangerous drugs on unsuspecting United States citizens," and recommended that "the CIA should not again engage in the testing of drugs on unsuspecting persons." Not a word about medical ethics, international codes, or anything else to indicate any genuine moral concern—not even a suggestion that the unknowing subjects of the experiments ought to be located and informed. This was how a prestigious governmental commission perceived its obligations and performed its duties.

Fortunately, the news media were not satisfied with this incomplete disclosure. The identity of the victim in the specific incident described by the Commission was soon determined to be Dr. Frank Olson, a civilian Army

employee. His "history of emotional instability" consisted of visits to a New York psychiatrist, retained by the CIA, after he had been subjected to the CIA's drug experiment. When the detailed circumstances of the experiment and Dr. Olson's death became widely publicized, the President of the United States expressed public apologies to his widow and children. Ultimately, after a suit had been filed, the case was settled privately and quietly by a \$2 million payment from the government.

Other examples of governmental drug experimentation on humans also came to public attention. One involved a 42-year-old hospital patient, Harold Blauer, who died in January 1953, approximately 2½ hours after receiving an injection of a mescaline derivative. (Mescaline is a hallucinogenic drug derived from a type of cactus plant and is similar to LSD in its effects on the mind.)

Blauer, along with an undetermined number of other patients, had been given injections of mescaline derivatives during the course of a 29-day project conducted by the New York State Psychiatric Institute under an Army contract. At no time was there knowledge on the part of any of the patients or their families as to the nature of the experiment, nor was any informed consent obtained.

Some comments by the acting Mental Hygiene Commissioner of New York State, Dr. Hugh F. Butts, after disclosure of the circumstances of Blauer's death, are especially relevant:

It was not uncommon practice at that time for medical and psychiatric researchers to use drug treatment without the detailed knowledge and special consent of patients. This was thought necessary to avoid false reactions. Such practices could not occur today because patients are protected by laws and regulations that have been specifically enacted to prevent such occurrences.³

After the public disclosures of the Olson and Blauer cases, the news media turned up numerous other instances of unethical experimentation with hallucinogenic drugs on unsuspecting human subjects involving several government agencies. At least 7000 persons had been so treated by the U.S. Army alone. The Rockefeller Commission report had also alluded to experiments on "unsuspecting persons in normal social situations," on both the West and East Coasts during the 1950s and 1960s.⁴

Later, it was learned that the U.S. Atomic Energy Commission, predecessor to the Energy Research and Development Administration, sponsored and monitored various experiments from the 1940s through the 1960s on human subjects, including children, in which the subjects were exposed either to radiation or to the highly toxic metal plutonium. In the radiation tests, 79 inmates of the state penitentiary in Oregon, men and women, were exposed to doses of radiation to determine the effects on the reproductive organs. No follow-up studies had been performed in recent years, but as a result of the disclosure, prison officials agreed to conduct medical evaluations to detect adverse aftereffects.

In the plutonium exposure tests, 18 men, women, and children, all thought to be terminally ill, were injected with plutonium in amounts ranging from 2 to 145 times the maximum permissible dose under current standards. The subjects were not told what the substance was. The injections were performed between 1945 and 1947 at various hospitals in four different states. Astonishingly, although all the subjects were thought to be terminally ill at the time, three were still alive 40 years later.⁵ Obviously, aside from the ethics of the experiment itself, such long survival of “terminally ill” patients raises serious questions about the ability of researchers to determine such conditions in their choice of subjects.

LSD

The Justice Department recently settled a lawsuit by nine Canadians who asserted that the CIA, unknowingly to them and their relatives, made them the subjects of mind-control experiments in the 1950s. The plaintiffs were patients of a psychiatrist who received money from the CIA to do research into drugs that could be used to control human behavior. According to government records, the nine plaintiffs were not told they were the subjects of experiments. They were subjected to heavy doses of the hallucinogen LSD, powerful electric shock treatment two or three times a day, and doses of barbiturates for prolonged periods of drug-induced sleep.

Documents that became public showed that the CIA had used private medical research foundations as a conduit for a 25-year, multimillion-dollar research program to learn how to control the human mind. Through a front organization called the *Society for the Investigation of Human Ecology*, the agency funneled tens of thousands of dollars to pay for an array of experiments that involved LSD, electroshock therapy, and a procedure known as *psychic driving*, in which patients listened to a recorded message repeatedly for up to 16 hours.

The Nuremberg Code

Of course, there is nothing new about medical experiments on humans. Galen founded the experimental science of medicine before A.D. 200, and there are references to medical experiments on human subjects in the oldest literature. Nonetheless, public awareness of ethical and legal problems posed by medical research involving human subjects did not coalesce until the post-World War II trials at Nuremberg, where more than 25 “dedicated and honored medical men” were accused of having committed war crimes of a medical nature against involuntary human subjects. According to Telford Taylor, chief prosecutor at the Nuremberg Military Tribunals, the defendants’ “advances” in medicine were confined to the field of “thanatology,” the science of death. Of the 25 defendants, only 7 were acquitted; 9 were sentenced to prison, and the remaining 9 were sentenced to death.

After it became known, through these trials, what the Nazis had done under the guise of medical and scientific

research, there developed what has been referred to as the Nuremberg Code (see Appendix 18-1). The Nuremberg Code was the forerunner of the subsequent codes and guidelines that were adopted by different agencies and organizations in the ensuing decades. It addressed the question of what constitutes valid, legal, moral, and ethical experimentation. However, it did not explicitly deal with the subject of children. Probably nobody at that time thought it would be necessary. But it did deal with the subjects of consent, the voluntariness of consent, the right of a patient to withdraw if he or she wished, and the basic question of doing things in conformance with proper medical standards and safeguards. The Nuremberg Code prompted more interest and concern in these problems.

Declaration of Helsinki

In 1964, the World Medical Association promulgated a code that came to be known as the Declaration of Helsinki (Appendix 18-2). The Declaration of Helsinki was, in essence, adopted and given the imprimatur of the American Medical Association in November 1966. The AMA referred to it as *Ethical Guidelines for Clinical Investigation*. Earlier in 1966, the Public Health Service of the United States had issued some guidelines that were subsequently revised later in the year. Recently, the DHHS has also been attempting to draft some guidelines.

Children as Subjects

Apart from international codes, there have also been a number of court decisions in this country bearing on the questions of ethical experimentation and informed consent, particularly in reference to children. Under existing case law, although it is often forgotten, a parent cannot say to a neighbor or friend or a research team of scientists: “Take one of my children and if you wish to do something that is not going to be beneficial or advantageous to him, go ahead and do it anyway because I, the parent, give you permission.” A parent cannot legally do that. We are a nation governed by laws, and the law is clear in this regard. Neither parents, legal guardians, administrators of homes and hospitals for retarded children, government officials, nor university research teams, individually or collectively, are empowered to ignore or circumvent a basic and important concept of Anglo-American law, namely, that you cannot commit an assault and battery on another human being.

In 1944 the U.S. Supreme Court, in *Prince v. Massachusetts*, stated: “Parents may be free to become martyrs themselves, but it does not follow they are free in identical circumstances to make martyrs of their children before they reach the age of full and legal discretion when they can make that choice for themselves.”⁶ *Prince v. Massachusetts* has never been overruled by a subsequent U.S. Supreme Court decision.

Some people refer to an earlier case in Mississippi, *Bonner v. Moran*,⁷ in which a 15-year-old boy was apparently conned by an aunt into going to a hospital to give skin

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transplants for his cousin, the aunt's son, who had been burned. The boy did, but there was some question as to whether the mother of the donor really knew the facts of the treatment and the risks to her own son. She subsequently brought legal action against the hospital, but the court was far less than unequivocal in giving its opinion as to whether or not the mother could recover in damages. That case is sometimes quoted in defense of experimentation without consent, but the circumstances and facts were very peculiar and special for that case. There was good evidence to indicate that although the consent was not originally obtained from the mother, the procedure and risks were subsequently made known to her because the son went back repeatedly for more skin transplants and for treatment.

In any event, until such time as the Supreme Court definitively rules otherwise, or until the U.S. Congress enacts contrary legislation, the law prohibits experimentation on humans without informed consent. Furthermore, it is illegal to conduct experiments that are tantamount to assault and battery.

Rather than considering this subject as an academic or legalistic question, one should consider some specific examples. During and after World War II, physicians developed awareness that excessive oxygen could produce a condition known as retrolental fibroplasia (RLF) in children, which leads to blindness. In most instances, this condition was observed in premature infants who had been placed in an excessive quantity of oxygen. So it was decided to conduct an experiment, with no real informed consent from the parents and obviously not from the babies, in which one group of babies was placed in an excessive quantity of oxygen and another in an atmosphere with a much reduced amount of oxygen. Six of the babies became totally and permanently blind.⁸

Consider another experiment. Red blood cells are broken down in the liver of the human body. In some infants the liver fails to excrete bilirubin, the major degradation product in the breakdown of erythrocytes. Furthermore, in infants, unlike adults, bilirubin has the capacity to pass the blood-brain barrier and to precipitate in the brain a dangerous condition that can lead to permanent brain damage and, in some instances, death. Research had previously established that a chemical found in human breast milk seemed to alter, revise, or impede the biochemical processes within the liver by which bilirubin was normally excreted. The researchers wanted to see if that was also true in vivo. Therefore they prepared an experiment in which this chemical compound was given in significant dosages to babies. The experiment confirmed that there was a rather fast, quite substantial buildup of the bilirubin level in these children, with the possibility of subtle brain damage as a result. There was permanent brain damage in some of those children.⁹

In another situation, at Children's Hospital in Boston, there was great interest in the natural defense mechanisms of the human host in reaction to an organ transplant. Boston is a leader in the medical field, and Children's Hospital is one of its finest health care facilities. Yet here is

what they did in designing and conducting an experiment. Without obtaining any kind of an informed consent (in most of the cases, it was questionable whether they even obtained a basic consent, that is, the traditional kind that sufficed before the concept of informed consent developed in the medical malpractice field in the early 1960s), they performed a thymectomy on babies and youngsters who were undergoing surgery for various cardiovascular problems. They took out the thymus gland, which is known to play a role in the body's immunological defense mechanisms. They then attached a piece of skin on these children from unrelated individuals to determine what the bodily reaction of the thymectomized child would be to the skin that had been placed on his or her body. This was very interesting and important research. But was there any possible danger to the thymectomized youngster? And did not the parents, at the very least, have the right to have an intelligent, informed discussion from the physicians about what the possibilities of subsequent damage might be?

At Willowbrook State Hospital, Staten Island, New York, some researchers wanted more information about hepatitis in an epidemiological environment. They reasoned that in such an institution, the patients might get hepatitis anyway at some time in the future. So they took retarded youngsters, with no informed consent and most probably without any kind of consent, and gave them orally a fecal extract containing hepatitis virus to see what the medical results would be. They also did a supplemental clinical investigation in which they directly injected hepatitis virus into still other retarded children.¹⁰

Here is yet another example. Linoleic acid is known to be an essential nutrient, the deprivation of which has been shown to produce serious problems in animals. The effects of its deficiency have also been noted clinically in children. Nevertheless, at the University of Texas at Galveston, from 1956 to 1962, 445 babies, without informed consent, were deprived of linoleic acid. Seven of those children are known to have died of conditions directly related to the deprivation of this essential nutrient. Many others became seriously ill with a variety of dermatological conditions, pneumonia, and other problems.¹¹

In Pennsylvania in 1973 there was an exposé of another deplorable situation at the Hamburg State Home and Hospital in Berks County. It was shown that retarded children, with no consent of any kind obtained from their parents, not even informed consent, were injected with a meningitis vaccine. The vaccine had not been approved by the FDA and was not on the clinical market, but it was given to these children nevertheless. Said the researchers at a later date, "We thought that the administrator of the hospital was the legal guardian for these children for all purposes, and he told us it was all right to go ahead and do it." After hearings before the Department of Health, Education, and Welfare and the Department of Justice in Harrisburg, the Commonwealth of Pennsylvania put an end to that experiment and to other similar experiments that had not received approval or that had not been reviewed by appropriate agencies and authorities.

Ethics and Fetal Research

For years, scientists who wanted to do research involving human embryos and fetuses have found themselves in a catch-22. They could do their work with impunity and receive federal funds for it, so long as an ethics advisory board approved their proposals. The catch is that the board does not exist, and has not existed for nearly a decade.

The research on fetuses has thrived, although it has remained in the ethical shadows. The testing of new methods for prenatal diagnosis or in vitro fertilization, among other things, has been financed with profits from infertility treatments and standard prenatal diagnosis. The research at issue involves either embryos, including those created by in vitro fertilization, or intact fetuses obtained from miscarriage or hysterotomy, an early form of cesarean birth.

The ethics board was originally created in 1974, partly in response to fetal research in the 1960s and 1970s, which took place without federal restrictions. Although many experiments were unremarkable, some were profoundly objectionable. In the early 1960s scientists at one university immersed 15 fetuses obtained from abortions in a salt solution to see whether they could absorb oxygen through the skin. One lived 22 hours. An experiment at another university examined the fetal brain's metabolism of glucose; the researchers used heads severed from live human fetuses.

At the same time, more researchers were working on in vitro fertilization, in which eggs removed from a woman's body are mixed with sperm and one or more resulting embryos are implanted in her uterus. To develop the method, research with human embryos was required. After the U.S. Supreme Court struck down most restrictions on abortion in 1973, Congress appointed a commission for the protection of human subjects and asked it to rule on fetal research.

The commission ruled that fetal research was permissible. But it also ruled that no one could subject a fetus to be aborted to any more risk than one that was to be carried to term. It was an extremely restrictive policy, the commission recognized, but there was an out: an advisory board would decide, on a case-by-case basis, when this "minimal risk standard" could be waived. However, the ethics board was dissolved before it had a chance to rule on any case, and the DHHS has declined to appoint a new one.

Adult Experimentation

Of course, there have been similar problems in experiments with adults. Some of these have been widely publicized.

Between February 1945 and July 1956 at the Brooklyn Jewish Chronic Disease Hospital, injections of cancer cells were given to elderly hospital patients, with no actual or meaningful permission having been obtained from them or their families. Malignant tumor cells were injected directly into the veins of elderly people suffering from advanced parkinsonism, multiple sclerosis, and other kinds of severe neurological disorders. The principal researcher in that case was Dr. Chester M. Southam from Sloan-Kettering Institute,

who subsequently had his license suspended temporarily by the state of New York. When asked why he had not injected himself in the experiments since he had said that it was quite safe, he replied: "Well, you know there is always a possibility of some harm and let's face it, there simply are not too many cancer researchers around."¹²

The infamous Tuskegee syphilis study, initiated and monitored by the U.S. Public Health Service, was not terminated until 1972. In Macon County, Alabama, some 400 black men with syphilis, of a total of 600 subjects in the study, were deliberately deprived of treatment from 1932 on, purportedly to study the effects of allowing the disease to take its natural course. At least 28 of these men, and possibly as many as 107, are known to have died as a result of the disease. It has been argued that in 1932, the cure for syphilis was ineffective and sometimes worse than the disease, but certainly this was not true in the 1950s, 1960s, and 1970s, during which time the "experiment was continued and regularly reported."

This incredible experiment was thoroughly evaluated and criticized extensively by a specially appointed committee. In the Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel, Department of Health, Education, and Welfare (Washington, D.C., 1973), one of the panelists, Jay Katz, MD, stated:

In conclusion, I note sadly that the medical profession, through its national association, its many individual societies, and its journals, has on the whole not reacted to this (Tuskegee Syphilis) study except by ignoring it. One lengthy editorial appeared in the October 1972 issue of the Southern Medical Journal which exonerated the study and chastised the "irresponsible press" for bringing it to public attention. When will we take seriously our responsibilities, particularly to the disadvantaged in our midst who so consistently throughout history have been the first to be selected for human research?¹³

In April 1997, President Clinton offered a formal apology to the families and the eight remaining survivors of the Tuskegee syphilis experiments, identifying the experiments as a "blight on the American record." In addition, the U.S. government has paid a total of \$10 million in an effort to compensate the victims and family members for the incident.

Geriatric Research

In Philadelphia in 1964 and 1965, 13 elderly nursing home patients died as a direct result of drug experiments conducted on behalf of one of the large pharmaceutical manufacturers. The experiment had two stages. One drug was used to induce nervous system disorders and then another was introduced to control them. Although the Food and Drug Administration (FDA) was aware of the experiment and prepared a report on it in 1967, the report was withheld for many years and not released until the *Philadelphia Bulletin* obtained it under the Freedom of Information Act.¹⁴ There was much doubt as to whether informed consent had been obtained in this experiment.

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Reporting on his observations from 50 field inspections by the FDA in 1972, Dr. Alan B. Listook, Medical Officer in the FDA's Bureau of New Drugs, stated the following:

We have seen consent forms of senile patients signed "X-(her mark)" and have found others executed posthumously. On one occasion, where the obtainment of consent was the major reason for the FDA to conduct an investigation, we visited the subjects of the study, and discussed their understanding of the document they signed. It turned out that the women were not fully aware that they were participating in an experiment of any kind. They were not aware that they had been given a medication which had not been proven to be safe and effective.¹⁵

More than 3 years later, exactly the same kind of problem was reported again in a study conducted at a "distinguished university hospital and research center," not otherwise identified.¹⁶ According to this later study, of 51 pregnant women who had signed a consent form in an experiment on the effects of a new labor-inducing drug, 20 did not know they were the subjects of research, even after the drug had been administered, and did not learn of it until they were interviewed by the follow-up investigator. Most of the 51 women had not been aware that any hazards were involved and had been informed only that a "new" drug was being tested, and not that it was an experimental drug. Yet, their own private physicians referred many of these women to the hospital for study. Whether the private physicians were aware of the true nature of the experiment is not stated, but in any case, it is clear that having one's own physician is no safeguard in these matters.

The whole area of new drug investigations is a jungle from the standpoint of research ethics, quite apart from the specific question of informed consent. Again, a quote from the remarks of Dr. Listook is appropriate:

We have had examples of physicians submitting case reports recording the administration to subjects of much more new drug substance than was available to them. We have had police departments report the finding of case lots of investigational drugs by the roadside in trashcans.

On occasion we find records of months of treatment on an index card. We have looked at records of patients reported as having been treated for intractable angina and found no mention of heart disease, no electrocardiograms, and no noted treatment. We frequently find that laboratory results reported to the FDA cannot be substantiated by records in the physician's office or by contact with the clinical laboratory where the work was said to have been done.

In institutions such as mental hospitals or geriatric facilities, we often see therapy prescribed that makes a study impossible to interpret and thus invalid. Major tranquilizers are given during the study of psychoactive compounds; vasodilators are given during the study of drugs being evaluated for the same purpose. Investigational drugs are discontinued without the investigator's knowledge, and adverse reactions go unreported because of lack of communication or lack of awareness on the part of the ward staff.

I could quote horror stories about paroled inmates and discharged mental patients reported as being treated in situ for weeks after their release, of therapy duration and dosage and hospital clinical courses that did not approximate those reported....

We have come across individuals who were able to care for patients in their offices while they were on extended European vacations. Others, while not quite so versatile, have been able to come up with large patient populations for the treatment of widely divergent types of disease. We have the internist who does a study on an antiobesity drug and a few months later is found to be using the same patients in the study of an antihypertensive agent. In our review of the case reports we find no hypertension reported in the first study.¹⁷

In view of such findings, it would seem that these researchers were not being meticulous about getting informed consent. Yet it is from this very area—the development of new drugs—that we most often hear the arguments being advanced that research must not be fettered and that those of us who insist on adhering to the law are obstructing scientific progress.

BENEFIT VERSUS RISK RULE

In situations in which there is no potential therapeutic benefit to the subjects, it is customary to distinguish four levels of human experimentation:¹⁸

1. Benefit is reasonably believed to exceed the risk to the patient, and the study involves a patient who consents to this low-risk diagnostic or therapeutic procedure by coming to the physician. The patient is given information and shows that it is understood. He or she is not a subject, but rather a patient, and the needs of the patient come before any effort to gain knowledge. There is no legal problem in such a situation, except, of course, the one that physicians must contend with in all therapeutic situations, namely, obtaining an informed consent.
2. Benefit is reasonably considered to at least equal the risk, if not possibly exceed it. The patient is a volunteer. He or she may be a subject also, but if so, the relationship between the volunteer and the physician is made quite clear. At this level, we have a controlled experiment, but everyone knows what is happening, and there is definitely a strong possibility, in fact a probability, that the project may be of some therapeutic benefit to the patient.
3. The risk exceeds the benefit to the patient, but the risk is balanced by possible benefit to society. Here, the highest possible degree of informed consent is essential. Experiments in this field are still permissible, including those on children, provided the highest degree of informed consent is obtained from the patient or subject.
4. Risk exceeds benefit. The individual is either both the subject and the patient or purely just a subject. Consent from the individual either has not been obtained or has been obtained through deceit, the force of authority, or other improper means.

Usually, the last category is the issue. Because medical research trials commonly require that a convenient, stable subject population be monitored over weeks or months rather than days or hours, the medical scientist naturally turns to “captive” groups whose availability can be controlled. These groups include the following:

- Hospitalized or institutionalized patients
- Children
- Mentally abnormal persons
- Prisoners
- Persons under discipline (armed forces and police force)
- Laboratory assistants and medical students

In all these groups, factors are present that tend to make the individuals involved susceptible to pressures or influences that induce them to give their consent to experimentation. For example, prisoners hope for probation, soldiers for promotion, and students for higher grades. Use of such groups for medical experimentation is not invariably improper, but experiments conducted on such persons raise the question as to whether the consent obtained, if any, may have been the result of coercion or other influences that would place the project in Category 4.

In recent years, medical research in prisons has been prohibited in many states. The National Commission on Protection of Subjects has recently released its recommendations on allowable research on prison inmates. They are very stringent recommendations that would virtually eliminate such research from U.S. prisons.

This problem was particularly relevant in the case of children as experimental subjects. In the Hamburg State Home and Hospital case mentioned earlier, studies were initially undertaken without an informed consent. Indeed, there was no consent obtained at all. The physician in charge of the study “thought” that the administrator of the hospital was the legal guardian of these mentally retarded children!

Some time later, the physicians did send some kind of generalized consent form to the parents, and some of these were signed and returned. However, there is no question at all from a legal standpoint that this kind of consent is not a valid informed consent and would not hold up in the courts of Pennsylvania, even if the parents had been the subjects.

What if the pharmaceutical company involved with that meningitis vaccine believed it was essential to learn what the effects of that vaccine on children would be? Could that company, with its thousands of employees in this country and abroad, including all their research teams and top administrators, have gone to their employees and asked for volunteers?

Inasmuch as the meningitis vaccine that was being tested was of no direct therapeutic benefit to the children who were to receive it, even the parents within the pharmaceutical company could not have given a legal consent for their own children. Such experimentation would be considered assault and battery. And no one—even a parent—can give legal consent to have assault and battery committed on another human being.

Every one of these experiments on children involved subjects who did not have the necessary intellectual capacity to give a truly informed consent. They may have

been legally adjudicated *non compos mentis*, or perhaps they merely had been socially and economically deprived to an extreme degree, but invariably they were incapable of giving an informed consent.

It is imperative that everyone in positions of authority within government, medical institutions, health care facilities, and custodial homes appreciate that no matter what the altruistic and projected humanitarian aspects of medical research may be, human beings cannot be subjected to medical experimentation without a proper informed consent having been obtained from them. In the case of minors (especially retarded children), elderly or senile persons who are suffering from serious diseases and do not have a full grasp of their mental faculties, or people who are imprisoned or otherwise subject to coercion, very serious moral and ethical principles must be carefully considered by the research team before undertaking any experiments that place the subjects at risk.

No legitimate reason or justification exists for further delay or governmental procrastination on this subject. There is absolutely no question from a legal standpoint that experiments of this nature are in violation of the law and are against basic concepts of medical morality and ethics. Physicians and scientists, as well as governmental officials in charge of hospitals, homes, and institutions of various kinds, should realize that the civil and criminal laws pertain to them, also.

CRIMINAL AND CIVIL LIABILITY

Although the *Hyman v. Brooklyn Jewish Chronic Disease Hosp.*¹⁹ case makes mention of the “experimentation” question, it is of little value in ascertaining the legal guidelines for experimentation. The court confined itself to the narrow issue of whether a director of a membership corporation has a right to inspect the corporate records. In this case, the court held that possible corporate liability gives the director the right to inspection. As to the liability for the experimentation, the court ventures no unnecessary opinion. Assuming that experimentation is carried on under approved scientific techniques, it may be instructive to consider possible liabilities, viewing a researcher–subject relationship under criminal, tort, and contract law, recognizing that the categories are not always mutually exclusive.

Criminal liability, in the absence of statute, will attach when there is an intended harm constituting homicide or mayhem, or an unintended harm resulting from negligence by commission or omission of such character that it extends beyond ordinary negligence and is considered culpable negligence. If a volunteer dies during or as a result of “experimentation,” the criminal liability, if any, would be for homicide—murder or manslaughter.

The Pennsylvania statute (typical of most states) defines the crime of murder as follows:

All murder which shall be perpetrated by means of poison, or by lying in wait, or any other kind of willful, deliberate and premeditated killing or which shall be committed in the perpetration of, or attempting to perpetrate any arson, rape, robbery, burglary, or kidnapping shall be

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murder in the first degree. All other kinds of murder shall be murder in the second degree. The jury before whom any person indicted for murder shall be tried, shall, if they find such person guilty thereof, ascertain in their verdict whether the person is guilty of murder of the first or second degree.

Murder is the unlawful killing of another with malice aforethought, express or implied.²⁰ It is highly unlikely that a properly conceived and reliably approved research project undertaken by a competent specialist would qualify as an act of murder. If the research provides a strong possibility of death or severe injury, known in advance to the scientist in charge, malice may perhaps be implied. The statute provides a further definition: "Manslaughter, however, may be found without malice. Where the practice is such as to constitute a gross ignorance or culpable negligence or such a complete disregard of life or health, the courts have found voluntary or involuntary manslaughter."

Although no case involving experimentation that resulted in a conviction for voluntary or involuntary manslaughter can be found, it has been established that where such charges are brought, consent does not usually constitute a defense to criminal liability.

Professor Kidd of the University of California School of Law raises the question with specific reference to experimentation:

How far can one consent to serious injury to himself? The analogies are not close. Abortion, except for therapeutic reasons, is a crime, and the consent of the woman is no defense for the doctor. A person can not legally consent to his own death; it is murder by the person who kills him... A person may not consent to serious injury amounting to a maim.²¹

In general, criminal negligence in a physician (experimenter) exists when the physician exhibits gross lack of competency, inattention, or wanton indifference to the patient's safety, either through gross ignorance or lack of skill. It is assumed that the same standards would be applicable to scientists engaging in human experiments: "In case of permanent injury or disease rather than death, the possible criminal charge would be mayhem. This crime at common law and by statute generally is also founded on malice and as such would be governed by the same considerations alluded to above."²²

Basic to the law of torts, a second area of consideration as to the legal consequences of experimentation is the right of the individual to "freedom from bodily harm," so that any unauthorized invasion, or even threat, to the person constitutes grounds for liability. Consent is usually achieved through the use of a release, either written or oral, allowing the patient's person to be physically handled. In the normal physician-patient relationship, there usually is ample basis for finding informed agreement on the part of the patient for ordinary procedures by virtue of the recognized relationship between the parties. It is assumed that the physician is acting in good faith for the personal benefit of the patient who, by seeking professional assistance, may be assumed to consent to the treatment and

diagnoses given. In an experimental situation, the inference of consent is not so easily drawn, and there seems to be more of a need for formal consent:

There is scant legal authority on this problem [but]... abundant expert testimony is usually available to show that subjecting a patient to experimentation without disclosure and consent is contrary to the customs of surgeons and thus negligent, even though there may be no technical slip in actual performance of the experiment.²³

Specific to the problem of experimentation, tort liability may arise in cases of nontherapeutic, unnecessary, and legally questionable procedures involving criminal liability and public policy. For instance, in situations such as abortion and euthanasia, cases may be found in which, despite consent, the physician was held to tort liability. In none of these areas has there occurred experimentation by a scientist on humans for nontherapeutic reasons. In some states, a contract action is permitted on the theory breach of an implied agreement to treat with proper care and skill; the essence of the research contract lies in the complete understanding of the parties:

The medical research procedure by definition and by nature is a deviation from normal practice, even though all the specific elements involved may be well established, simply because medical practice ordinarily does not encompass employment of human beings primarily for the advancement of knowledge. There is no implicit understanding that conventional methods will be used and that the patient will be released as soon as his condition warrants. Consequently, the researcher has a more specific responsibility for full disclosure of his purpose, method, and probable consequences. Achieving a meeting of the minds is a far more critical element in the research contract.²⁴

Assuming there is a complete understanding, a research contract will probably provide a defense against liability in a reasonable execution of the contract obligation or performance of the experiment. However, such a contract is unlikely to serve as a complete bar to an allegation of negligence. The patient's own performance under the contract will not be the subject of a decree for specific performance by a court of equity as they are for "personal services."

In conclusion, it would seem that medical practice, generally conceived to be diagnosis, treatment, and care, is governed by state statute and supporting administrative licensing and regulatory bodies. Medical research experimentation on human subjects would appear to be outside the scope of these rules:

Case law, insofar as it appears to recognize medically related activity, generally characterizes such research as experimentation and holds it to be outside legitimate medical practice. Reported cases have not yet considered modern controlled medical research as such, and have not yet established limits within which human research may be pursued. Cases which have involved conduct labeled experimentation have been decided basically on issues of disclosure or consent, negligence, lack of qualification, improper

*activity (quack procedures, medicines or devices) or unlicensed practice of medicine usually arising in cases of departure from accepted diagnosis, therapy or other practice.*²⁵

Despite the Nuremberg Code, the Declaration of Helsinki, the AMA Ethical Guidelines, and numerous other declarations of similar import, apparently many physicians, scientists, and governmental officials still think that because humane benefits may be derived from these experiments in later years, anything is justified today, particularly if the groups being used as guinea pigs consist of retarded children, senile persons, prisoners, or other unfortunate groups with various physical, psychological, or economic handicaps.

A special national commission has been proposed to review all the various facets of this sensitive, important, and complex matter. This group is to have a dual purpose: first, to establish basic principles and guidelines that would be uniformly applicable in all proposed projects involving human experimentation; and second, to consider, evaluate, and approve each new research proposal involving any kind of experimentation on humans. Legislation would have to be enacted to require that all such proposals be submitted and approved before being implemented. Membership in such a commission should necessarily be broad, extending beyond the medical and scientific professions, and all its decisions and records should be subject to public disclosure.

In 1982 the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research completed a 2-year examination of federal rules and procedures for conducting research with human subjects. The commission concluded that most government supervisory agencies have insufficient data on compliance, and a review of a few well-documented (and widely reported) cases of misconduct on the part of research scientists showed that government oversight can be improved. However, the public must keep a balanced perspective.

Because successful therapies for humans can be established only by tests on human subjects, medical progress depends on the participation of volunteers in research to test new therapies. The prerequisites for such experimentation include at least the following: a reasonable theoretical base for the belief that therapy may be useful; preliminary tests on nonhuman subjects; a careful weighing of the possible benefits and expected risks of the experimental therapy, as well as an assessment of the available standard therapies; and the genuine voluntary consent of the human subject.

The presidential commission's study demonstrates that federally funded institutions need well-defined procedures for responding to reports of misconduct, ranging from falsified data on patients/subjects' charts to conducting studies with drugs not cleared for tests on humans. Some procedures should protect from reprisal those who report their concern (the so-called whistle-blowers). Such procedures also should protect scientists accused of misconduct from publicity and loss of federal funds, at least until a preliminary finding is made that the accusations have some basis in fact. For the sake of all concerned, the institutional response

should be prompt, thorough, and fair. The 23 governmental agencies and institutions involved in research on human subjects (e.g., the DHHS, the National Science Foundation) need clearly defined standards for investigations and sanctions.

INNOVATIVE THERAPY

To understand the concept of innovative therapy, it is useful to consider first the activities referred to as standard medical practice. The National Commission defined standard practice for the Protection of Human Subjects of Biomedical and Behavioral Research as "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatments, or therapy to particular individuals."²⁶

The commission was established by Congress.²⁷ Its purpose was to conduct a comprehensive investigation and study to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research, evaluate existing guidelines for the protection of human subjects, and make appropriate recommendations to the Secretary of Health, Education, and Welfare concerning further steps, if any, to be taken.

The commission identified innovative therapies as a class of procedures that were "designed solely to enhance the well-being of an individual patient or client," but had not been tested sufficiently to meet the standard of having "a reasonable expectation of success." Innovative therapies have been defined as activities "ordinarily conducted... with either pure practice intent or with varying degrees of mixed research and practice intent that have been sufficiently tested to meet standards for acceptance or approval."

Dale H. Cowan²⁸ has stated that the difference between innovative and standard practices may be simply the difference between a beginning and an advanced level of the practice of medicine. However, as noted by R. J. Levine, in referring to the Belmont Report,²⁹ the attribute that defines innovative therapies is the "lack of suitable validation of [their] safety and efficacy," rather than their "novelty." A practice might not be validated because there is (1) a lack of sufficient testing to certify its safety and efficacy for an intended class of patients or (2) evidence that previously held assumptions about its safety and efficacy should be questioned.

In general, practices or therapies that are standard or accepted have risks and benefits that are known. Additionally, some basis exists for thinking that the benefits outweigh the risks. By contrast, the potential benefits and risks of innovative therapies are less well known and predictable. Consequently, their use exposes patients to a greater likelihood that the balance of benefits and risks may be unfavorable due either to the therapies being ineffective or entailing greater, possibly unknown, risks. Thus standard medical practice can be distinguished from innovative therapies on the basis of the extent of knowledge that exists regarding their likely risks and benefits.

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The commission described experimentation or research as *an activity designed to test a hypothesis, permit conclusions to be drawn and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.*³⁰

Levine defined research involving humans as

*any manipulation, observation, or other study of a human being—or of anything related to that human being that might subsequently result in manipulation of that human being—done with the intent of developing new knowledge and which differs in any way from customary medical (or other professional) practice.*³¹

The distinction between innovative therapy and experimentation can be drawn by focusing on the four levels of research listed previously. Like research, innovative therapy generally represents a departure from standard medical practice.

Federal regulations require that all research involving human subjects conducted by the DHHS, or funded in whole or in part by a grant, contract, cooperative agreement, or fellowship from DHHS, be reviewed by an institutional review board (IRB) established at each institution in which the research is to be conducted. The regulations define research as “a systematic investigation designed to develop or contribute to generalizable knowledge.” The regulations further specify minimum requirements for the composition of IRBs and require that each institution engaged in research covered by the regulations must file a written assurance to the secretary of DHHS that “it will comply with the requirements set forth in [the] regulations.”

To approve research by the regulations, IRBs must determine that a number of requirements are satisfied:

1. Risks to the subjects are minimized.
2. Risks to the subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
3. Selection of the subjects is equitable.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative.
5. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of the subjects.

RADIATION EXPERIMENTS

In December 1993, the U.S. Department of Energy publicly disclosed that for the preceding 6 years it had ignored clear evidence of extensive illegal experiments conducted by distinguished medical scientists in the nation's nuclear weapons industry that took place over three decades after World War II, in which various groups of civilians were exposed to radiation in concentrations far above levels that are considered safe at this time. These experiments, conducted at government laboratories and prominent

medical research institutions, involved injecting patients with dangerous radioactive substances, such as plutonium, or exposing them to powerful radiation beams. Allegedly, this work was undertaken to determine what the effect of radiation would be on soldiers and civilians if a global atomic war occurred. The experiments dealing with testing radiation on humans are listed in Table 18-1.

Other experiments of a similar nature took place at a state school in Fernald, Massachusetts, from 1946 to 1956, in which as many as 125 mentally retarded teenage boys were given radioactive iron and calcium in their breakfast cereal. Consent forms sent to the parents indicated that this study was intended to help researchers better understand human metabolism and nutritional needs. No mention was made that radioactive elements would be used.

Records from the Massachusetts Institute of Technology indicate that 23 pregnant women at the Boston Lying-In Hospital (now part of Brigham and Women's Hospital) were injected with radioactive iron in the early 1950s to allow researchers to study maternal-fetal circulation. In yet another experiment conducted around the same time at Massachusetts General Hospital, patients were given radioactive iodine to study thyroid function and body metabolism, even though the researchers acknowledged they did not know what the long-term effects would be.

Altogether, as of early 1994, U.S. government officials acknowledged that more than 30 experiments involving the use of radioactive materials or radiation, in which the subjects or their parents and guardians were not apprised of the true nature of the studies and therefore could not have given legally acceptable informed consent, took place during a three-decade period beginning in 1946. There may well have been more that are yet to be uncovered.

The government had previously resisted paying compensation to any of these individuals. However, from October 1991 to May 1993, the government spent \$47.1 million to reimburse the legal expenses of the private corporations that operated its nuclear weapons plants. The then Energy Secretary, Hazel O'Leary, proclaimed her definite intention to obtain compensation for all victims of these unethical experiments.

It is important to note that the General Accounting Office first disclosed some of these tests in 1986 in a report to Congress. However, when Representative Edward J. Markey of Massachusetts, chair of the congressional committee that reviewed this report, asked the government for more information and urged full disclosure of all such experiments, he was firmly and repeatedly rebuffed by both the Reagan and Bush administrations.

A senior official of the Atomic Energy Commission, in a 1950 memorandum to one of the prominent physician-scientists involved with some radiation experiments in the Boston area, observed that these medical experiments might have “a little of the Buchenwald touch.” Thus it would appear that both the government officials and medical researchers who planned and conducted these radiation experiments were aware that these studies violated the 1947 Nuremberg Code, which was adopted after the Nazi war crimes trials and is regarded as the universal standard for experiments involving human beings.

Location(s)	Date	Those Affected	Experiments
Vanderbilt University, Nashville	Late 1940s	About 800 pregnant women	Subjects were studied to determine the effect of radioactive iron on fetal development. A follow-up study of children born to the women found a higher-than-normal cancer rate.
Oak Ridge National Laboratory, Oak Ridge, Tennessee	Mid-1970s	Nearly 200 patients with leukemia and other causes	Subjects were exposed to high levels of radiation. The experiments ended after a 1974 government investigation.
University of Rochester, Oak Ridge Laboratory, University of Chicago, and the University of California Hospital in San Francisco	1945–1947	18 people	Subjects were injected with high concentrations of plutonium, apparently without their informed consent. Many patients were chosen because medical specialists believed they suffered life-threatening illnesses.
Oregon State Prison	1963–1971	67 inmates	Prisoners' testicles were exposed to x-rays to help researchers understand the effects of radiation on production and function of sperm. The inmates signed consent statements indicating that they were aware of some of the risks, but the statements did not mention that radiation could cause cancer.
Washington State Prison	1963–1970	64 inmates	A similar study subjected prisoners to high levels of radiation. The purpose was to determine the minimum dose that would cause healthy men to become temporarily sterile.
Columbia University and Montefiore Hospital in the Bronx	Late 1950s	12 terminally ill cancer patients	Subjects were injected with concentrations of radioactive calcium and strontium-85, another radioactive substance, to measure the rate at which radioactive substances were absorbed into various human tissues.

From The Department of Energy, the Atomic Energy Commission, and Congress.

Table 18-1 Radiation experiments on humans

Currently the U.S. government is aggressively pursuing settlement with the subjects of the Defense Department's radiation experiments in which the victims were unknowingly injected with uranium or plutonium. The federal government indicates that 16 of the 18 victims of the experiments have received a total of \$6.5 million in compensation.

In addition, the Clinton administration sought to expand the current 1990 Radiation Exposure Compensation Act to include the family members of 600 now deceased miners who worked in government-operated uranium mines. The proposed expansion resulted from a presidential advisory committee finding that the high level of exposure to radon experienced by the miners between 1947 and 1991 was due to the government's failure to adequately ventilate the mines.

QUESTIONABLE HUMAN RESEARCH AND EXPERIMENTATION PRACTICES

In addition to the large number of alleged illegal experiments involving radiation and radioactive compounds, several other highly controversial situations have been brought to light in the past few years involving research projects and experimentation, in which informed consent, official and academic guidelines, and other applicable legal and ethical considerations were ignored by the physicians, scientists, and officials in charge of those studies.

The Medical University of South Carolina was accused of testing pregnant women for illicit drug use without their consent and then transmitting that information to local law enforcement officials. This drug testing program was apparently adopted as a means of forcing drug-addicted women who were pregnant to stop using drugs by threatening them with jail if they refused to cooperate with the hospital's regimen of prenatal visits and also attend an established drug treatment program. Almost all the women in the program were African Americans, and several of them were actually arrested and prosecuted for illicit drug use as a result of the disclosure of this information by the university hospital to the police. Dr. Charles R. McCarthy, formerly chief of the Office of Protection of Research Risks at the National Institutes of Health, concluded that this project "fits the definition of an experiment." He indicated that federal rules regarding human experimentation require that subjects give informed consent before being made part of an experiment, and that the patient has the right to refuse to participate and still be given appropriate and necessary medical treatment.

The *Boston Globe* recently reported that the infamous Timothy Leary, the 1960s drug guru, gave inmates at the Concord State Prison in Massachusetts doses of psilocybin, a powerful hallucinogenic drug, without their knowledge or consent. This compound can produce hallucinations, perception distortion, and psychosis and is considered to be psychologically addictive. These tests took place in the 1960s when Leary was a faculty member at Harvard University.

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He was eventually fired from his position at the prison by state officials, although not until these illegal tests had been under way for many years.

In late 1993 a rash of international articles reported that postmenopausal women were being impregnated with donated eggs fertilized with their husbands' sperm. In England, a 59-year-old woman gave birth to twins, and a 61-year-old Italian woman also gave birth after such a procedure. Numerous cases of a similar nature were also reported in France. Harvested eggs from aborted female fetuses were permitted to mature and then, via artificial insemination, were used to impregnate these elderly women. This experimental process, which had first been utilized in mice by Dr. Roger Gosden, a research scientist in Edinburgh, Scotland, has raised many ethical questions and has precipitated specific legislation in France and elsewhere that would ban the use of such a technique in postmenopausal women.

In the summer of 1993, two French physicians were charged with manslaughter in connection with the death of a child, who died after contracting Creutzfeldt-Jakob disease, a rare viral illness that attacks the brain after a long incubation period. Several other children were thought to have been afflicted also, but had not yet died. This disease, which is incurable and leads to rapid dementia and death, developed after the administration of pituitary gland extracts given to children who suffered from dwarfism. The pituitary glands had been acquired from 1983 to 1988 from corpses in Bulgaria and Hungary. Many of the deceased donors had been patients in psychiatric hospitals and infectious wards.

A current controversy with fascinating legal and ethical overtones is that of human cloning. Federally sponsored research dealing with in vitro fertilization (IVF) has been held in abeyance since 1980, but in 1993 the Clinton administration attempted to gain federal support for research on IVF and the resultant human embryos. The NIH Revitalization Act of 1993 nullified the requirement for ethics board scrutiny of IVF research proposals.

A scientific debate has yet to resolve the question of exactly what a clone is. Dr. Robert Stillman of George Washington University Medical Center reported his findings at a meeting in October 1993 of the American Fertilization Society. He claimed to have cloned human embryos, splitting single embryos into identical twins or triplets. Because human sperm can be frozen and used at a later date, it could be possible for parents to have a child, and years later use a cloned, frozen embryo to give birth to an identical twin, possibly as an organ donor for the older child. A technique has already been developed for making identical twins in animals (e.g., cattle) by dividing the embryo one or more times and letting the new clusters of cells develop into two genetically identical organisms.

In 1993 an internationally known medical researcher, Dr. Peter Wiernik, publicly admitted his role in having provided illegal injections of an experimental drug for 16 brain tumor patients in 1987, using them as human guinea pigs. Wiernik acknowledged a 5-year cover-up in an agreement worked out with federal prosecutors earlier in 1993, whereby he was demoted and reprimanded, but not

subjected to criminal prosecution. The patients, all of whom were terminally ill and have since died, were told about the experimental nature of the drug, but were not informed that it lacked approval from the FDA. Wiernik had received FDA approval to use this drug, interleukin-2 (IL-2), in kidney cancer experiments. However, he gave leftover IL-2 to two neurosurgeons for treatment of patients with brain tumors. The FDA had never approved such treatments.

The FDA proposed a major change in the rules for reporting side effects from drug trials in 1993. This proposal came on the heels of publicly released information indicating that several people had died after having been given a new drug for hepatitis B in a series of experimental drug trials. A total of 5 of 15 patients who took the drug for 4 weeks or more died. It was determined in retrospect that five other patients in earlier experiments most probably died as a result of taking that same drug or its experimental predecessor. The drug involved was fialuridine; in the earlier experiments, it was a closely related drug, filacytosine. The scientists or the drug companies reported none of the deaths to the FDA, supposedly because the individuals conducting the experiments assumed that the drug had not caused the deaths.

In late 1993 articles appeared in newspapers throughout the world dealing with the use of cadavers in car crash tests at Heidelberg University in Germany. These experimental studies had been partly financed by the U.S. National Highway Traffic Safety Administration. Similar tests reportedly had been conducted at the University of Virginia and at the Medical College of Wisconsin, and also at Wayne State University in Detroit, the latter at the behest of the Centers for Disease Control and Prevention (CDC). Many questions were raised about whether an informed consent had been obtained by the legal next-of-kin before these corpses were used. The tests in Germany included the dead bodies of 200 adults and 8 children. German law permits the use of cadavers for research as long as the relatives' consent is obtained.

In 1976 John Moore, a 33-year-old man, was diagnosed with hairy-cell leukemia at the Medical Center of the University of California at Los Angeles (UCLA). His treating physician was Dr. David W. Golde, a hematologist and researcher at the UCLA Medical Center. A splenectomy was performed as part of the treatment. Golde recognized the commercial and scientific value of Moore's spleen and other bodily tissues and materials at the time he recommended the splenectomy. The spleen was taken to a hospital research unit to develop a cell line for commercial use. Golde and another researcher, Quan, then developed and patented a cell line from Moore's cells that produced lymphokines, a genetic product of considerable commercial value. The two researchers, a pharmaceutical company, and UCLA entered into a contract with the Genetics Institute worth more than \$330,000 for the products that would be developed from this patented cell line over a 3-year period.

After the splenectomy, Moore returned to the hospital on several occasions over 7 years at the request of Golde and had samples taken of his blood, skin, bone marrow

aspirate, and sperm. These were done specifically for commercial and not therapeutic purposes. Moore was never informed at any time by Golde of these research activities, or of the commercial value of his cells. When Moore ultimately discovered that his cells had been used to develop this cell line, he sued the researchers, various companies, and UCLA. The trial court dismissed all the claims, but an intermediate appellate court reversed and held that Moore had stated a cause of action for conversion. On appeal, the California Supreme Court, two justices dissenting, reversed and held that Moore had no property interest in his cells and therefore no cause of action for conversion. However, the court unanimously held that Moore had set forth facts sufficient to state a cause of action for breach of fiduciary relationship and lack of informed consent against Golde for failing to disclose his research and commercial interest before the splenectomy and before the removal of Moore's other body tissues and blood in subsequent visits to UCLA. A petition for writ of certiorari to the U.S. Supreme Court was denied.

In 1994, after the publication of a series of articles on the plutonium injections, President Clinton appointed an advisory committee on human radiation experiments to investigate the matter and gave it access to thousands of secret documents. Jonathan D. Moreno, a biomedical ethicist at the University of Virginia, worked for the committee, and then went on to examine the broad history of experiments that the U.S. Government had secretly conducted on human subjects in the interest of national security from World War II through the Cold War.

During World War II, both military and civilian agencies sponsored numerous experiments with human subjects in connection with investigations of the new antibiotic penicillin, agents against malaria, and protections against poison gases. The subjects were conscientious objectors, prison inmates, hospital patients, students, and Army recruits. Most were volunteers who had been informed of the risks. But others participated without their consent, including tens of thousands of soldiers who were exposed to poison gases to test protective clothing and gas masks.

Despite the Nuremberg Code, the Atomic Energy Commission had no general policy governing experiments with human subjects. The Defense Department had a policy after 1953, at least for experiments in atomic, chemical, or biological warfare, but it was not widely disseminated.³²

CONCLUSION

A discussion of the liability of a physician for experimental procedures including human research requires an initial examination of the two competing interests that must be balanced in any experimental situation. There is the obvious interest of the patient to be free from the abuses to which uncontrolled experimentation can lead—from the most grotesque examples of the atrocities of Nazi Germany to the violation of the rights of individuals to be free from becoming unwilling participants in any form of experimentation. The interest of the physician and the interest of society as a whole must be balanced against the interest

of the individual. If physicians are limited strictly to previously established procedures, all innovation and progress in the field of medicine would cease. The courts have recognized both of these interests in attempting to deal with the problem of when the physician should bear the burden of the effects of experimental procedures.³³ They have laid down the principle that one who experiments with an innovative treatment is responsible for all the harm that follows. Later cases articulated the need for the advancement of medicine, and in these cases the court stated that it is a recognized fact that, if the general practice of medicine is to progress, a certain amount of experimentation must be carried on.

Complicating the problem of balancing these interests is the difficulty of defining experimentation.^{34,35} Courts have confused judgmental decisions and experimentation. In the opinion of one court, a physician is presumed to have the knowledge and skill to use some innovation; yet courts have in the past mislabeled that area of permissible judgment as "experimentation." However, any time a physician's procedures do not follow accepted medical practice, he or she is moving in the direction of experimentation and the distinction between innovation and experimentation becomes blurred. On the other hand, the courts have determined that the mere fact of departure from the drug manufacturer's recommended dose does not make the departure an "experiment." A procedure does not rise to the level of an experiment if the physician has previously used the method successfully, the procedure has been described in the literature, and the choice has been reasonably and prudently calculated by the physician to accomplish the intended purpose. However, surely it is not enough that the intentions of the physician be reasonable to find that a previously unapproved procedure is not an experiment.

When drawing the line between experiment and judgment becomes difficult, the courts are likely to be influenced by the fact that no approved therapy is available. The physician then is faced with the choice of no treatment or innovation. And in examining the type of innovation chosen by the physician, the court will look at the rationale of the physician in making that choice and the extent to which that choice was a significant departure from previous standards of care.

Another factor that has been proposed as being important in deciding what is considered experimentation is the distinction between the curable and the terminally ill patient. It has been argued that the terminally ill patient with no hope of recovery from accepted medical procedures should be free to choose from any form of treatment and should not be restricted in his or her choice by laws that were designed to protect the patient from the risks of experimentation. A distinction between curable and terminally ill patients is not valid, however, when the protection of the rights of an individual from the use of experimental drugs is concerned. It has been held that a physician treating terminally ill patients with an unapproved drug may be subject to criminal penalties.³⁶ The U.S. Supreme Court has ruled that the Federal Food, Drug and Cosmetic Act, which restricts the use of experimental drugs, contains no exemptions for the terminally ill patient.³⁷

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Although a number of courts have recognized a legal right to recover for damages resulting from experimentation by the physician, no cases to date have actually turned on the issue of experimentation alone. The courts have seemed reluctant to base liability squarely on the issue of experimentation, perhaps because the issue of experimentation is composed of a number of elements. Instead, they have relied on a number of other legal theories for finding liability.

The first and most important is that of informed consent. One court has stated that without informed consent for an investigational procedure, a physician commits a battery.³⁸ Liability for experimental procedures has been predicated on the lack of informed consent of the patient in a number of cases.³⁹ In one case involving psychosurgery on a mental patient and a procedure that was totally novel and unrelated to any previously accepted procedure, lack of knowledge on the subject made a knowledgeable consent impossible.⁴⁰ However, most courts have accepted the idea that an informed consent is possible even when the knowledge surrounding the procedure is limited. Some believe absolute liability should be imposed on the physician for experimental procedures because they amount to abnormally dangerous activity under 402(a), Restatement (Second) of Torts. However, informed consent before the administration of an investigational drug amounts to voluntarily encountering a dangerous activity that bars recovery under 402(2).

If a physician adopts a method not recognized as sound by the medical community, the physician may be liable if it injures the patient in any way. Any variance from established standards can lead to liability. This "any variance" approach has been modified by most courts. It is generally recognized that where competent medical authorities are divided, a physician will not be held liable if he or she follows a form of treatment advocated by a considerable number in the profession. This represents the "respectable minority approach."⁴¹

It is important to consider whether the physician undertook a form of treatment that a reasonable and prudent member of the medical profession would undertake under the same or similar circumstances. This standard is an appropriate one, but in the area of experimentation there is a need for more specific guidelines to be articulated by the courts.⁴² For example, the test might include factors such as (1) the qualifications of the physician in question to do the particular procedure involved, (2) the rationality of the procedure based on the extent of departure from accepted procedures and the indication of need for the procedure under the circumstances, and (3) the risk of the procedure versus the benefit to be derived from it.

A third legal theory used in experimentation cases is based on the patient's right of privacy. The right to control one's body is part of the right of privacy inherent in our Constitution. Experimentation has been considered a violation of this right.

The physician may be able to guard against liability for experimental procedures with a covenant not to sue. The patient agrees before treatment not to sue if injured as a

result of the experimental treatment. When the procedure, although experimental, may have some value and represents a last chance for help, the physician may secure an agreement not to sue if the procedure is not helpful, provided the patient is fully advised.

In addition to the case law that has developed regarding experimentation, there is some federal and state statutory law in this area. Most important within the federal province is the Federal Food, Drug and Cosmetic Act and the regulations promulgated thereunder. These are designed to regulate the influx of new drugs in the market. Section 505(i) of the Act⁴³ exempts from premarketing approval drugs intended solely for investigational use if they satisfy certain criteria. Experimental drugs are available only to authorized investigators. At authorized institutions their use (as well as any experimental procedure) is subject to the IRB under the regulations of the DHHS. The board examines (1) the knowledge to be gained from the study, (2) prior experimental and clinical findings to determine the necessity and timeliness of using human subjects, (3) potential benefits to the subjects, (4) potential risks and procedures to minimize them, (5) confidentiality procedures, (6) the consent process, and (7) the proposed subject population.

The approval of a study does not mean that the investigator is then insulated from personal liability for harm suffered by the subjects in the study, but it substantially decreases the risk, especially with regard to liability based on failure to secure a subject's informed consent. These procedures are not universally mandated by law, but they apply when research is supported by DHHS funds or submitted to the FDA.

State statutes designed to protect subjects from the risks of experimentation tend to focus on specific matters rather than setting general guidelines for review of research.⁴⁴ These statutes regulate investigational drugs, fetal research, psychosurgery, confidentiality of information, and privacy. Only the state of New York statutorily requires institutional review committees for human research. Their function is basically the same as that of the IRB.⁴⁵ The state of Louisiana is the only state that defines the crime of human experimentation.⁴⁶ State statutes regulating human experimentation are a reasonable exercise of the state's police power.

Endnotes

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3. Associated Press dispatch, Washington, D.C. (Aug. 13, 1975).
4. UPI dispatch, Salem, Oregon (Mar. 4, 1976).
5. UPI dispatch, Washington, D.C. (Feb. 22, 1976) (E. DeLong).
6. *Prince v. Massachusetts*, 321 U.S. 158 at 170 (1944).
7. *Bonner v. Moran*, 126 F.2d 121 (D.C. Cir. 1941).
8. Pappworth, *Human Guinea Pigs: Experimentation on Man* (1967).

9. The New Republic, Dec. 3, 1966 at 10.
10. 288 N. Engl. J. Med., 755, 791, 1247 (1973).
11. Med. World News, 4 (Apr. 13, 1973).
12. Med. World News, 6 (June 5, 1964); 151 Science 663 (1966).
13. Med. World News, 15 (Aug. 18, 1972); Curran, *Legal Liability in Clinical Investigations*, 289 N. Engl. J. Med. 730 (1973).
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16. Barber, *The Ethics of Experimentation with Human Subjects*, 234 Sci. Am. 25 (Feb. 1976).
17. Hosp. Trib., 1 (May 14, 1973).
18. *Human Experimentation*, Med. World News, 37ff. (June 8, 1973).
19. *Hyman v. Jewish Chronic Disease Hosp.*, 206 N.E. 2d 3381 N.Y. (1965).
20. 18 Purdon's Statutes §2501 *et seq.*; 18 Pa. C.S.A. §2501 *et seq.*
21. Kidd, *The Problem of Experimentation on Human Beings: Limits of the Right of a Person to Consent to Experimentation on Himself*, 117 Science 211, 212 (1953).
22. *Id.*
23. *Id.*
24. *Id.*
25. *Id.*
26. The commission was established by Congress in Title II, Part A, §201(a) of the National Research Service Award Act of 1974, Pub. L. No. 93-348, 88 Stat. 142. The purpose of the commission was to conduct a comprehensive investigation and study to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research, evaluate existing guidelines for the protection of human subjects, and make appropriate recommendations to the Secretary of HEW concerning further steps, if any, to be taken. *Id.* at §202(a)(1)(A) (hereinafter referred to as *the commission*).
27. *Id.*
28. Dale H. Cowan, *Innovative Therapy versus Experimentation*, Tort and Insurance L.J. (Summer 1986).
29. National Commission, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, DHEW Pub. No. (OS) 78-0012 (1978) (hereinafter referred to as the *Belmont Report*).
30. *Supra* note 26.
31. R.J. Levine, *The Boundaries between Biomedical or Behavioral Research and the Accepted and Routine Practice of Medicine*, Belmont Report, Appendix I, Paper No. 1, DHEW Pub. No. (OS) 78-0013 (1978).
32. J.D. Moreno, *Undue Risk: Secret State Experiments on Humans* (W.H. Freeman & Company 1999).
33. *Carpenter v. Blake*, 60 Barb. (N.Y.) 488, *rev'd on other grounds*, 50 N.Y. 696 (1872).
34. *Fortner v. Koch*, 272 Mich. 273, 261 N.W. 762 (1935).
35. *Brooks v. St. Johns Hickey Memorial Hosp.*, 269 Ind. 270, 380 N.E. 2d 72 (1978).
36. *People v. Privitera*, 23 Cal. 3d 697 (1979).
37. *U.S. v. Rutherford*, 582 F. 2d 1234, *cert. granted* 99 S.Ct. 1042, 439 U.S. 1127, *cert. denied* 99 S.Ct. 1045, 439 U.S. 1127, *revised*, 99 S.Ct. 2470, 442 U.S. 544, *on remand*, 611 F. 2d (1979).
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39. *Ahern v. Veterans Administration*, 537 F. 2d 1098 (1976).
40. *Kaimowitz v. Michigan Dept. of Mental Health* (Civil No. 73-19434-AW), Cir. Ct. Wayne Co., Mich. (1973).
41. *Colton v. New York Hosp.*, 414 N.Y.S. 2d 866 (1979).
42. *Fiorentino v. Wegner*, 272 N.Y.S. 2d 557 (1966).
43. Federal Food, Drug and Cosmetic Act, §501(i), 21 U.S.C. 335(i).
44. California Health and Safety Code §§24176-24179.5 and 26668.4.
45. New York Public Health Law 2440-2446 (Supp. 1976).
46. La. Stat. Ann. Title 14, 872 (1974).

General References

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APPENDIX 18-1: THE NUREMBERG CODE

The Nuremberg Code provides as follows:

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated so as to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.
The duty and responsibility for ascertaining the quality of the consent rest upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparation should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage if he has probable cause to believe, in the exercise of good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

APPENDIX 18-2: THE DECLARATION OF HELSINKI

The Declaration of Helsinki provides as follows:

It is the mission of the physician to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of his mission.

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

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

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

Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.
2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical person.
3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.
5. Special caution should be exercised by the physician in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the physician must be free to use a new therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health, or alleviating suffering.
If at all possible, consistent with patient psychology, the physician should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, counsel should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.
2. The physician can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

Nontherapeutic Clinical Research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom clinical research is being carried out.
2. The nature, the purpose, and the risk of clinical research must be explained to the subject by the physician.
- 3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.
- 3b. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.
- 4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.
- 4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating team should discontinue the research if in his or their judgment, it may, if continued, be harmful to the individual.

From 1 and 2 *Trials of War Criminals before the Nuremberg Military Tribunals: The Medical Case* (U.S. Government Printing Office, Washington, D.C. 1948).
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