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OFFICE OF THE SECRETARY

Mr. Edward J. Bauser
Executive Director
Joint Committee on Atomic Energy
Congress of the United States

Dear Mr. Bauser:

I am herewith transmitting for the information of the Joint Committee on Atomic Energy an AEC staff report on the results of an inquiry as to whether informed consent was obtained from patients injected with plutonium during a Manhattan Engineer District research project either at the time of injection in 1945-1947 or during the follow-up studies in 1973.

The inquiry uncovered certain irregularities in the observance of ethical standards. Upon reviewing this information, the Commission recommended that appropriate corrective action be taken. Enclosed also for the information of the Joint Committee is a report to me from Dr. James L. Liverman, Director, Division of Biomedical and Environmental Research, outlining the measures taken or planned to implement the Commission's recommendations.

In view of the sensitivity of this information, it is requested that you handle it on a limited distribution basis.

Sincerely,

Signed
John A. Erlewine

General Manager

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DISCLOSURE TO PATIENTS INJECTED WITH PLUTONIUM

INTRODUCTION

This is a report of the results of an inquiry requested by the U. S. Atomic Energy Commission and authorized by the General Manager on April 17, 1974. The inquiry was directed to the question of whether informed consent was obtained from patients injected with plutonium either when injected in 1945-1947 or during recent follow-up studies in 1973.

BACKGROUND

Reasons for the Study

A study of the metabolism of plutonium in man was prompted during World War II by concern over the exposure of large numbers of workers to this newly created element when kilogram quantities of plutonium were produced for the first time at Hanford early in 1944. The fact that plutonium is toxic had been established already in animal experiments. Allowable limits for deposition in the human body were arrived at by utilizing information obtained from radium studies in man, early results of plutonium experiments in animals and the respective physical properties of plutonium and radium. The limits were revised from time to time as new information became available.

The estimation of body burdens in exposed individuals proved to be exceedingly difficult. The emission characteristics of the plutonium isotopes of interest (Pu-238 and Pu-239) were such that estimation of body burdens could be based only on the analysis of excretion specimens. Equations for the calculation of body burdens from urine or stool specimens required data concerning excretion rates. Animal experiments undertaken to provide such data produced results that varied between species, thereby nullifying the opportunity to extrapolate to man. Studies conducted on man involving the introduction of known quantities of the element into the human body were viewed as the only solution to the problem.

The Laboratories

The principal laboratories that conducted biological experimentation in support of the Manhattan Project were located at the Universities of California, Chicago and Rochester. The laboratory in Berkeley of particular interest to this inquiry was known then as the Crocker Laboratory; it was part of the University of California Radiation Laboratory. Experiments involving administration to human subjects of radioactive isotopes of diagnostic or therapeutic interest had been conducted at the University Hospital in San Francisco for several years by University personnel from both the Berkeley and San Francisco campuses.

The name of the Manhattan Engineer District (MED) laboratories at the University of Chicago was the Metallurgical Laboratory. Some MED personnel also held clinical appointments at Billings Hospital, the teaching hospital of the University.

Biological experimentation was conducted for MED at the University of Rochester Atomic Energy Project (AEP). Joint appointments at the Strong Memorial Hospital of the University were held by certain members of the AEP professional staff.

In addition to the university hospitals, a hospital operated by the MED at Oak Ridge was involved in the study.

The Study

The study was loosely coordinated between the laboratories. On March 23, 1945, a meeting was held in Los Alamos at which a request for help in making arrangements for a human tracer experiment to determine the percentage of plutonium excreted daily in the urine and feces was submitted to an MED staff member. It was suggested that a hospital patient at either Rochester or Chicago be selected and injected and that the excreta be sent to Los Alamos Scientific Laboratory (LASL) for analysis. On April 10, April 26 and May 14, 1945, patients were injected at Oak Ridge, Chicago and San Francisco, respectively. An interviewed scientist expressed the opinion that the continuation of the study beyond the first three cases was motivated by uncertainties caused by the variation in the data obtained from those cases. There is nothing in the record that suggests otherwise. A planned experiment that called for the study of ten patients was conducted in Rochester with the injections occurring from October 16, 1945 to April 3, 1946. An eleventh patient was injected at Rochester on July 16, 1946, because technical difficulties were encountered in one of the original cases. In addition to the planned Rochester experiment, two patients were injected in Chicago on December 27, 1945 and two in San Francisco on April 26, 1946 and on July 18, 1947, respectively. All patients were adult except a five year old child in San Francisco and an 18 year old patient in Rochester. It is likely that the first patient was injected by an MED officer, the next sixteen by MED contractor personnel and the last by AEC contractor personnel (after official assumption of MED contracts by the AEC on January 1, 1947).

According to early documents, the criteria considered in choosing subjects for the study were age, life expectancy and relatively normal kidney and liver function. Those selected were over 45 years of age with five exceptions and suffered from malignant tumors or other chronic diseases such that survival for more than ten years was considered unlikely. In

several cases, however, survival has been longer than anticipated. Nine patients died within three years after injection; one each died in 8, 11, 14 and 20 years; one was lost to follow-up; and four are alive today. The causes of death in all deceased patients were the originally diagnosed illnesses or other diseases unrelated to the plutonium injections.

Although the quantities of plutonium injected ranged from 2.4 to 145 body burdens, 13 of the patients received 7-10 body burdens (using the current body burden value of 0.04 μCi). The maximum permissible body burden is the term applied to the permissible occupational limit for an internally deposited radioisotope. Between March 1945 and 1950, the accepted value for the plutonium body burden was 0.06 μCi; since 1950, it has been 0.04 μCi for the plutonium isotopes relevant to this report. All injections were intravenous except the last, which was intramuscular in a leg that was amputated for treatment of a malignant tumor four days after the injection.

In 1967, a Berkeley radiobiologist learned that a patient injected in 1945 had lived for a period of 20 years. That information stimulated her to investigate the whereabouts of the other injected patients. She discovered that four patients were still living at the time of her inquiry; they are still alive. One of these patients had been injected in San Francisco and the other three in Rochester. In 1973, follow-up studies were carried out on three of the four patients in a project sponsored by the Center for Human Radiobiology (CHR) of the Argonne National Laboratory (ANL). The physician currently in charge of the metabolic ward at Strong Memorial Hospital in Rochester cooperated in these studies by obtaining excretion specimens during hospitalization of the patients. The specimens were analyzed for plutonium content at CHR and portions of some specimens were also analyzed at LASL.

Policies Relative to Informed Consent or Disclosure

The criteria for a legally and ethically acceptable disclosure of the nature of an experimental procedure to be conducted on a human subject and for the manner of consent by the subject have undergone evolutionary changes over the years. In current usage, informed consent is a term which implies recorded acknowledgement by the patient that he has received proper disclosure and has voluntarily consented to the experimental procedure. Informed consent, defined in this manner, was required for studies that were conducted in 1973 but was not required for studies conducted in 1945 and 1946. To avoid confusion with the strict informed consent required now, the term "disclosure" will be used in discussions of patient consent that pertain to the early period.

Formalized standards for patient consent to experimental procedures did not exist prior to 1946. The practices varied from one institution to another and were frequently left to the discretion of individual investigators. The Judicial Council of the American Medical Association late in 1946 adopted the following policy statement relative to ethical considerations in human experimentation:

> "In order to conform to the ethics of the American Medical Association, three requirements must be satisfied: (1) the voluntary consent of the person on whom the experiment is to be performed; (2) the danger of each experiment must be previously investigated by animal experimentation, and (3) the experiment must be performed under proper medical protection and management."

The AMA policy statement was vague by present standards and when compared with the AEC policy adopted shortly afterward (see below).

Security considerations could have interfered with whatever disclosure the investigators in these plutonium studies may have considered at that time. The word plutonium was classified until the end of the war. During wartime, investigators may have regarded any reference to the nature of the studies as a violation of security. Written statements would have constituted an additional breach of security. An atmosphere of secrecy for security reasons continued into the postwar period.

The AEC established a policy of formalized patient consent in April 1947, which, to the best of our knowledge, anticipated the adoption of such policies by other governmental agencies. At that time the General Manager stated in a letter to the Chairman of the AEC Interim Medical Advisory Committee on Clinical Testing that "it should be susceptible to proof from official records that, prior to treatment, each individual patient, being in an understanding state of mind, was clearly informed of the nature of the treatment and its possible effects, and expressed his willingness to receive the treatment. In view of your recommendation, the Commission does not request that written release be obtained in such cases, but it does request that in every case at least two doctors should certify in writing (made part of an official record) to the patient's understanding state of mind, to the explanation furnished him, and to his willingness to accept the treatment."

The National Institutes of Health first issued unpublished guidelines concerning institutional review and informed consent for grant projects involving the use of human subjects in 1966 and required all grantees to comply with those guidelines. A revision of the guidelines was published as a booklet for wider dissemination on May 1, 1969. Upon the recommendation

of the AEC Advisory Committee for Biology and Medicine, the booklet, titled "Protection of the Individual as a Research Subject," was adopted as policy by the AEC in 1970, and its contractors were required to provide assurance of compliance with the provisions of the booklet. The NIH document was later supplanted by the current DHEW Publication No. (NIH) 72-102, December 1, 1971, "Policies for the Protection of Human Subjects," and was in turn adopted by AEC. The guidelines characterize informed consent as "the agreement obtained from a subject, or from his authorized representative, to the subject's participation in an activity. The basic elements of informed consent are:

1. A fair explanation of the procedures to be followed, including an identification of those which are experimental;

2. A description of the attendant discomforts and risks;

3. A description of the benefits to be expected;

4. A disclosure of appropriate alternative procedures that would be advantageous for the subject;

5. An offer to answer any inquiries concerning the procedures;

6. An instruction that the subject is free to withdraw his consent and to discontinue participation in the project or activity at any time."

In recent years, the subject or his authorized representative has been required to sign a consent form approved by the Institutional Review Committee of the university or hospital unless a variance from that established procedure is documented in the Committee minutes and in reports of Committee actions.

EVIDENCE FOR DISCLOSURE OR INFORMED CONSENT

Chicago

1. Orientation

Three injections were made during the period of April 26 to December 27, 1945, by staff of the Health Group, Metallurgical Laboratory, University of Chicago. The Health Group included the Industrial Hazards and Clinical Sections; the Chief of the Clinical Section was also Deputy Chief of the Group. A detailed report of two of these cases was written jointly by a chemist and the Chief, Industrial Hazards Section; the assistance of the Chief, Clinical Section, was

acknowledged. The chemist conducted plutonium analyses on the excreta of the patients and on tissue specimens obtained at autopsy. The Chief of the Health Group is deceased; the chemist and the Section Chiefs are alive and were interviewed.

2. Disclosure

The chemist said that the Chief, Clinical Section, both injected the patients and obtained oral consent from them after explaining that the radioactive substance to be injected may prove to be of greater benefit to others than to themselves. The Chief, Clinical Section, said that he did not recall anything about the injections and that they might have been made by another physician, the only other professional staff member with a "Q" clearance. The latter physician, when interviewed, denied any connection with the study. The Chief, Industrial Hazards Section, said that he did not recall any specific information concerning the program despite being shown the above mentioned report of two cases and copies of signed memos concerning the patients from him to the Chief of the Health Group.

A member of the faculty of the University of Chicago Medical School has located two of the three patient files but not the third. He said that one contained no reference to the injection program while the other contained a notation by a medical student that the patient's family was eager to have the plutonium treatment started.

Oak Ridge

1. Orientation

One patient was injected at the Oak Ridge Hospital on April 10, 1945. The hospital was operated by the MED, and Commissioned Medical Officers served on the hospital staff. The injected patient's records along with other hospital files were destroyed in a fire at a much later date.

2. Disclosure

A physician, who was then a Commissioned Officer, told the interviewers that he had made the injection. He is reported to have made the same statement to other interested persons in the past. He stated further that no disclosure was made to the patient. This physician is reported to have required psychiatric care in recent years but appeared completely lucid to the interviewers, one of whom is a physician on the AEC staff.

The physician further stated that he made the injection only after receiving a written order from the superior medical officer who, he said, had selected the patient for the study. The latter officer prepared a protocol in which reference was made to the injection in the past tense. When interviewed, the superior officer said that he had no recollection of the incident.

Rochester

1. Orientation

Eleven patients were injected at Rochester during the period between October 16, 1945, and July 16, 1946. The injections were part of a planned experiment conducted jointly by the University of Rochester AEP and LASL. In the division of responsibilities, the specimens were collected in the Strong Memorial Hospital of the University of Rochester, and the analyses for plutonium content were conducted at LASL. The hospitalized patients were transferred to a special metabolic ward where they remained for several days for training in the proper provision of specimens and for the collection of baseline urine and stool specimens before injection; they remained in the ward for a few weeks after injection for further specimen collection. The chief of the metabolic ward, who conducted the study, is deceased. He is reported to have selected the patients and made the injections. The following persons, who were associated with the project, are alive and were interviewed during the inquiry:

a. the physician assistant to the chief of the metabolic ward during the period of the study,

b. the Director of the AEP to whom the chief of the metabolic ward reported (brief interview by telephone),

c. the scientist in the Rochester AEP to whom correspondence relating to the experiment was addressed, and,

d. the physician who took over the care of two surviving injected patients when the chief of the metabolic ward left Rochester in 1948.

Strict security precautions were observed in the AEP so that close associates were frequently unaware of details of each other's activities. The assistant to the chief of the metabolic ward said that the AEP was highly compartmentalized and that activities were conducted on a need-to-know basis. The assistant characterized the chief as a basically shy person who was especially secretive about the MED programs.

2. Disclosure

Examination of the hospital charts of eight deceased patients failed to disclose any reference to injections having been made or to disclosure to patients, but there were orders for transfer of patients to the metabolic ward and for the collection of excretion specimens. A University staff physician examined the files of the three living patients and said that they contained no reference to consent or disclosure. None of the persons interviewed had knowledge that disclosure was or was not made in the Rochester cases.

The following evidence may be cited to support a contention that disclosure may have been provided to the patients. Two interviewed physicians said that they regarded the chief of the metabolic ward as a highly ethical physician and considered it almost inconceivable that he would not have provided disclosure to the patients. One scientist, who was associated with the project, stated that he was not familiar with this program, but he knew that adequate disclosure to patients was made in another study conducted at Rochester at about the same time. Finally, an opportunity to disclose was provided when patients were transferred to the metabolic ward since physicians are expected by patients to justify transfers within hospitals.

San Francisco

1. Orientation

Three patients received injections at the University of California Hospital, San Francisco, on May 14, 1945, April 26, 1946, and July 18, 1947, respectively. The last, one of the four living patients, was the only patient injected with plutonium after the AEC was formed on January 1, 1947. The deceased physician Director of the Crocker Laboratory, University of California, appears from documentation to have been responsible for the program during the period of the first two injections. The names of a physiologist associate of the Laboratory Director and of a second physician appear in the hospital chart of the first patient. In addition, there are references to the second physician in the chart of the second patient. A third physician (deceased) apparently made the injection and signed a disclosure statement on the third patient's chart. The second physician and physiologist were interviewed.

2. Disclosure

Relative to the first two cases, the Director, Crocker Laboratory, reported to the then Director, Division of Biology and Medicine (DBM), AEC, during a conversation in December, 1947, that patients had been injected with plutonium in San Francisco. He further stated that the patients were informed that they were to receive a radioactive substance having certain properties, according to the recollection of the then Director, DBM. The physiologist and second physician did not offer any information relative to disclosure. The physiologist did say that he prepared the solution for injection in the first case and handed the syringe to the second physician. However, the physiologist reported that he was not present before or during the injection. When interviewed the second physician did not recall any relationship to either case. The records in the first two cases presented no evidence of disclosure in spite of references to special radioactive procedures and related orders for tissue or specimen collection.

The hospital chart in the third case contained a statement signed by three witnesses and the responsible physician, attesting that the experimental nature of the radioactive tracer injection was explained to the patient, who agreed to the procedure. It was further stated that the patient was fully oriented and sane. This statement conformed to guidelines issued by the AEC in April 1947 as quoted above.

Argonne and Rochester (1973)

1. Orientation

In 1973, the Center for Human Radiobiology initiated a follow-up study of the surviving patients and a program of exhumation of the bodies of those deceased for whom permission could be obtained. Urine and fecal specimens were to be collected in the metabolic ward of Strong Memorial Hospital and analyzed at the CHR and, secondarily, at LASL as stated above. Two Rochester patients were hospitalized for the treatment of disease in January and June, 1973, respectively. Specimens were collected for plutonium analysis during those hospitalizations. A third Rochester patient was neither contacted nor studied during 1973. However, her physician has been informed of the injection. The surviving San Francisco patient, who now lives in Texas, was brought to Rochester for specimen collection in June 1973. He was examined at the CHR while en route to Rochester. All costs at Strong Memorial Hospital incurred as a result of these studies were reimbursed by CHR.

Beginning in April 1973, the next of kin of several deceased patients were contacted to obtain permission for exhumation. The contacts were made by staff of the Southwest Field Station of the Massachusetts Institute of Technology Radioactivity Center, a CHR satellite. The body of a Rochester patient was exhumed on September 24, 1973, and subsequently studied at the CHR.

The CHR is a component of the Radiological and Environmental Research Division (RER) at ANL. Interviews were conducted with the Director, RER; the Section Head of RER in charge of the CHR; and the Medical Director, CHR. Three persons associated with CHR, who participated in obtaining permission for exhumations, were interviewed. The physician in charge of the metabolic ward of the Strong Memorial Hospital was interviewed.

2. Informed Consent

In 1973, informed consent in accordance with current standards was required for studies conducted on human subjects. However, these patients were neither informed of the purpose of the studies nor did they sign consent forms.

The two Rochester patients were accustomed to participating in clinical studies, unrelated to this matter, involving the collection of excretion specimens. Even the lengths of the 1973 hospitalizations, which were primarily for unrelated medical purposes, were not extraordinary. Thus, it is likely that no undue discomfort was experienced by the patients. The attending physician, who had been informed in 1948 that these patients had been injected with plutonium, did not disclose to the patients or obtain consent from them for the stated reason that disclosure might be harmful to them in view of their advanced age and ill health.

The Texas patient required transportation to Chicago and Rochester to participate. However, he was eager to have his physical condition evaluated, having inquired of the University of California Hospital in 1966 whether the Hospital ever finances trips for patients to come back for tests and observation. The University Hospital did not respond affirmatively because of lack of funds. The CHR, not knowing that disclosure had been made to and oral consent obtained from the patient in 1947, approached the Texas patient through his attending physician to conduct "a follow-up study on treatment he received for a sarcoma in July 1947. We are especially interested in cases of this sort, and his is of particular interest since he has this unusual malignant tumor and has shown such a long survival time." After the study, the patient wrote to the CHR to affirm his gratitude for the personal treatment accorded him.

CHR instructions to staff to obtain permission for exhumation in ten deceased cases stated that the purpose of exhumation was to examine the remains in order to determine the microscopic distribution of residual radioactivity from past medical treatment. Relatives of seven of the ten deceased were contacted. To the best of our knowledge, all were told that the purpose of exhumation was to determine the composition and effects of an "unknown" mixture of injected radioactive isotopes. Disclosure to all but one of the next of kin could be judged misleading in that the radioactive isotopes were represented as having been injected as an experimental treatment for the patient's disease.

In a report dated April 8, 1974, relative to studies carried out at the CHR during 1973, the Chairman of the ANL Review Committee for Research Projects Involving Human Subjects recommended that the CHR inform these patients that examinations conducted on them are to establish the presence or absence of residual radioactivity stemming from the plutonium that they received many years ago. The Committee further stated that it made its recommendation in the belief that informed consent, when given by a patient, should be based on full information about the reasons for the examination.

Summary of Disclosure and Informed Consent

With respect to the 1945-1947 period, there was positive evidence of disclosure in one case. This was the only case injected with plutonium after the AEC came into existence and after its General Manager issued a directive in April 1947 that disclosure and consent, signed by witnesses but not necessarily by the subject, be made part of the official record. There were oral statements attesting to disclosure by a witness to the injections in three additional cases and by an informed employee in two other cases. A principal attested orally to nondisclosure in another case. In the remaining cases, persons regarded as potential witnesses to injections by personnel conducting the inquiry were either deceased or stated that they could not remember the events under consideration.

The hospital record contained a signed and witnessed statement to the effect that disclosure and consent had occurred in the 1947 case. In one case, the patient record was lost; in another, the record had been destroyed in a fire; in the remaining 15 cases the records contained no notation with respect to injection or disclosure.

Relative to the study undertaken in 1973, informed consent was not obtained from surviving patients who were the subject of the study. However, there is no reason to believe that the patients suffered harm or discomfort as a result of the studies. Consent, following improper disclosure, was

obtained from the next of kin of an exhumed patient. Improper disclosure was made to the next of kin of additional deceased patients who have not been exhumed.

The above inquiry was conducted by the Division of Biomedical and Environmental Research in conjunction with the Division of Inspection.