Total body irradiation (TBI) or partial body radiation (PBI) has been employed as a therapeutic modality for various types of widely spread neoplasia since 1923 (1) and was used to treat 88 patients at the University of Cincinnati Medical Center (UCMC) from February 9, 1960 through November 15, 1971. At this time the program was suspended at the request of the President of this University, pending the outcome of several investigations of the project. Central to the suspension of our clinical and research activities were two issues: the funding source of the project, the Defense Nuclear Agency (DNA) (formerly Defense Atomic Support Agency), a part of the Department of Defense (DOD), and the question of adequacy of patient informed consent. Neither uniformly favorable peer review of the TBI project, nor the nonclassified nature of our many presentations at scientific meetings, publications, and technical reports prevented the issue from producing considerable controversy within the University community, medical and lay press and even among members and staff of the Congress of the United States.

We have been concerned with the issues raised by this entire process in the years since the stormy period of its occurrence. Answers to the following problems are beginning to appear in the wake of the events to be described.

1. Are DOD funds inappropriate in supporting any University-based research, especially involving humans?

2. Can a university or its medical school withstand pressure from United States Senators and their staff, especially the threat to withhold federal funds if confidential information is not released?

3. How can media and faculty suspicion be overcome if their questions are not immediately answered?

4. How can one balance the needs of the media with the right of patient privacy?

5. How can one demonstrate that a signed consent was given by a truly "informed" patient?

We therefore describe the genesis of these questions for consideration by the medical community.

HISTORICAL BACKGROUND OF TBI AT UCMC

Since 1923, TBI has been employed for therapy of malignancy in numerous medical centers (1,2,3). An unsolicited proposal for funding of technical personnel and certain laboratory tests to be performed while therapeutic TBI was given was first submitted by UCMC to the Department of Defense September 25, 1958. At this time the Defense Department was funding considerable medical research. DNA, however never paid for UCMC direct patient care of the acquisition of patients into the therapeutic study (4). Approval for funding was obtained, and subsequent research activities involved five departments of the UCMC (Radiology, Medicine, Pediatrics, Surgery, Psychiatry). The first patient was treated February 19, 1960 (2).

Conditions for treatment were summarized by the investigators in 1962: 'it is essential to consider further well-planned studies (of TBI) in patients so

long as the following criteria are fulfilled:

"1. There is a reasonable chance of therapeutic benefit to the patient.

"2. The likelihood of damage to the patient is no greater than that encountered from comparable therapy of another type.

"3. The facilities for support of the patient and complications of treatment offer all possible medical services for successful maintenance of the patient's well being.

"The type of patient usually selected for whole body radiation is an individual with cancer which is far enough advanced either by direct extension of tumor or by metastatic spread, so as to eliminate considerations of attempts at curative therapy. Usually these patients receive nonspecific supportive treatment or palliative treatment by surgery, radiation, or chemicals. The consequences of these forms of therapy are usually helpful but sometimes the sequelae or complications of the various treatments are in themselves life-threatening and constitute a hazard to the patient. Hence, whole body radiation therapy is no more likely to produce untoward sequelae or complications than many other currently accepted treatments of other types." (5) The National Institutes of Health (NIH) became aware of the TBI program with utilization of the General Clinical Research Centers (GCRC) at University Hospital, and Children's Hospital beginning in 1969. The NIH had approved all applications for support from these units for continued operation at the Centers, including the TBI study (6).

From 1960 to 1971 approximately 80 cancer patients per year received preliminary evaluation for TBI; of 112 final candidates only 7 or 8 per year with metastatic tumors (total 85) could actually be treated because of the great

demands on the small staff caring for each patient. Twenty-four patients were rejected because of performance status, lack of measurable metastases or availability of better therapeutic options. Three children with Ewing's tumor who had received doses of local radiotherapy intended to be curative were also given TBI prophylactically. UCMC at that time provided care only for medically indigent patients but five private patients were referred. Thus of the 112 patients considered, 88 received TBI or PBI (2). TBI doses up to 200 rads, or 300 rads PBI, were administered to patients with carcinoma of the colon and rectum (29), bronchogenic carcinoma (15), breast adenocarcinoma (15), Ewing's tumor (4), and 25 individuals with other neoplasms, employing a cobalt-60 teletherapy unit. Survival was better with TBI-PBI than with chlorambucil for lung cancer or than 5-fluorouracil for colon cancer, or than androgen-estrogen therapy alone for breast cancer using comparative data from other series ("historical controls") (2).

INFORMED CONSENT

A specific consent form for human research in NIH funded projects was first required by United States Public Health Service Policy and Procedure Order Number 129 of July 1, 1966, and by Food and Drug Administration Regulation No. 11415 on August 30, 1966. These were followed by "AMA Ethical Guidelines for Clinical Investigation", November 30, 1966 and "Supervision of Experimental Subjects: Recommendations of the Royal College of Physicians", August 12, 1967 (7). During the project period from 1960-1965, when the NIH was not involved, a note indicating patient consent for TBI was usually, but not always, found in the patient's chart. On May 1, 1965 (prior to NIH guidelines), written consent form was initiated. The practice was to have the patient sign a simple consent

form in the presence of a witness.

The method of obtaining informed consent from 1968 to 1971 was as follows: the patient was given all information concerning the risks and benefits from the radiation including the necessity for frequent blood and urine tests, the methods to be employed for his protection, the necessity for a two week study period prior to therapy, and the right of the patient to withdraw at any time from the study. It was further stated that the results from these tests might be of use to help protect and treat injured individuals in the event of a nuclear accident or war. This whole explanation lasted 20-45 minutes. No patient refused treatment. When the consent form was given the patient, he was told not to sign it, but rather to discuss it with his family, friends, or lawyer, and a second meeting was scheduled in a few days. At this time the patient-advocate was encouraged to be present and the entire explanation was repeated again. Only after informed consent had been sought twice, on different days, with the patient-advocate present the second time, and after the patient could explain in his own words what he had been told, was the consent form signed. Since our view had been that the sources of research funding were irrelevant to the patient, information was never supplied to the patient that the money to pay for hospital costs (if the funds were from the GCRC) came from the NIH, nor that certain blood and urine tests (but never the costs of medical care) were funded by the DNA. We found support for this attitude in reviewing two symposia (8,9) and a book edited by Dr. Henry Beecher (10) on informed consent in which no reference is ever made to the need to indicate to the subject the source of funds which support research. The point is further underscored in a statement by Frank H. Westheimer, Professor of Chemistry at Harvard: "The present attack on freedom of research seems to me to rest on the

assumption that we can predict, because of the financial sponsorship of the project, that its results will be harmful." (11) No funding was sought from other agencies because, within the limits of our capabilities, we regarded the funding as adequate and free of any control, financial or otherwise, by DNA over patient selection or care. The results of our research were never classified and received the usual peer review during the publication process.

A request for reprints of the TBI work came from a Mr. Roger Rapaport in November, 1970. A letter from the Project Director to him on April 19, 1971 indicated the dual goals: cancer therapy and a further understanding of the effects of wide field radiation. It was made clear that the money was for "laboratory personnel and services only", that the study was approved by the Faculty Committee on Human Research of the UCMC. Mr. Rapaport was provided with the names of three other physicians at major medical centers employing TBI and on May 28, 1972, data on radiobiological dosimetry (12) was also sent. In the summer of that year, in his book, The Great American Bomb Machine (13), this author quoted from the technical reports to DNA on the need for human data on radiation effects, concluding with the comment that the Cincinnati group tells the patients it "hopes the whole body radiation will cure or at least alleviate their cancer", despite the fact that no patient at UCMC was ever told the treatment was curative.

In September, 1971, following a request from a Mr. Paul Jacobs expressing an interest in the cancer program, consent was given for an interview for what was described as an educational program, a National Educational Television (NET) series called "The Great American Dream Machine". It was agreed to allow the representatives to interview several patients solely concerning their medical

treatment, pending their consent. Only one patient who had received TBI was interviewed, and she described her clinical improvement following TBI. She became suspicious and angry when asked by the television crew if she knew she was being used for Defense Department purposes and terminated the interview. This patient confirmed, during subsequent medical examination on January 11, 1972 that she did know, as did all patients, that the data from her radiotherapy might be of use "on the battlefield". The granddaughter of this patient, who was also present at the interview, wrote that the N.E.T. television crew who had come to her home: (1) told the patient that the interview was for "medical purposes" and that they had been asked to come out to their home by the Medical Center where they worked; (2) had the patient sign a release form which she did not understand and which was not explained to her; (3) refused to let the granddaughter look at this release form; (4) tried to get the patient to say she has been paid to participate in an experiment. The second (non-TBI) patient interviewed, who was receiving only local radiotherapy, and was not in the study, was asked how he felt about a treatment when tests were funded, in part by the Defense Department. He replied, "I'd do anything to help our boys", and the NET interviewer dismissed the patient.

We were similarly unprepared for the dialogue with Mr. Jacobs' colleague Mr. Saul Landau, before the television camera, which rapidly took on an accusatory tone although we had been told the NET filming was to discuss our therapeutic efforts. Mr. Jacobs and another television crew flew to Wyoming to conduct an identical interview with the vacationing Project Director. "The Great American Dream Machine" was subsequently canceled and the footage on TBI was never shown publicly, but as the controversy grew the filming would have important implications. Although Jacobs agreed to allow the researchers to

review the material prior to any showing, we have yet to see any of the taped material. The freelance television reporters who worked on this project later were quoted in a local newspaper: "They never doubted General Hospital* persons involved in the project were 'sincerely interested in the patients' welfare'". (14)

On October 6, 1971, a Washington Post reporter, Mr. Thomas O'Toole, attempted a telephone interview and was referred to the Project Director then in Washington. After that interview, in which another Post reporter, Mr. Stuart Auerbach, participated, Mr. O'Toole called again the next day questioning why the I.Q.'s of the patients were "so low" (mean 87, range 60-115). These findings were virtually identical to findings with patients at University Hospital in a 1969-1970 study by another group. Fifty-eight percent of our patients were black, with a mean education of 6.7 years schooling, similar to that of the hospital population as a whole. O'Toole raised question of informed consent and the two-stage consent procedure was again explained. He was also informed that the study had been reviewed by the Faculty Committee on Human Research.

On Friday, October 8, 1971, a front page headline of the Washington Post proclaimed "Pentagon Has Contract to Test Radiation Effect on Humans" with a similar article appearing simultaneously in the New York Times. The Post article's second sentence stated, "The prime purpose of the study, according to the contract, has been to understand better the influence of radiation on combat effectiveness of troops." A discussion of funding led to the following: "This has been enough to buy (sic), study and treat 111 patients in 11 years." This statement may have been elicited by our technical reports to DNA which did not discuss therapy, since DNA was not funding treatment.

*Now University of Cincinnati Hospital

The Washington Post stated that the researchers "published little", despite the existence in the fall of 1971 of 37 publications and presentations, in addition to annual, unclassified, technical reports to DNA. The Post emphasized that the study was uncontrolled, not recognizing the use of phase 1 and 2 toxicity and efficacy studies for treatments under clinical evaluation (15). The article re-emphasized that the UC Faculty Committee on Human Research and the patients were not told the source of funding. A letter to the Washington Post editor from the UCMC researchers objecting to and correcting the content and phrasing of the article was never published.

On Monday, October 11, the TBI program was explained in detail in a press conference held at UCMC, including the fact that the DNA funded no direct patient care. Conspicuously absent data from our study at that time were the results of an actuarial analysis of patient survival compared to other modalities of treatment. Since we had planned to continue the TBI study for two more years, no such analysis was available. A media representative challenged the speakers: "The whole question this morning is whether we have guinea pigs in Cincinnati or not."

At this time the issue was politicized when Senator Edward M. Kennedy wrote Defense Secretary Melvin Laird, a letter quoted in the Congressional Record, "I was shocked and disturbed to learn from today's Washington Post, that the Defense Department is sponsoring research on radiation effects on human beings without informing the individuals involved of the military purposes of their irradiation. I believe this project represents an incredible infringement of individual liberty and establishes a dangerous precedent for the reduction of human rights in our society" (16). The Cincinnati Enquirer, October 13, 1971

printed": 'Senator Taft (Robert Taft, Jr., R-Ohio) is trying to find out everything he can', a spokesman for him said. "He is extremely interested in this, but will not have any comment until he finds out more about it.' Representatives William Keating and Donald Clancy, both Republicans from Cincinnati also recommend caution 'until all the facts are known.' Kennedy has no more facts than we do right now', Representative Keating declared in an interview, 'and therefore, it seems to me he has no right to make such charges against the project.'" (17)

The London Times, believing the Post story in toto, ran an editorial October 11, 1971 entitled "Hospital Wards Are Not Battlefields" which concluded "...had the Cincinnati experiment been publicly reported it would no doubt have been stopped long ago". The innuendo of secrecy was there to stay. On that day the San Francisco Examiner headline read, "Dying Patients Got Radiation for the Pentagon." The press would never distinguish between a patient with inoperable but treatable cancer and one "dying", "doomed", or "terminal" and our patients were constantly referred to in these latter terms. On October 15, Senator Mike Gravel (D-Alaska), whose only reference was Rapaport's "Bomb Machine", entered in the Congressional Record comments on the "grisly story" of the project (18). L'Express of Paris headlined "Les Cobayes (guinea pigs) de Cincinnati" (19). The UC News Record, the student newspaper, asked (October 22, 1971), "Why have not personal charts and data concerning vital information about the patients been made public?" with no consideration of the need for patient informed consent for such action or the right of the patient to privacy. Nevertheless our refusal to make such data available to the press on demand only fueled journalistic suspicions. Then the Defense Department entered the controversy and the Cincinnati Enquirer printed on October 14: "A top civil defense official

declared Thursday the lives of 50 million or more Americans may one day depend on findings from the Pentagon-University of Cincinnati radiation research project." The article added that DNA insisted that the "cost of the university program in therapy and patient care is borne entirely by General Hospital".

The publicity of the ensuing months brought letters and telephone calls pleading for TBI from families of cancer patients (which could not be given), as well as communication to us and other University officials accusing us of "genocide".

ARE EIGHT INVESTIGATIONS ENOUGH?

Investigation I

At the request of U.C. President Dr. Warren Bennis, the Dean of the College of Medicine organized and Ad Hoc Committee of the Faculty (November 12, 1971) to investigate the TBI project, (although for the prior five years we had been though the peer review process). Nine members of the committee were professors of the faculty of the College of Medicine and the other two were nationally known scientists from the main campus of the University. This committee conducted extensive interviews, reviewed large numbers of documents, spent hundreds of man-hours and completed its sixty-nine page report (plus several hundred pages comprising nine appendices) in January, 1971 (6). It was made public February 16, 1972. The committee summarized its work in part as follows;

"The methods used in selection of patients for this (study) were satisfactory."

"The patients treated in the whole body radiation study received

excellent care in respect to both their medical illness and psychological needs. The psychologic support to these patients far exceed the support usually given to the dying patient." "Follow-up care and evaluation was performed in a detailed manner for six weeks by the study physicians, and subsequently provided in the Tumor Clinic." (p. 32) "The investigators have had complete scientific freedom. There is nothing in the record to indicate that any specific kinds of test or treatment were dictated or even suggested by the supporting agency." (p. 45) "If further studies are planned, the support for such programs should be sought from a federal health agency or foundation interested in cancer research." (p. 46) This was the committee's sole pronouncement on funding, but, as will be described later, it was used by the U.C. President to justify termination of Defense Nuclear Agency funding before an application to the NIH could be finalized. "The committee wishes to be on record as opposed to any outside investigating body interviewing a patient and/or his family because it believes that such interviews would violate the patient's rights and would be in violation of the guidelines provided by the United States Public Health Service of the Department of Health, Education and Welfare." (p. 56) "The design of the experiment from the beginning did incorporate measures to improve the care of the patients" (p. 61) "The design of the experiment was adequate to define the toxicity of the radiation used and to indicate the safety and efficacy of the use of autologous bone marrow transplantation. It is not adequate to evaluate the effect of treatment on survival rates." (p. 6) This was somewhat inaccurate, as our TBI patients

with lung, colon and breast cancer, survived longer than unmatched contemporaneous patients with these tumors either untreated, or treated by two other accepted methods (2). "The design of the experiment lacked carefully selected measures to evaluate palliation". (p. 61) Indeed our end point for efficacy was survival, but other paramteters (enumerated in reference 2), were examined, although some of these were subjective patient responses. Most importantly, "Since the Committee cannot at this time rule out a positive effect of whole body irradiation, a well-designed study to compare whole body radiation with other forms of therapy is recommended."

Investigation 2

Several members of the Ad Hoc Committee of UCMC had provided scientific and/or clinical consultation to the TBI project, thus having had prior access to information from participation in the work. However, this could be construed as biasing the report favorably. Therefore all the relevant data were also sent to members of the National Academy of Sciences by the President of the University. These reviewers confirmed the validity of the U.C. Committee report.

Investigation 3

Meanwhile, back at the Senate, interest in TBI had not subsided. A staff member (appointed, not elected) of Senator Kennedy's Subcommittee on Health (of the Senate Committee on Labor and Public Welfare), Ellis R. Mottur, wrote UC on November 24, 1971, requesting an interview with officials of the Medical Center and with the researchers.

On December 6, Mottur and another staff member, Philip Caper, M.D., came to Cincinnati. The full Senate subcommittee did not authorize this visit. Mr. Mottur and Dr. Caper requested and received a full description of the TBI project. Mottur emphasized his concern about DNA funding and even suggested that these (unclassified) data could be used by the Defense Department as an offensive weapon. Dr. Caper, who had come from the NIH to Senator Kennedy's subcommittee staff as an expert in medical investigation, was unfamiliar with the concepts of Phase 1, 2, 3 studies for evaluation of new treatments (this was a phase 1 and 2 project) and was supplied with an explanatory document (15).

Finally Mr. Mottur asked to talk to the patients, to determine for himself what they understood. We indicated that this would not only be an invasion of privacy but also psychologically deleterious, and refused. Mottur objected that since he had expertise in the psychology of human behavior, the interviews would not harm the patients. Such interviews, we insisted, must require fully informed consent such as we had obtained for the television interviews, when the context of the interview was represented to us as being entirely different. Mr. Mottur felt that the question could be asked in an anonymous fashion so that the patients would not be distressed at an inquisition from Senate investigators. He did not want the Faculty Committee on Human Research to be consulted and even raised the possibility of his being concealed behind a screen, unknown to the patient, to listen to such an interview. On December 22, the Director of the UC Medical Center denied to Senator Kennedy and Mr. Mottur access to the patients or their families or even to reveal their identities. In this he was supported by Ohio Statute 4371.22, which prohibits "willful betrayal of medical trust", Statute 2317.02, upholding the principle of privileged communication, and an

Ohio Supreme Court opinion defending the patient's right to protection from "publicity" and "resultant mental suffering". Senator Robert Taft was not attacking Senator Kennedy's investigative attempts, so Senator Kennedy wrote Senator Taft on December 17, 1971 that he had actually qualified his earlier comments in the Washington Post by saying "If the news report is accurate, I believe this project represents an incredible infringement of individual liberty...", but that qualifying word, "if" does not appear in his statement in the Congressional Record. (16) Senator Kennedy added, in his December 17 letter to Senator Taft, "Since the initial story appeared on October 8, however, we have also received a large amount of information and comments on the project from a variety of sources throughout the country. This information contains some significant discrepancies with the official account of the project. Careful evaluation of this information was not able to remove these discrepancies."

There were indeed two discrepancies. The UCMC senior project director did not interview the patients initially and did not know that the patients' physician was informing each patient of the potential value of the blood and urine tests for individuals exposed to radiation. Secondly, and of great discomfort to the U.C. officials, was the inadvertent but serious failure of the investigators to mention that we had previously permitted patient interviews under what we incorrectly perceived as different circumstances, for a National Education Television program, to discuss their perceptions of the value of their therapy.

Senator Taft responded on December 23, ". . . I feel it is vital that a thorough study and report be made by professionally qualified experts. In this

regard I repeat my prior position--that the demand by staff members, unauthorized by committee action, to interview patients and patients' families raised doctor-patient relationship questions, as well as questions regarding the obligation of the institution and of the doctor, for the welfare of the patients. Certain proper safeguards against abuse or improper use of information obtained should be set by the committee. Until this has been done, my recommendation and position is that any such interviews should be deferred."

Escalation occurred January 4, 1972 when there appeared in the Cincinnati Enquirer, under the headline "Kennedy Aide Says UC Refusal Endangers Funds for Research", the following:

> "The University of Cincinnati may jeopardize its federal medical research funds by refusing the request of congressional investigators to interview cancer patients in its 'whole-body radiation' project, a Senate Health Committee spokesman said Monday.
>
> "'UC would be a lot better off by cooperating with us' said Ellis Mottur, scientific advisor to the Senate Labor and Public Welfare Committee and to its Health Subcommittee.
>
> "'If it is deemed essential that we talk to the patients, we will do so--there are no two ways about it'" (20).

Mr. Mottur was not misquoted, for an article in the Cincinnati Post of the same date, January 4, reported "Ellis Mottur, subcommittee aide, said Kennedy now has three options:

> "Write University officials again asking why patients or their families may not be allowed to submit to interviews if they choose.

Kennedy has promised to protect patients' anonymity. Mottur said University officials could attend the interviews and patients' faces could be hidden if they desire.

"Ask the Secretaries of Defense and Health, Education and Welfare to pressure UC into allowing the Subcommittee to seek interviews with patients. Both federal departments supply funds for either the Center or the project.

"Subpoena University and Medical Center officials and their records. Mottur doubted that Kennedy would opt for use of the subpoena power." (21)

On January 11, 1972 Senator Kennedy wrote the new UC President questioning why National Educational Television had been allowed to interview patients (actually only the one woman who received TBI, as detailed above) and the Senate subcommittee had been denied access to patients. Eight days later Senator Kennedy received a reply from UC that letters had been sent to the patients (or their parents in the case of 3 children treated) "to determine if they wished to give their consent to questioning by representatives of your Subcommittee." The note to Kennedy continued, "We have, as I have written earlier, obtained the opinions of a number of experienced physicians as to the potential harmful effects of this inquiry upon the patients' well-being, and are, moreover, in the course of obtaining the opinions of others. We will communicate these to you when they are in hand. It has been the uniform judgement of those we have consulted up to this time, that should some of the patients consent to the interview you have requested, there may be unfavorable consequences to their health."

The letter to each patient read as follows: "Dear . . . A member of the United States Senate wants to send a person to talk with you about your sickness and treatment. They want me to give them your name and tell them where you live, but I have refused to give them this information without your O.K. Do you want me to give them your name? Please let me know if you answer is yes or no by writing a note on the bottom of this letter and mailing it back to me in the attached envelope."

All patients refused to be interviewed and typically added comments such as "The answer is no. I do not wish to be interviewed or disturbed by anyone."

Investigation IV

The American College of Physicians was then contacted by UCMC and recommended two oncologists of nationally recognized reputation be invited to Cincinnati to review the TBI project and express an opinion on patient interviewing. These separate visits were made shortly thereafter. On February 19, 1972, Joseph F. Ross, M.D., Professor of Medicine, U.C.L.A., wrote "In my opinion to conduct such interviews would be definitely deleterious to the physical and emotional status of these patients and medically is definitely contraindicated." B.J. Kennedy, M.D., Professor of Oncology, University of Minnesota School of Medicine, added on February 14, "One can presume that the articles in the public press regarding the current controversy are not in the best interest of the patient. Reference to 'doomed patients' or 'human guinea pigs' would certainly have an impact on the patients' well-being, no matter how stable they may be. To contribute further to such an emotional upheaval by

committee interviews would be cruel."

On February 17 a letter was sent to Senator Kennedy advising him of the University's final refusal to grant interviews with patients based on the unanimous negative response of the patients and consultants. The possibility of Senate hearings on our TBI research thus seemed less likely and none were every held. But in the summer of 1972 Kennedy and his staff were to use another government agency, the General Accounting Office (GAO), to investigate the project and would deny that the GAO report existed when it proved favorable to UC. Two other inquiries must be detailed first, however.

Investigation V

After Senator Mike Gravel (D. Alaska) had entered his quote about TBI as a "grisly story" in the Congressional Record (18), he then requested the American College of Radiologists (ACR) to look into our work. On November 29 and again December 16, 1971, a committee (consisting of Henry Kaplan, M.D., Chairman and Professor, Department of Radiology, Stanford University Medical School; Samuel Taylor, III, M.D., Professor of Medicine, Rush Medical School; and Frank Hendrickson, M.D., Chairman, Department of Radiation Therapy, Presbyterian-St. Luke Hospital, Chicago) made a detailed inquiry of the TBI project including a site visit. Their findings were communicated to Senator Gravel in a 13 page letter from Robert W. McConnell, M.D., President of the ACR. In part Dr. McConnell wrote: "We have made our inquiry and our broad conclusions are as follows:

"1. In the normal context of a clinical investigation, the project is validly conceived, stated, executed, controlled and followed

up. The appropriate scientific and professional committees of the University of Cincinnati have performed their functions during the course of the project.

"2. The process of patient selection based upon clinical considerations conforms with good medical practice.

"3. The records, publications and patient follow-up are voluminous and commendable.

"4. The procedure used for obtaining patient consent is valid, thorough and consistent with the recommendation of the National Institutes of Health and with the practice of most cancer centers."

"5. Should this project come before the Senate or one of its committees in some fashion, we would urge your support for its continuation." However, Senator Gravel was not pleased with this report and wrote Dr. McConnell on February 4, 1972, suggesting that the document had not addressed itself to most of the issues he had raised. In a reply dated March 7, Senator Gravel was told by Dr. McConnell, "after receipt of your letter of February 4, we reviewed our previous response to you. It seems to us that your letter totally reversed the conclusions which we reported to you. Our answers to your original questions represented the considered assessment of three of the most highly qualified cancer specialists in the country." Further inquiry was refused by the ACR.

To Senator Kennedy's displeasure was thus added that of Senator Gravel. Then Senator Gravel wrote a group of the local Junior Faculty Association (JFA)

consisting of 15-25 untenured members. "As you will see from the enclosed letter to the ACR (the Feb. 4 letter), I am not satisfied with its report on the Saenger radiation experiments--while the ACR report is evasive, disorganized, and deficient in almost every piece of relevant information, the JFA report (see Investigation VI) is extremely well-organized and to the point--My next point is that we do not try too hard to save lives, and in the context of cheap life, Dr. Saenger's experiments seem to be a symptom of a very much larger callousness." (22)

Investigation VI

An assistant professor of English, self-appointed as chairperson of a Junior Faculty Association Subcommittee on TBI, visited the UC President soon after October, 1971 publicity to express concern about the existence of the TBI project. At our Laboratory she demanded, and received, all the information, reprints and references (where reprints were unavailable) which she had requested. Three months of public silence from the group was broken when, on January 25, 1972, the Columbia Broadcasting System called us to request an interview "after the press conference". The JFA Subcommittee had decided to publicize its study of the project by using the media. However, the Vice-President of the JFA was also at that news conference to issue the following statement:

> "The individuals--David Logan, Henry Anna, and Martha Stephens--issuing "A Report to the Campus Community" today are acting on their own and not in any way duly authorized by the JFA. JFA has not authorized a press conference or release to the news media of this report. The JFA membership has not had an opportunity to read and

taken seriously by anyone properly informed about this project."

to vote on the report as currently worded. The JFA has not authorized in principle a report with the type of conclusions or judgements included in this report. I, as Vice-President of the JFA have been denied (by the President, David Logan) the opportunity of a delay and a meeting to have these matters challenged by the membership. Some of the questions in the report are ones which should be asked and some of the information is relevant overall; however, the report should be judged in the context of the above information." (23,24)

The unsigned "JFA" report, not reviewed by any senior scientist or member of the UC Administration, was drawn from unclassified technical reports to DNA written since 1960. These documents of necessity did not analyze therapeutic outcome but were directed to the interest of the funding agency (DOD), i.e. the results of the tests performed on the patients after radiotherapy. Where were the survival data, asked the authors? "We can only conclude," said the JFA release "that the purpose of irradiating cancer patients at General Hospital was primarily to study radiation injury for the DOD and that incurable cancer patients were used because (a) they were going to die anyway and (b) they 'might' benefit from radiation in terms of reducing pain or slowing the spread of cancer." The authors then examined patient survival and concluded that radiation killed many of the cancer patients. The concept of relating results to a comparable untreated group had eluded the three "JFA" authors and the press. The JFA simply refused to believe the patients gave informed consent, despite the voluminous documentation noted above. Finally, these three Instructors (of English and Political Science) comment on the report of the American College of Radiology: "We are confident that this report will not be taken seriously by anyone properly informed about this project."

This JFA press conference led to a local headline: "UC Faculty Group Would End Whole Body Radiation Program". It was published side-by-side with the ACR report in Drug Research Reports (25), inferring that the two had equal validity. The report was subsequently duly accepted at a JFA meeting, apparently according to appropriate by-laws, but less than ten people were present at that meeting. The legitimacy and scientific validity of the JFA report have never been questioned (26). A written refutation of the JFA report from the author's Laboratory dated February 10, 1972 was never released because:

a. counsel had advised that rebuttal data be saved for possible Senate hearings (which were never held);
b. it had been agreed with the UC Administration not to make any public statement but rather to work through a single spokesman unassociated with the TBI project;
c. A manuscript had been prepared (and subsequently published (2)) and it was felt improper to release such data to the press prior to the peer review process.

However, the reticence of the Medical Center to release pertinent information (due to the difficulty of instant actuarial analysis while also maintaining all professional responsibilities and being reinvestigated so often, as well as concern to retain vital data for Senate hearings) made the press suspicious.

Investigation VII

The General Accounting Office (GAO), an agency of the Congress, was asked in a Kennedy letter of December 23, 1971 (4), to investigate the project, as was

learned first from a page one newspaper account of January 18, 1972 (27). The scope of the investigation was said to be solely "to determine if federal money is paying for full-body radiation treatment of terminal cancer patients" (27). "University officials insist that Federal money is used only to pay for tests after treatment, not for the treatment itself" (27). The distinction was a vital one in the minds of all concerned. The same article suggested that the GAO would have access to patient records, but this was denied that agency. The GAO inquiry involved not only financing but, once again, the history of the project, informed consent, experimental design, etc.

The response of the Comptroller General of the United States (the head of the GAO) to Senator Kennedy's demand for an investigation came in a letter dated May 26, 1972 (4). The letter states that "funds of the Defense Nuclear Agency had been used only to pay for supplementary laboratory analysis of patients who had received whole body irradiation in order for the Defense Nuclear Agency to gain information in areas that are relative to national defense". However, on July 27 and again on August 1, 1972, Senator Kennedy's staff denied that the final GAO report existed (28). On August 1, Senator Kennedy entered what purported to be the Comptroller General's letter into the Congressional Record, but the portions of that letter exonerating the UC TBI project were deleted (29). Senator Taft obtained a copy of the unedited GAO letter, and the Cincinnati Post then reported, on a back page, "Senator Edward M. Kennedy has been sitting on a government report showing no evidence could be found that Pentagon money paid for actual whole-body x-ray treatments of dying (sic) cancer patients at the University of Cincinnati (28).

Investigation VIII

The UC chapter of the American Association of University Professors also studied the project. The chairman of that investigative subcommittee stated, "We found no ethical guidelines were violated".

Investigation IX (almost)

The National Medical Association was asked to investigate the project by Kennedy and Mr. Mottur but turned them down (30).

AFTER THE INVESTIGATIONS--WHO LISTENS?

The investigative balance sheet on the medical ethics of the TBI project thus showed the following: Con: One group, the Junior Faculty Association of UC; Pro: The UC Faculty Committee on Human Research, the Cincinnati Children's Hospital Medical Center Committee on Research, Daniel Drake Memorial Hospital Committee on Human Research, the American College of Radiology, two oncologists recommended by the American College of Physicians, the American Association of University Professors, an Ad Hoc Committee of our own peers at UC, two separate General Clinical Research Committees of the UC Medical Center and Children's Hospital Medical Center and the General Accounting Office of the United States Congress (ten groups in all). Both the ACR and the UC Ad Hoc Committee had recommended further clinical evaluation of TBI with the recommendation that we apply to "a federal health agency or foundation interested in cancer research" (6).

Following the last recommendation, the preparation of a grant request to the NIH was begun in March, 1972 with assistance and support of members of the Faculty Committee on Human Research at least one of whom (the chairperson) had sat on the Ad Hoc Committee on TBI. The DNA contract was to end March 31, 1972, but it had been assumed that funding would be continued at least until an NIH study section had reviewed a new proposal, a process requiring a number of months. Without continuing interim financial support for this period, members of our staff, technologists, and supplies for on-going research would be unfunded, and this work would have to be discontinued.

At this time former President Nixon ordered the mining of North Vietnamese ports which further inflamed anti-war feeling around the country. A small but vociferous local health organization, whose goals included separating UC from Cincinnati General Hospital, stated in an April, 1972 press release "We feel that an end to the Radiation Project is an anti-war protest". The link between the Vietnam war and DNA funding of the TBI project was now a recurrent theme. When added to the false charges that we were negotiating with DNA behind the backs of the UC Administration (31), pressure was mounting on the UC administration to take action on the TBI project, regardless of the investigative results presented above.

On April 21, 1972 the afternoon newspaper (Cincinnati Post) reported that the UC President had refused the DNA renewal of our contract. The U.C. T.B.I. project director had been warned of this action only an hour or so before the newspaper account, by a University official but not by President Bennis. The justification for refusing the DNA money was, according to a UC press release of that date, that the Ad Hoc Committee report had suggested that money "should be

sought from a federal health agency or foundation interested in cancer research". In fact, the first draft of a Phase 3 study on TBI for NIH funding had already been submitted to the Faculty Committee on Research and Office of the Dean, U.C. College of Medicine, March 21, 1972 but the UC President was inexplicably told this had not been done, and no opportunity was given to the investigators to provide him with a copy. A great many investigative bodies and levels of administrative hierarchy had been inserted between the President of the University and the TBI investigators. Lack of such direct communication proved quite harmful to the project. On May 9, the UC President stated, "Any new whole body radiation research can be undertaken only under the following conditions, stemming from the Suskind Report (Ad Hoc Committee):

"A. Funding from sources other than DOD.

"B. Only with certain specific tumors that have proved to be responsive to whole body treatment.

"C. A new review of our research proposals by the Faculty Committee on Human Research of the College of Medicine.

"D. Subsequent review by the University Research Council, chaired by Provost Robert O'Neill.

"E. A final review by the president of the University who would consult with experts external to the University before any approval is given (32)."

However, under a headline, "Petitions Blast UC War Machine", the President had been quoted as stating "'I have no power to end DOD contracts. Even if I had

the power I would not do it as long as there is educational relevance and educational value'. There would be an effort on his part to make sure there would be no anti-personnel effects of the research, he added" (33). Within a week after the contract had been cancelled a local newspaper reported that studies of biological effects of the laser (in volunteer human investigators) were being funded by DOD at the University of Cincinnati (34). However, the Director of the University of Cincinnati Medical Center made it clear that "before a proposal for research funding submitted by a University of Cincinnati faculty member and approved by an outside funding agency can become a contract, it must be signed by a senior administrative official of the University" (31).

Writing in the Saturday Review seven months later, the UC President indicated the immense pressures to which he had been subjected: "Last year perhaps 20% of my time was taken up by a problem at the General Hospital... Some terminal cancer patients, with their consent, had been subjected to whole-body radiation as possibly beneficial therapy. The problem, hopefully, has subsided (after a blue-ribbon task force recommended significant changes in the experiment's design). But I have also invested endless time on a matter only vaguely related to the prime purposes of our university-and wound up being accused by some of interfering with academic freedom" (35). The UC President had been forced to act to protect the University from external threats from Washington (20,21) and from internal agitation by the JFA group and anti-war students. He was most concerned that Congressional hearings would be damaging to the investigators, the Medical Center and the entire University.

SUBSEQUENT PUBLICITY

The TBI project continued to be a cause for certain groups to pursue. One

of these sallies came from Senator Gravel who announced, in the National Enquirer on September 24, 1972, five months after the UC President had terminated the contract and 11½ months after the first Washington Post article, "The Pentagon is subsidizing the use of human guinea pigs in radiation experiments". The following month, again in the National Enquirer, Gravel informed his audience that "Pentagon subsidies for the use of human guinea pigs in radiation experiments at the University of Cincinnati have been cut off-by University officials. I have received word of the University's decision shortly after my story on this appalling situation appeared in the September 24 issue of the National Enquirer". This UC action had occurred April 21, 1972. Senator Kennedy in October, 1972 placed in the Congressional Record a statement referring to the TBI project: "In this case, the care of the patient was secondary to the experiment with total body radiation" (36), which Senator Taft was quick to rebut (37).

The adverse publicity continued, disregarding the published data. Accompanying an objective account in Medical World News of a paper on TBI therapy presented at the American Roentgen Ray Society in October, 1972, there appeared an insert which began "Frequently denouncing the whole-body irradiation project as a travesty of medical ethics and linking it with the Tuskegee syphilis study (MWN, Aug 18), Senators Gravel and Kennedy continue to demand more explanation" (38). From South Africa, in February, 1974, came a letter requesting explanation of an article headed, "Horrifying Experiments in America. They're Using People as Atomic Radiation Guinea Pigs" (39). An Americans for Democratic Action affiliate published an article about the TBI work in July, 1974 headlined, "Radiation Death for the Pentagon" (26). An allusion to the project appeared in the New England Journal of Medicine in 1974, stating, "We

are all for advancing the frontiers of knowledge, as the expression goes, but not at the expense of studying the reaction of terminal cancer patients to radiation that exceeds the recommended dosage. If there are not criminal statutes that apply to such mutilation and perversion of 'treatment', there should be, but assuming their absence, then lapses of decency and good taste should not be elevated to the category of ethical imponderables on which reasonable persons may differ" (40).

And yet, on November 26, 1973 an N.I.H. official inquired of the General Clinical Research Center of Cincinnati Children's Hospital Medical Center what the status of our research on TBI in pediatric bone tumors was. At that time a child of a Congressman had just been diagnosed as having osteogenic sarcoma.

AND WHAT ABOUT THE PATIENTS?

Five of twelve patients living in September, 1971 were still alive in 1976, four functioning in society and one residing in a nursing home five years after the last TBI was given. One died in 1976, 3 in 1977, and one is still alive in 1986. Whether this was due to the TBI therapy or patient selection one cannot judge without the aborted Phase 3 study. But the patients were uniformly angered at the attempted invasion of privacy. Fortunately, use of terms like "doomed" and "terminal" in the media did not weaken the doctor-patient relationship. The letter of one mother of a young child is reprinted verbatim, with her permission:

"As I have stated before, I wish for no interview with the Senate, concerning my son's health. I believe this is very personal to my family and all the Doctors involved in _____'s case. This whole thing about the whole

body radiation on T.V. and the newspaper has upset _____ very much. Only last week I went to _____'s school for a PTA meeting, six different teachers came up to me and told me how _____ had seemed upset at school. Some older children came up to _____ and said 'I didn't know you had terminal cancer', well _____came home and started asking a lot of questions about the paper stating 'Doomed Patients' that were dying from the whole body radiation treatment, then he wanted to know how much longer he has to live."

Multiple issues have been raised by our experience. DOD funding for medical research involving patients was felt to be inappropriate in the Viet Nam era but a recent printout obtained by Congressman Willis Gradison (Oct. 10, 1985) indicated 81 such DOD funded projects including threats of withholding federal funding.

Intramural and extramural pressure including threats of withholding federal funding forced a respected University president to cancel a U.S. government grant. Patient confidentiality was, however, upheld through the entire process despite multiple assaults from outside the Medical Center. We learned that refusal, delay, or inability to provide instant patient-related information can arouse great mistrust and anger from the media on whom the pressure to make deadlines may be enormous.

If our procedure for obtaining for obtaining informed consent by presenting the facts twice on separate days in the presence of patient advocates (41) is insufficient to satisfy critics, what fairer procedure exists? Should the source of funding of a project be stopped because the project, ethically conceived, may be of value to national defense? Should informed consent

routinely include an explanation of funding sources as was recently suggested, based on a physician reading of our experience in the New York Review of Books (as interpreted by the same Paul Jacobs who had contracted with "Dream Machine") (42)? How does one legislate protection of patients' privacy from the press and politicians? Of what value are investigations, by multiple prestigious professional groups, when their findings can be so easily ignored? Can the decisions of a Medical Faculty Committee on Research be reviewed and potentially reversed by non-medical university officials? Finally, just who is it that oversees the overseers of research? (43).

BIBLIOGRAPHY

1. Chaoul H, Lange K: Ueber Lymphogranulomatose und ihre Behandlung mit Rontgenstrahlen. Munchen med. Wchnschr., 70:725-727, 1923.

2. Saenger EL, Silberstein EB, Aron B. et al: Whole body and partial body radiotherapy of advanced cancer. Am J Roentgen, Rad Ther, Nucl Med 117:670-685, 1973.

3. Lushbaugh CC, Comas F, Edwards CL, Andrews GA: Clinical evidence of dose-rate effects in total-body irradiation in man, in Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology, Edited by D.G. Brown, R.G. Cragle, T.R. Noonan. April 29-May 1, 1968, Oak Ridge, Tenn. CONF-680410, United States Atomic Energy Laboratory, 1968, p. 17.3.

4. Staats EB: Comptroller General of the United States, Letter to Edward M. Kennedy, 26 May 1972.

5. Saenger EL, Friedman BI. An appraisal of human studies in radiobiological aspects of weapons effects, Prepared for DASA under Contract DA 49-146-X2-9-029, 14 Nov. 1962, p. 2.

6. The Whole Body Radiation Study of the University of Cincinnati, A Report to the Dean of the College of Medicine by the Ad Hoc Review Committee of the University of Cincinnati, Jan., 1972.

7. Appendices V, VI, The changing mores of biomedical research, Ann Int Med 67:76-77 (Suppl. 7), 1967.

8. Ethical Aspects of Experimentation with Human Subjects, Daedalus 98:219-597, 1969.

9. Ladimer I (editor), New dimensions in legal and ethical concepts for human research. Ann N.Y. Acad Sci 169:293-593, 1970.

10. Beecher HK, Research and the Individual--Human Studies. Little, Brown and Co., Boston, 1970, pp. 358.

11. Westheimer FH: "The freedom of universities... is not a natural law", Harvard Bulletin, 23 March 1970, p. 21.

12. Silberstein EB, Chen I-W, Saenger EL, Kereiakes JG: Cytologic-biochemical radiation dosimeters in man, in Biochemical Indicators of Radiation Injury in Man, I.A.E.A., Vienna, 1971, pp. 181-214.

13. Rapoport R: The Great American Bomb Machine, EP Dutton & Co., Inc., New York, 1971, pp. 89-96.

14. Horton A: Full-body radiation, Cincinnati Post, 18 Jan. 1972, p. 24.

15. Higgins GA, Controlled therapeutic trials, Arch Surg 102:160-161, 1971.

16. Congressional Record--Senate, S16372, 15 October 1971.

BIBLIOGRAPHY (Cont'd)

17. Webb R, Cincinnati Enquirer, 13 October 1971, P. 1.

18. Congressional Record -- Senate S16370, 15 October 1971.

19. Bonnot G, Les cobayes de Cincinnati, L'Express, No. 1058, 18-24 October, 1971.

20. Webb R, Cincinnati Enquirer, 4 Jan 1971, p. 9.

21. Horton A, Cincinnati Post, 4 January 1972, p. 4.

22. Moores L, University of Cincinnati News Record, 25 February 1972, p. 1.

23. Bogart D, Statement For Press Release, 25 January 1972.

24. Boxman W, Cincinnati Enquirer, 26 January 1972, p. 1.

25. Drug Research Reports, Vol. 15, No. 7, 16 February 1972, pp. 521-535.

26. Kaufmann ES: Radiation death for the Pentagon, The Leaves of IVO, (Independent Voters of Ohio, An Affiliate of Americans for Democratic Action), July, 1974, p. 2.

27. Horton A, Cincinnati Post, 18 January 1972, p. 1.

28. Grohl J, Cincinnati Post, 3 August 1972, p. 41.

29. Congressional Record -- Senate, 1 August 1972, S12376.

30. Cincinnati Post, 19 January 1972, p. 43.

31. Horton A, Cincinnati Post, 25 April 1972, p. 33

32. University of Cincinnati News Record, 12 May 1972, p. 2.

33. Behlen R, University of Cincinnati, News Record, 12 May 1972, p. 1.

34. Cincinnati Enquirer, 28 April 1972, p. 1.

35. Bennis W, The University Leader, Saturday Review, 9 Dec 1972, pp. 43-44.

36. Congressional Record, 10 October 1972, S17281.

37. Congressional Record, 12 October 1972, S17631.

38. Medical World News. November, 1972, p. 70 D.

39. Ludlow D, Scope, 10 December 1971, pp. 13-15.

40. Greenberg D.S.: Ethics and nonsense. New Eng J Med 290:977-978, 1974.

BIBLIOGRAPHY (Cont'd)

41. Silberstein EB: Extension of two-part consent form. New Eng J Med 291: 155-156, 1974.

42. Morgan JP, Wardell WM, Weintraub M et al: Clinical trials and tribulations. Arch Int Med 134:380-383, 1974.

43. Page IH: What price protection? JAMA 235:286, 1976.