Ladies and Gentlemen, I have a statement regarding the so-called "whole body irradiation" case at the University of Cincinnati Medical Center.

At the outset, I think it will be useful to review some history of this project.

Doctor Eugene L. Saenger, who is now Professor of Radiology at the UC Medical Center, became interested in a concept study of radiation therapy in cancer when he was chief of the radioisotope laboratory of Brooke General Hospital at Fort Sam Houston, Texas, in 1954-55. At that time, he was impressed with the benefits in patients undergoing systematic ~~he recognized the lack of systematic~~ studies in the course of treatment for burns, and thought that a like approach might have equally ~~on the effects of whole body irradiation on patients~~ Care and will for patients with cancer. When he came back to UC in 1955, he continued his interest in this direction ~~radiation therapy~~.

Since Doctor Saenger knew of the Defense Department's interest in the area of radiation, he conceived the idea of requesting support from the ~~Department~~ research funds, without which the studies could not proceed. The first research draft was prepared for submission to the Defense Atomic Support Agency on Sept. 25, 1958.

Not ~~In 1960, the University first submitted~~ A formal research proposal was made to this agency with Doctor Saenger as principal investigator in 1960. It should be stressed that this ~~proposal was initiated by UC and~~ was in no way solicited by the D-A-S-A. The proposal was accepted and the Defense Department has contributed $471,482.79 through fiscal year 1971, ~~and~~ approved an additional $70,000 through fiscal 1972 which ends June 30.

Amount for

but Three

Eighty-two patients, all of whom had terminal cancer that did not respond to other forms of therapy, have been treated with whole or partial body irradiation in the project. Of these, there are 13 survivors.

The UC ~~proposal that the whole body irradiation~~ project has been reviewed and approved on at least two occasions by the National Institutes of Health as well as the funding agency of the Department of Defense.

In October 1971, published accounts of this project elicited quite a bit of public interest, including in due course, an inquiry from the U.S. Senate Health sub-committee chaired by Senator Edward M. Kennedy. Since then, considerable information has been published, some of which has led to a misinterpretation of the project, its purpose and the university's ~~outlook~~ views toward it.

The University Medical Center had been conducting this project in keeping with the highest ~~acceptable~~ standards of concern ~~where research with humans is done~~ for patient welfare as there have been, changes and upgradings ~~in the~~ as the sophistication ~~of such treatment~~ has progressed over the years.

Nonetheless, in view of questions raised by the non-medical sector, we undertook to make a searching investigation of the entire whole body irradiation project. At the same time, it was decided to halt ~~this project~~ The study until a determination could be made of its future course, ~~on the basis of~~ subsequent to a sound medical and ethical investigation. This has now been effected. ~~It should be emphasized that no patients are being currently treated with whole body radiation at the Medical Center.~~

Our investigation has had two principal thrusts:

In December, distinguished A committee of the American College of Radiology conducted an investigation of the project at our request. In January, this committee issued a report stating that it was being conducted in an ethical and scientific manner and should be continued.

On Nov. 12, 1971, Doctor Clifford G. Grulee Jr., Dean of the College of Medicine, commissioned a "Blue Ribbon Committee" of UC faculty members to conduct a thorough study of the project with special consideration to scientific content, method of treatment, evaluation of data, ethical aspects and medical benefits. This committee consisted of eight senior members of the medical faculty with broad knowledge and interest and two representatives from the non-medical faculty.

That brings us up to date.

The "Blue Ribbon Committee" has completed its study and has reported its findings. I want to publicly compliment the members of this committee for the tireless and, at times, exhaustive manner in which they looked into this entire project. These people have been most dedicated and have, I think, demonstrated a great depth of wisdom.

Up to now, we have appeared to be quite shy about discussing this case in public. I submit there has been validity for this. As medical people, our first obligation is to the patient--in this instance a person who is in a grave condition. We are still not certain of the effect likely to result from, say, the publication of such a person's name with the resultant likelihood of the patient being thrust into the public limelight; or, the effect of being interviewed by Senate investigators, regardless of the tact with which it is done.

physician knowledgeable in these matters

I have just asked two eminent ~~doctors~~ to come to Cincinnati for the purpose of consulting with us on this point.

Moreover, concerned that the mandates of medical ethics, the laws of this state, and the We are ~~also required by state law and by a~~ specific regulation of the ~~the~~ Department of Health, Education and Welfare ~~to retain the privacy of the patients involved~~. This guideline ~~specifies~~ clearly states that (and I quote) the patient, "has the right to be secure in his person, to receive proper professional care, to enjoy privacy and confidentiality in the use of information about himself and to be free from undue embarrassment, discomfort and harrassment." (end of quote)

I should say here parenthetically that this privacy requirement was unfortunately, and I think innocently, broken at one point of the research. This occurred when a group from National Education Television was given permission to interview three patients in the project. Although the interviewing apparently was not satisfactory and the outcome was never released, our physician made a mistake here and it will not be repeated. ~~I have to thank Senator Kennedy for informing us of this incident.~~

~~Another reason for our reluctance~~ We have been deeply reluctant to talk until now of our committee deliberations. ~~is~~ that we have been determined to permit ~~the "Blue Ribbon Committee"~~ investigation to be completed without pressure as to time or undue comment. Since the report is now in hand, I feel I can discuss it with you.

You ought to know the composition of the Committee. Here again, we have kept their names quiet until now because ~~they~~ we wanted them to ~~should~~ have had the opportunity to work in an atmosphere of privacy.

The chairman of the committee is Doctor Raymond R. Suskind, Director of the Department of Environmental Health.

Other members are as follows:

Doctor Bernard S. Aron, Associate professor of Radiology

Doctor Gene Conway, Professor of Medicine

Doctor Robert S. Daniels, Director, Department of Psychiatry

Doctor Paul Herget, Director, Cincinnati Observatory and Fellow of the National Academy of Sciences.

Doctor Evelyn V. Hess, Professor of Medicine and chairman of the Faculty Research Committee

Doctor Daniel L. Kline, Director, Department of Physiology

Doctor Harvey C. Knowles Jr., Professor of Medicine and Director of the General Clinic Research Center

Doctor Alvin M. Mauer, Professor of Pediatrics

Doctor Milton Orchin, Professor of Chemistry and Director, Hoke S. Greene Laboratory of Catalysis -- and

Doctor Edward L. Pratt, Professor of Pediatrics and Director, Children's Hospital Research Foundation.

The committee met numerous times, investigated all available documents on the project and interviewed all of the medical personnel ~~Doctor Saenger~~ involved and others ~~on the medical staff~~ on several occasions.

In the introduction to its final report, the committee makes a very significant point and I want to quote it here:

"In the committee's judgment, the circumstance which led to its appointment is a symptom of the intense concern for the rights and dignity of every citizen. The convening of the committee provided the opportunity of discussing in considerable depth, not only the scientific merit of a single program,

but also the recent evolution of, as well as the customs and practices in, biomedical research involving human subjects. We hope that in providing answers about the project under review, we have underscored the need to exert great care and good scientific judgment in the planning of research programs, particularly those involving human subjects." (end of quote)

The committee insisted throughout that its work be viewed as a medical study and, therefore, that its final report should be so considered. It is a bulky report, three inches thick, and replete with terms known and understood principally by the medical profession. For this reason, the committee has asked that the full text of the report not be released in a manner that cou ld lead to further misunderstanding. I honor this request.

However, conclusions and recommendations of the committee are clear and fully understandable to the layman. I am going to make public those details. Furthermore, I want to stress that there is nothing secret about any of the report. A copy will be retained in the Medical Center library ~~where you are~~ for those who may wish release to view it. its voluminous details.

The committee went thoroughly into the history of whole body irradiation research and treatment, noting that as early as 1942 two doctors reported the treatment of 270 patients but with "discouraging results."

It should be explained that the ~~history of whole body irradiation research~~ of the total modern approach to our therapeutic measures at UC and at ~~many other~~ all reputable medical centers in the nation--falls into three phases: Phase 1 involves the

study of the toxicity (or in simple language, damaging effect) that may result from ~~the whole body irradiation~~ any method used in treatment ~~of cancer of far-advanced stages~~. Phase 2 takes up an assessment of the effectiveness of the process (such as any measurable changes in the disease being ~~the tumor size~~, change in the well-being of the patient, improvement of patient's general condition and the effect on the ~~cure or survival~~ rate of cancer), Phase 3 is a comparison of the new treatment with other forms of treatment currently in use and a determination of the relative merits of the two methods.

At the time the UC studies were begun, there were a number of quite-advanced studies on the use of whole body radiation on radio-sensitive tumors (tumors that respond to radiation.) The committee could find no evidence that whole body radiation was used for tumors that were resistant to radiation or on solid tumors of chest and abdomen at that time.

Before getting into the committee's recommendations, I want to discuss a point that has become very controversial and misunderstood; namely, the consent of patients to become involved in this research.

The committee went thoroughly into this aspect and concluded that care for the patient has been a hallmark of this project from its inception. Prior to 1965, however--at UC and at most other medical centers where similar work was in progress--the committee found that consent of patients was usually in a verbal form, such as in a conversation between doctor and patient. ~~Neither was there any formal review of study plans of projects involving human subjects prior to 1965, here or elsewhere~~.

According to, little

The committee states that it could find ~~no~~ evidence prior to 1965 in which the UC study group obtained other than verbal consent of patients.

In 1964, the so-called Declaration of Helsinki ~~provided a formal declaration of~~ formalized the rights of individuals involved in human experimentation and ~~the United States~~ all reputable scientists generally subscribed to that declaration. The American Association of Medical Colleges drafted its first code of ethics on the subject in 1965. The Surgeon General ~~first received~~ U.S. Public Health Service required formal institutional review of federal grants dealing with human investigation in February of 1966. The ~~present~~ method of consent, as utilized here and elsewhere, has ~~resulted from study contributed in part by our own faculty~~ paralleled that in use the country over and has been revised from time to time in good part by conscientious efforts of our own faculty.

Quoting from the committee's report on this aspect: "While the specific form of the informed consent has varied through the years, the quality and the appropriate nature of the consent have been consistent. Patients have generally exhibited a remarkable degree of understanding, both about the procedure to be followed and the experimental nature of the whole and partial body radiation." (end of quote.)

As for the ~~funding~~ financial support of the project by an agency of the Defense Department, the committee felt that this had no bearing on the ~~project~~ study other than that it supplied needed funds. The committee noted that the Defense Atomic Support Agency has never made suggestions regarding the design of the experiments, that nothing about the project has been classified, that the contract between UC and D-A-S-A has been identical with

other external funding agencies and that "there is nothing in the record to indicate that any specific kinds of tests or treatment were dictated or even suggested by the supporting agency."

Doctor Saenger had the following to say to the committee on this aspect: (again I quote) "The background (for this study) came from my observations over twenty years that cancer patients treated with radiation might be benefitted by more careful evaluation of treatment effects. Because of my knowledge of the interest of the Department of Defense in radiation effect on humans, it seemed to me that this branch of the government offered a logical source of funds for the laboratory phases. The inappropriateness of having any Defense Department control of patients' care was recognized from the inception." (end of quote)

The committee noted that patients were not specifically advised ~~of~~ that financial support was derived from the Defense Department since ~~as the committee reported,~~ in "no other projects, irrespective of source of support, has it been considered necessary to so inform patients involved in clinical research." The committee found that the internist in charge of those patients has informed ~~each one~~ almost all verbally that the data obtained from their individual studies ~~may~~ might be of help to soldiers or to civilian populations in the event of nuclear catastrophe.

With this rather lengthy but, I think, necessary background, I want to move now to the Blue Ribbon Committee's summary and recommendations:

Pt. II.

SUMMARY ~~ONE~~ AND RECOMMENDATIONS:

1. The treatment of wide-field or whole body radiation is in progress at many other centers for (radio-sensitive) forms of cancer. Such tumors, however, comprise a very small segment of the study under review.

2. For radio-resistant tumors which are spread widely from the primary site, such as cancer of the bronchus, colon, and breast, the evidence at hand when the UC studies were initiated, justified the development of a Phase II therapy program (assessment of effectiveness of whole body radiation.) With regard to radio-resistant tumors, the dissemination of which is limited to one region, as in cancer of the colon, the supportive animal data is still inconclusive and unconfirmed. The human data developed since 1960 has not been encouraging except for data on colon cancer of the UC study itself, which are incomplete. If the UC study can develop positive evidence of effectiveness, it would justify the mounting of a Phase III (comparison) study of whole body radiation in colon cancer.

Pt. II: Summary

~~SUMMARY TWO~~

Work on the total body irradiation project began in 1960, prior to the advent of Faculty Committee on Research (F.C.R.). Fifty patients had been treated when the protocol was first submitted to the FCR in 1966. After lengthy review, provisional approval was granted by the Dean in 1967. Because of changes in the study plan and because a new principal investigator became involved, the protocol was re-submitted in 1970, and the most recent revision was approved in August of 1971.

RECOMMENDATIONS

The committee recommends:

1. That the Faculty Committee on Research be supplied with adequate administrative, secretarial and financial help to enable it to perform its ever increasingly complex and heavy work load. Such help would enhance the follow-through on recommendations and effectiveness of the follow-up system.

2. That representatives from the pre-clinical and younger clinical faculty be appointed to contribute their knowledge and skills to the decision-making process. This will disseminate a broader understanding of the problems of peer review within the faculty.

Part III:

SUMMARY

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

The patients treated in the study received excellent care in respect to both their medical illness and psychological needs. The psychologic support given to these patients far exceeded that 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.

RECOMMENDATIONS

If and when a Phase III study (comparison of present and new method) is planned, much larger populations of patients will be required. In that event, it will be necessary to develop

close cooperation with other departments. In future studies, plans should be made to provide long-term follow-up for all patients by the physicians involved in the study.

P. I IV:

SUMMARY ~~FOUR~~

There is no evidence that the D-A-S-A funding was made contingent on work, ideas, or suggestions proposed by D-A-S-A. The work was carried out with the complete scientific freedom appropriate for research conducted in University facilities.

RECOMMENDATIONS

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. I V:

SUMMARY ~~FIVE~~

The informed consent for the partial and whole body irradiation project reflected the processes characteristic of the University of Cincinnati and the nation. Prior to the mid 1960's, documentation of informed consent tended to be brief and non-specific. Subsequent to that time, the written documentation of informed consent has been improved for all university investigative projects including this one.

Personnel have taken precautions to avoid embarrassment, discomfort or harassment to the patient and his family. The patients' rights have been safeguarded in appropriate fashion except for the instance in September 1971, involving inverviews for an NET film. The general and specific medical care of the patients involved in the study was of a high order. The precence of professionals interested in psychological and social

phenomena enhanced those aspects of care.

The cognitive and emotional psychological investigation was based on the opportunity to learn more about responses in two poorly understood circumstances: (1) to dying and death, and (2) to partial or whole body radiation. The positive findings include: (1) transient loss of some cognitive capacities occurred for three days after radiation; (2) these losses were more marked in those individuals who already demonstrated some basic intellectual deficits, and (3) these findings were complicated by high anxiety levels, moderate depression and the effects of impending death.

RECOMMENDATIONS

1. Informed consent should be obtained as it is now. Revision of the consent forms should be considered in relation to the use of the phrase "sound mind and body." The procedure for withdrawal from the project should be improved.

2. 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.

3. Improved guidelines should be developed by the University for handling publicity involving patients, medical care or research.

SUMMARY

The design of the experiment, from the beginning, did clearly incorporate measures to improve the care of the patients.

During the progress of the investigations, procedures that reduced the physical and emotional stress of the patients were added, for example: the psychological support and the use of bone marrow transplantation.

The design of the experiment was adequate to define the toxicity of the radiation used and to indicate the safety and efficacy (effectiveness) of the use of bone marrow transplantation. It has however been not adequate to evaluate the effect of the treatment on survival rates.

The design of the experiment lacked carefully-selected measures to evaluate palliation (alleviation of pain, psychological well-being etc.) No rigid criteria of palliation were laid down. A defined set of observations to be made at each visit were not selected prior to 1966. Thus, comparisons of palliation within the group over the years or with similar patients treated by other methods are difficult; all the more so because the reports of ~~other~~ carried out by others which we reviewing studies ~~that we received~~ were likewise weak in their measures of palliation.

No systematic approach based on prior biological knowledge of the effects of radiation was utilized in the plan to find an indicator of radiation or to elucidate metabolic changes. Survey techniques were used.

RECOMMENDATIONS

At the present time, it is generally accepted that biostatistical guidance can improve clinical investigations. We

urge that biostatisticians, competent and experienced in medical investigations involving patients, be brought in at the conception of clinical studies, such as these reviewed here, particularly to aid in the design of the experiment, rather than be called in at the delivery, merely to analyze the data. The College of Medicine must support biostatisticians familiar with clinical investigation.

VII

SUMMARY

The data provided to the Committee regarding the effectiveness of whole body radiation suggests that survival of the patients in this study does not appear to differ from survival with the use of chemotherapy (medication). Since the manner in which the data on palliative effects was developed was inadequate, no conclusions can be drawn from them.

RECOMMENDATIONS

a well-designed study to compare whole body radiation with other forms of therapy is recommended. The specific tumor groups which appear most likely to show significant results are those of the colon and lung. Adequate populations of patients with these tumors are available at this Medical Center. These tumors afford the best opportunity for objectively measuring effects.

Finally, I come to my own viewpoint and recommendations as Director of the University of Cincinnati Medical Center. These thoughts have been transmitted to President Bennis. I assume that the Blue Ribbon Committee study, the American College of Radiology study, my own recommendations and such

other reports, studies and evaluations of this project as have been made or will be made will be weighed by the president in reaching a final conclusion as to the future of this project.

My recommendations reflect my uneasiness with the varied character of the information that has been collected from time to time. This has not been an indication of nefarious purposes, but rather a result of incomplete experimental design. To insure valid criteria for procedure ~~an inherent superficiality and dis-~~ ~~organization. The watchdogging~~ could be ~~the responsibility of the Director of the Radiotherapy Department~~ shared by the Faculty Committee on Research.

There has been more than sufficient time utilized in developing the preliminary phases of the study and it should enter now into Phase III activities (carefully-planned comparative study with other therapeutic methods.) It should moreover be limited for general purposes to the types of tumors that have often been treated by whole body radiation (hematopoietic neoplasms, Ewing tumor, and disseminated neuroblastoma.) The solid tumor category should also be pursued but only one, or at the most two of these (cancer of the colon and lung.)

Since more than one form of therapy is anticipated A larger number of cases should be included per year in order to reach conclusions more rapidly than has been the case heretofore. The nature of the study should now be directed essentially toward a determination of palliative effects--that is, the effects having to do with relief of pain and improvement in the patient's well-being. A clear definition of the

criteria for determining this must be established.

The consent form as presently constituted is a good one but it contains certain legal phrases that make it unwieldy; these should be modified. The committee indicates that the mechanisms of patients' voluntary withdrawal from the project should be specified. I think this is unnecessary but the opportunity for this should be emphasized.

The university in general and the Medical Center in particular should develop clear guidelines in respect to patient relationship with the news media.

The committee recommends solicitation of support of the project from another source than the Department of Defense. I can understand the reason for this recommendation but I do not concur in it.

To sum up, I believe the study should be continued but with the ~~s[illegible]~~t limitations I have indicated.