

Summary
Government-Sponsored Human Research

by Stuart C. Finch, M.D.

During World War II the Federal Government sponsored many large population research studies. Most were considered part of the war effort with an opportunity for disabled, retarded or other institutionalized persons to participate. Agreement of the experimental subjects from the subjects and physicians or guardians usually was obtained, but rarely were there any detailed ethical considerations or discussions regarding cost/benefit or alternatives such as we consider routine today. Malaria, heat killed bacteria, influenza virus and even gonorrhea was given to prisoners or other institutionalized persons.

The wartime practice continued through the 1950's and into the 1960's, mostly supported by Federal funds. Awareness of possible unethical research really commenced in the mid 1960's, but there was no significant change until the 1970's. The first set of government regulations regarding the protection of human subjects in research was published in 1973. Since that time virtually all medical investigators and institutions have followed the guidelines regarding the ethics of human research which have been established by the Department of Health and Human Services.

Radiation research during the 1940's through the 60's generally was of two types. The first involved using small amounts of radioactivity as a tag or label to identify the location or rate of turnover of a substance in the body. To the best of my knowledge none of these studies has resulted in any adverse long-term effects. The second type were those designated to evaluate the short or long-term effects of localized exposure to certain types of radiation. Medical knowledge was gained through both types of studies, which were conducted in accord with the practices of the time. I doubt that any of those early studies on confined or impaired persons would be acceptable by current standards.

Finally, I do not believe that any U.S. military studies were specifically designed to evaluate the effects of ionizing radiation in military personnel. The amounts of residual ground radiation in Hiroshima and Nagasaki were insufficient to result in leukemia or other cancers by the time that U.S. military personnel arrived in either area. Only one of the almost 600 weapons tests (operation Smoky) to date appears to have resulted in a significant increase in leukemia. The number of observations were small so that caution has been recommended in interpretation of the results.

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Medical research prior to World War II was very poorly defined in terms of ethical standards (Rothman, DJ, Ethics and human experimentation; Henry Beecher Revisited, NEJM, 317, 1195-1199, 1987). The usual objective was some form of new therapy directed at self, family member or desperately ill patient. Jenner first gave smallpox vaccine to a member of his own family. Pasteur first gave rabies vaccine to a child with rabies and Banting first gave insulin to a person in advanced diabetic coma.

The situation changed dramatically with World War II. The Federal Government's Committee on Medical Research (CMR) authorized many research studies on large populations. Most of the studies were considered part of the war effort with an opportunity for disabled, retarded or other institutionalized individuals to participate. The general feeling was that everyone should play a role in the achievement of victory, and to that end it was considered very reasonable for incapacitated persons to participate in medical studies which might save the lives of soldiers who also were risking their lives without having had the option of voluntary consent. Agreement of subjects or their guardians for entering a research study was generally expected, but rarely were there any ethical considerations, detailed discussions concerning procedures, risks, benefits, costs or alternatives such as we consider routine today. In other words, the standards were much different and the ethics were completely utilitarian.

During the war years many investigators responded enthusiastically to the outpouring of millions of government dollars for studies on a massive scale. There was little concern about giving malaria to over 500 prison volunteers and many institutionalized psychotic patients in Illinois for the purpose of testing antimalarial drugs. Influenza virus was administered to retarded and correctional institution children in order to test a flu vaccine. Prisoners, orphanage and retarded persons in Illinois, Ohio and New Jersey were infected with a virulent strain of heat killed bacteria in order to evaluate the effectiveness of immunization. Volunteer prisoners were even infected with gonorrhea in a treatment study, but in that instance, only after having received a two page description of the study as the outcome of some previous discussions regarding both the ethical and legal implications of the research plan.

The wartime practices carried over through the 1950's with prospects of winning the war against degenerative and contagious disease (Rothman,DJ; NEJM, 317, 1195 -1199, 1987). The National Institutes of Health continued to support large clinical studies similar to those conducted during wartime. Ethics changed very little as they were not challenged. Some well publicized studies during this period included the Willowbrook State School study of infectious hepatitis, the Jewish Chronic Disease Hospital study regarding the rejection of injected liver cancer cells and the San Antonio contraceptive study involving impoverished Mexican-American women. The Nuremberg code had been written in 1947, but it was not well publicized and few American investigators found little relevance of it to their types of research.

Early in the 1960's, however, things began to change. The Natanson vs Kline legal decision in 1960 regarding the charge of negligence for a physician who did not properly inform a patient in a research study of the nature of a study and its risks, and the thalidomide tragedy in Germany in 1961 were factors in raising some attention to ethical standards for NIH and other organizations involved in medical research. Some medical school clinical research centers created institutional committees to review research projects. A few medical schools organized broader review boards. In 1964 the Declaration of Helsinki was written by the World Medical Association. It was the first real formal document that defined standards for physicians involved in medical research. It was not until the Beecher article was published in the New England Journal of Medicine in 1966, however, that the medical research community really began to seriously consider the ethics of human medical research (Beecher, H.K.; Ethics and Clinical Research, NEJM, 274, 1354-1360, 1966). In that report Beecher indicated that of 100 consecutive human studies published in ethical journals which he had reviewed he found that 12 were blatantly unethical and only 4 even mentioned informed consent. Virtually all of the 21 studies which he reported in the article were performed on institutionalized subjects between 1950 and 1965 at major medical schools and supported by leading government agencies. Change in the late 1960's also was fueled by the revolt against authority, the development of protection groups and the interest of lawyers.

Progress for the protection of human subjects in research progressed rapidly in the early 1970's. The Canterbury vs Spence decision in 1972 concluded that law standards rather than those established by physicians should be the criteria of informed consent. The first set

of proposed regulations on the protection of human research subjects was published in 1973 by OHEW, and the following year the final regulations were released in the form of 45 Code of Federal Regulations 46. These and other government publications called for the formal development of Institutional Review Boards at research institutions which would ensure proper informed consent for every person involved in a research study, careful evaluation of the risk/benefit ratio of human research, restrictions on the use of persons in confined circumstances, and follow-up of progress in research. In 1974 the National Research Act also was signed into law. It created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission summarized the basic ethical principles and guidelines for the resolution of ethical problems that surround the conduct of human research in the Belmont Report of 1979. The principles of this Report have provided the basis for a constantly evolving government policy on human research. The most recent Federal Regulations, are entitled Protection of Human Subjects (Title 45, Code of Federal Regulations, Part 46, revised June 18, 1991). These regulations apply to all human research conducted, supported or controlled by any Federal Department or Agency either within or outside of the United States. Since the early 70's physicians and their institutions involved in human research generally have closely adhered to the Code of Federal Regulations for the Department of Health and Human Services.

Human studies involving the use of ionizing radiation proliferated in the 1940's through the 1970's. They generally were of two types. The first and most frequent involved the use of radioactive isotopes for the purpose of studying the normal or abnormal

metabolism of some element or biological substance within the body. The radioactivity provided a tag or label to identify the location or rate of turnover of the substance under study. Most of the amounts of radiation were small with short physical half-lives and/or rapid biological elimination. Examples of such studies were those employing radioactive iron, iodine, potassium, and chromium. A few similar studies, however, were conducted in patients with advanced illnesses with radioactive substances with long half-lives (i.e. thorium, radium, plutonium). Many of these studies have added immensely to our knowledge of disease and its therapy, and the sites of internal localization and turnover of environmental radioactive elements. To the best of my knowledge none of these studies has resulted in any adverse long-term effects. The second type of studies were those designed to evaluate the short or long-term effects of localized exposure to certain types of ionizing radiation. The only study of this type with which I am familiar was that performed in the 1960's involving the irradiation of the testicles of a group of inmates in Washington State Prison for the purpose of determining the smallest dose which would produce sterility. It is my understanding that all of the inmates in this study were scheduled for vasectomy, but some subsequently are reported to have eluded the procedure. One eventual consequence of this study was said to be the universal policy of lead apron shielding of the gonads of persons receiving x-rays while in a dental chair.

It is important that the types of human radiation studies of the 1940's, 50's and 60's be carefully considered as to whether the radioactivity was used to trace a substance in the body or to study the effects of radiation exposure. Also, the type and amount of radiation

exposure in terms of either early or late risk of adverse effect should be taken into consideration. Furthermore, it is important to judge the propriety of these studies in accord with the accepted ethical principles and research philosophy of the war years and thereafter up to the 1970's. In retrospect, few if any of the medical radiation studies or those involving the utilization of confined or impaired persons during the post war era would be acceptable by current standards.

I am unaware of any prospective U.S. military studies that were designed to evaluate the effects of ionizing radiation exposure in military personnel. There have been, however, numerous follow-up studies of military personnel who possibly were exposed to excessive amounts of radiation during weapons testing or from ground radiation in Hiroshima and Nagasaki. Overall there is no statistically significant evidence of either increased leukemia or cancer in about 250,000 nuclear test participants in tests of about 588 nuclear devices. The only exception was the Smoky test in Nevada in 1957. In that study of about 3,000 men a significant excess of leukemia was observed during a follow-up period of about 20 years. The results of this study are to be interpreted with caution, however, as the size of the study population and the number of leukemia cases are small. Residual ground radiation initially was small in even the most contaminated areas of Hiroshima and Nagasaki, since both detonations were well above ground. Measurable amounts of ground radiation in the most contaminated areas disappeared to insignificant levels within a few days. Studies of the Hiroshima and Nagasaki residents who entered or worked near the atomic bomb hypocenters have not demonstrated increased leukemia or cancer. In my opinion the involvement of U.S.

military forces which commenced in supervisory capacities in both cities, several weeks to several months following the detonations, strongly mitigates against any potential carcinogenic effect from ground radiation exposure in either city.