RADIATION RESEARCH IN THE VA INVOLVING HUMAN SUBJECTS

HEARING

BEFORE THE

COMMITTEE ON VETERANS' AFFAIRS

HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

FEBRUARY 8, 1994

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CONTENTS

MATERIAL SUBMITTED FOR THE RECORD

RADIATION RESEARCH IN THE VA INVOLVING HUMAN SUBJECTS

TUESDAY, FEBRUARY 8, 1994

HOUSE OF REPRESENTATIVES,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC.

The committee met, pursuant to call, at 9 a.m., in room 334, Cannon House Office Building, Hon. G.V. "Sonny" Montgomery (chairman of the committee) presiding.

Present: Representatives Montgomery, Evans, Penny, Rowland, Long, Edwards of Texas, Waters, Bishop, Kreidler, Stump, Smith of New Jersey, Spence, Everett, Bachus and Linder.

OPENING STATEMENT OF CHAIRMAN MONTGOMERY

The CHAIRMAN. The committee will be in order.

This morning we will hear testimony about medical research.

Secretary Brown, we welcome you as well as Dr. Susan Mather whom we have seen all over the country, and also Mary Lou Keener, who is the General Counsel.

We would like to know the progress VA has made in uncovering and securing records about the use of radiation in human subjects which took place in the VA hospitals beginning in the 1940's. We also have VA physicians who actually performed some of the medical research which has been the subject of so much medical attention in the last 2 months.

In addition, we have convened a panel of experts who were not involved in research and who are very knowledgeable about the risk of radiation to humans or about the ethics of using humans in medical research. Now, to my colleagues, the purpose of our hearing is to learn what happened and to make this information available to the public.

There have been amazing advances in human knowledge generated by thousands of well-known American scientists during the 20th century. Several of those scientists will testify before us today and tell us about their pioneering work involving radiation, and we would like to thank the scientists and our guest witnesses for being here this morning and thank you for taking the time to come a long way to be with us.

Although many of us are familiar with the topic of radiation health effects because of the committee's work on compensation for atomic veterans, the testimony today concerns a different type of exposure through medical research, and, as I said, we are here to listen and to learn.

I welcome all the witnesses today. Some of you are appearing as private citizens. As I mentioned earlier, you have traveled a great distance to help us understand the scientific and ethical issues presented by these experiments.

I yield to the ranking minority member, Mr. Stump, for any comments he would like to make.

Mr. STUMP. Thank you Mr. Chairman. I do have a statement for the record, but I would like to thank you for calling this very timely meeting and welcome the Secretary, and, Doctor, we are glad to have you with us this morning and look forward to your testimony.

Thank you Mr. Chairman.

[The prepared statement of Congressman Stump appears at p. 51.]

The CHAIRMAN. Thank you.

Mr. Evans.

Mr. EVANS. Thank you, Mr. Chairman.

OPENING STATMENT OF HON. LANE EVANS

First, I would like to begin by sharing Congressman Gutierrez's apologies for not being here with us this morning. Veterans from his district are served by VA Hines Medical Center in Chicago, which was one of the facilities named as the place where radiation experimentation took place. He, of course, will work very closely with our committee. He is very interested but could not be with us here today.

I can't help but feel that Federal agencies, particularly the Department of Defense, have felt that they could do whatever they wanted to our armed forces personnel. During the past 50 years, troops have been subjected to the number of agents, such as ionizing radiation, mustard gas, Agent Orange, and LSD, without being made aware of the potential risks. While these men and women are willing to fight for our Nation and possibly be injured and killed in battle, I doubt that any of them ever believed that some of the greatest dangers that they might face would be coming from our own Federal Government.

I know we will be focusing today largely on VA experimentation within the VA hospital system, but I don't think we can forget the so-called atomic veterans, the men and women who are victims of Government experimentation, as well.

Recently, 28 of our colleagues, including 12 members of this committee, joined me in requesting that the President include these men and women in the ongoing investigation, and I would like to have a copy of this letter included in the record, Mr. Chairman, and I will yield back.

[The prepared statement of Congressman Evans with attached letter appears at p. 53.]

The CHAIRMAN. Thank you.

Dr. Rowland.

Mr. ROWLAND. Thank you, Mr. Chairman.

Very quickly, I want to thank you for holding this very important hearing on the human radiation experiments involving the intentional exposure to ionizing radiation. I am pleased that Secretary Brown will testify to update us on the progress by the VA in determining the use of radiation in human subjects in VA hospitals. In

order for it first to be established, this process must be open and accessible to all veterans and their families.

Mr. Chairman, I would ask that all of my statement be included in the record.

The CHAIRMAN. Without objection, so ordered.

[The prepared statement of Congressman Rowland appears at p. 58.]

The CHAIRMAN. The gentleman from New Jersey.

OPENING STATEMENT OF HON. CHRIS SMITH

Mr. SMITH of New Jersey. Thank you very much, Mr. Chairman.

I would like to welcome Secretary Brown and our distinguished panel, ask that my full statement be made a part of the record and briefly say that East Orange medical facility, which is in my home State of New Jersey, is one of those that has been found to be on the list, and I am looking forward to trying to get further information. We have been in contact with the hospital and with the VA.

Apparently there are little or no records about what went on, particularly as it relates to individual patients. Certainly in my view that does not cut it because those veterans who may have been unknowingly and unwittingly exposed to harmful doses have a right to know what was going on with regard to their treatment. I am also concerned and will be asking the Secretary to speak to the issue of the bronchio-alveolar carcinoma presumption which was not provided.

One of my constituents, Mrs. Joan McCarthy's husband, who was part of the Wigwam experiment years ago, died of this rare lung disease which is attributable to plutonium and not to smoking—he was a nonsmoker anyway. Even the VA's own Advisory Committee on Environmental Hazards has pointed out that this is one of those cancers that is linked to plutonium. He was sprayed during that experiment in the 1950's, and I would hope that the nonaward of a presumptive disability could be reviewed and hopefully reversed and that his widow be provided that benefit.

I again would ask that my full statement be made a part of the record.

The CHAIRMAN. Without objection, the full statement will be put in the record.

[The prepared statement of Congressman Smith of New Jersey appears at p. 51.]

[The statements of Congresswoman Corrine Brown and Congressman Joseph P. Kennedy appear at pp. 59 and 60.]

The CHAIRMAN. If no other members have any comments, the chair recognizes the Secretary of Veterans Affairs, Mr. Brown.

STATEMENT OF HON. JESSE BROWN, SECRETARY, DEPARTMENT OF VETERANS AFFAIRS, ACCOMPANIED BY DR. SUSAN MATHER, ASSISTANT CHIEF MEDICAL DIRECTOR FOR ENVIRONMENTAL MEDICINE AND PUBLIC HEALTH; MARY LOU KEENER, GENERAL COUNSEL; AND EDWARD P. SCOTT, ASSISTANT SECRETARY FOR CONGRESSIONAL AFFAIRS

Secretary BROWN. Thank you, Mr. Chairman and members of the committee. I would like to thank you so very much for inviting me to describe what the Department of Veterans Affairs is doing about

questions that have been raised about human radiation experiments. From the moment I heard reports of improper human research, I pledged that VA would conduct a full and complete review of its research activities in this field and that I would make my findings public.

I want to emphasize that this controversy and our determination to give a full accounting of any VA involvement should not distort the contributions that VA has made in the field of nuclear medicine. VA is a full participant in the President's working group on human radiation. Let me emphasize our determination to give a full accounting of any VA involvement. This should not distort the contributions, as I have said, that VA has already made.

VA hospitals pioneered many of the early uses of atomic materials for medical diagnosis and treatment. Today's medicine is enhanced by the use of radioisotopes and, of course, nuclear materials developed in VA hospitals by VA researchers.

I share your concern that we must have a full accounting of any radiation research on any human subject. Right now, we are pulling all related records in the VA system together, even those from universities and contractors. We should complete this review by the end of this month.

However, we do have some preliminary information. For the initial report, which covered the period from 1947 to 1961, we surveyed 168 hospitals; 54 of those facilities had radioisotope units, which is what they were called in the earlier days. Thirteen had located protocols used during that period for radioisotope research; seven have names of patients who participated in at least some research projects; 31 have publications available on specific research projects done during that period.

The White House Advisory Committee on Human Radiation Experiments will decide the ethics and the scientific standards. It will evaluate the experiments. I am making it my business to know if at any time this agency violated the trust of any veteran who came to us for treatment. I am proud of VA's record of leadership in this field of research.

As early as 1947, news accounts of our work indicate that VA was complying with standards established by the Atomic Energy Commission. In 1953, there were 33 radioisotope units at VA hospitals across the country. By 1958, the number had grown to 48. We know that these local activities were reviewed by experts from outside the VA. We also know that VA Central Office was reviewing that work in the early 1960's. VA set up its own Atomic Medicine Office in the 1940's.

It is still not clear to us why this division was classified as confidential. There may have been some concern about the impact exposure to atomic energy might have on veterans' compensation claims. Mr. Chairman, I am personally deeply upset that VA would have concealed that information. We will reconstruct exactly what the policy was, why it was adopted and, most importantly, what the consequences were for the veterans involved.

VA was given responsibility for legitimate and appropriate activities relating to national and civil defense. These include training and preparing health care personnel to deal with civilian and military exposure to atomic weapons, but as far as we have been able

to determine up to this point, none of those roles would have warranted a cloak of secrecy.

Some may say that applying today's standards of ethics and morality to a bygone era is an inappropriate second guessing of decades-old actions. I disagree. We owe to the individuals who may have been adversely affected and their families the truth and nothing but the truth. We owe them proper redress for any harm that may have been caused them, and as those who hold the public trust, the lessons of history reinforce the need for full accountability for our actions.

Mr. Chairman, this concludes my remarks. I have provided my formal statement to you for the record with some other documents and will now be happy to respond to any questions you or members of the committee may have.

[The prepared statement of Secretary Brown, with attachments, appears at p. 61.]

The CHAIRMAN. Thank you, Mr. Secretary, for that strong statement.

I have only one question. In recent testimony before the Energy and Commerce Committee, a physician commented on total body radiation experiments done in the late 1960's at the University of Cincinnati. Dr. David Eagleman said that the medical purpose of this study was suspect and, as a result, the research resulted in the deaths of at least eight, I guess, veterans and probably—I am not sure it was veterans—and probably more than 21 of the participants. Are you familiar with this experiment?

Secretary BROWN. No, I am not, Mr. Chairman, but we will certainly follow up on that information. This is the first I have heard of it.

The CHAIRMAN. Okay. Then, for the record, we are not sure whether any VA patients were involved.

We have the statement here, Mr. Secretary, and I think it would be very important that you get this and look at it because it would be good for the record to find out how involved the veterans hospital was in that area.

Secretary BROWN. Yes, sir, we certainly will follow up on that.

The CHAIRMAN. Mr. Stump.

Mr. STUMP. Thank you, Mr. Chairman.

Mr. Secretary, what is the VA's timetable for its internal investigation and also the timetable for the interagency working group?

Secretary BROWN. We anticipate that we should probably be finished with an initial review by the end of this month. I think that the general, loose timetable is probably a year, but we are not necessarily bound by that. We are going to move forward, and we are going to be responsive in terms of time, based upon the information we have available to us. We want to do a good job, and we want to take our time to make sure we leave no stone unturned.

Mr. STUMP. Thank you.

Thank you, Mr. Chairman. I do maybe have a couple of questions that I would like to submit for the record later.

The CHAIRMAN. Without objection, and I hope the Secretary—I know he will—will answer these questions that are in the record.

Secretary BROWN. Yes, sir.

The CHAIRMAN. Mr. Lane Evans.

Mr. EVANS. Thank you, Mr. Chairman.

Mr. Secretary, when I met with the former director of nuclear medicine at Iowa City's VA Hospital a couple of weeks ago, he indicated that during the 1940's and 1950's VA typically retained research records for 5 to 7 years and then, as I recall, either turned them over to the individual investigators or to remote kind of storage facilities. Didn't VA in fact turn the research records over to the investigators themselves or put them in remote storage?

Secretary BROWN. Mr. Evans, at this point we do not know. It was our initial impression that all the records were centralized in the late 1950s or early 1960s to Central Office, but upon further review we found that was not the case. That was one of the reasons we had to survey all our facilities. We are now finding evidence that some of those records are stored there.

This, of course, does not necessarily rule out the possibility that some investigators retained the records. We will certainly investigate that additional lead.

We are looking at everything. We will be looking at the investigators, if they are available, or, if records are still available, we will be looking at the records of our affiliates. We will be looking at the records of contractors we may have entered into agreements with. Any source we believe may contain information about this subject, we will explore.

Mr. EVANS. If at least 54 hospitals had radioisotope units but only seven actually have patient names, how will it be possible for us to identify those veterans who may have been injured as a result of this research?

Secretary BROWN. We don't know. That is one of the things that we are doing. We are taking this thing very seriously.

For instance, I have asked our General Counsel to kind of oversee this entire operation, and she is taking a very strong legal position in terms of making sure that the records are safeguarded, that there are rules that are going to govern the movement of those records until we have had a chance to make sure that we look at all of them to try to identify—if it means—I am sure by reviewing those records, hopefully we will have gained additional information about the veterans that participated in this research.

So we are just going to have to look at everything that is available, and, in addition to that, we have been publicizing our toll-free number, which is 1–800–827–1000. There we have received about 5,000 calls already from individual vets, and of that, about 1,400 or so we have taken additional information from.

So we are just looking at everything that we can to get information that will allow us to identify veterans and also to gain additional insight into exactly what occurred between the late forties and all the way through the seventies.

Mr. EVANS. All right. One step further. If a veteran believes that he or she was subjected to human radiation experiments, but the research records can no longer be found, how are we going to be able to review that veteran's claim? And given COVA's decision in the Gardner case, if a veteran who was injured by VA-sponsored experiments—then those injuries by this decision are considered service-connected—are you going to expect those kinds of claims

from veterans? And how would they demonstrate their illnesses resulted from radiation exposure 30 to 40 years ago?

Secretary BROWN. I really don't know at this point.

In any disability claim, the first thing we have to establish: Number one, that either it happened in the service (in this case you are talking about primarily 1,151 claims), or that it was a direct result of negligence. But, as you mentioned, in the Gardner case, there would be an expansion of the 1,151 cases which would be covered.

If veterans go into a hospital and leave worse off than when they were admitted, then compensation can be paid as if it were service-connected. We are going to have to sort that all out, in terms of the rules that govern service connection and residual disability.

So we are looking for a number of things. We are looking for cause and effect, and we are looking for actual injuries that occurred. Once we figure that out, we will have some indication of how to proceed on all these claims.

If any veteran was harmed unfairly as a result of participation in any research project, then we have under our present guidelines the ability to compensate them. This is separate and apart from what will take place under the interagency council.

Mr. EVANS. Mr. Chairman, I have a few other questions I would like to insert into the record and ask the Secretary to respond.

The CHAIRMAN. Without objection, those questions—I know this Secretary will answer them.

Mr. EVANS. Thank you.

The CHAIRMAN. Thank you.

Chris Smith of New Jersey.

Mr. SMITH of New Jersey. Thank you very much, Mr. Chairman.

Mr. Secretary, what were the informed consent requirements? We know that informed consent has evolved and become much clearer to the patient as to what his or her risks may be in any given type of operation or treatment. What kind of informed consent procedures were in operation during the years in question?

Secretary BROWN. We are at this point trying to figure that out based upon our complete review of the record. But I am very, very proud that VA did take leadership with respect to consent in 1958.

Our General Counsel, through an opinion issued on June 25, 1958, issued guidelines that govern informed consent. I am going to ask our General Counsel to give us a brief explanation of exactly what that decision entailed.

Ms. KEENER. The General Counsel's opinion that was issued in 1958 essentially set forth very stringent standards of informed legal consent, and some of the specifics that were included in this opinion stated that the participant must voluntarily consent to the experiment, that the consent must rest upon an understanding of the hazards involved; the volunteer was able to withdraw from the experiment at any time; and, before the experiment was initiated, steps had to be taken to reduce the hazards such as research with animals prior to the time that humans were exposed. So these kinds of standards were issued by the General Counsel in an opinion in 1958, and we think that this was probably the outset in the first within any of the governmental agencies.

The opinion also went on and gave specific language that should be incorporated into an informed consent document to be used in this type of research.

Mr. SMITH of New Jersey. I would ask that the 1958 General Counsels' opinion be made a part of the record.

(See p. 74.)

Mr. Secretary, thank you for that answer. How does the VA dispose of its waste from its nuclear medicine programs and medical research treatment? And can you give some indication of how that was done in the past and currently?

Secretary BROWN. I am going to ask Dr. Mather to answer that.

Dr. MATHER. I think we really probably should provide that for the record, but there is a procedure for that. I am not sure when it began.

(Subsequently, the Department of Veterans Affairs provided the following information:)

The possession, use and disposal of radioactive materials in the VA's clinical and research programs is licensed and regulated by the Nuclear Regulatory Commission (NRC) and controlled by VA policy and procedures at the facility level. Generally, there are three commonly available methods for disposal of radioactive material, (1) decay-in-storage at the VA facility, (2) disposal of small quantities into the sanitary sewer system, and (3) shipment through a commercial broker to an authorized burial site.

Decay-in-storage is the most effective disposal method since it depends on the physical processes of nuclear disintegration to reduce the quantity of activity naturally over a period of time. Containers and other waste are usually stored for ten half lives which reduces any activity present to less than one percent of the initial activity. Before these materials are finally released to the facility waste stream, instrument surveys are made to insure that measurable activity is not discarded. Decay accounts for the largest reduction of nuclear waste materials.

Small quantities of soluble and dispersible materials may be disposed of into the sanitary sewer system. Total quantities and average monthly concentrations in effluents are strictly controlled by NRC regulations. This is not a major disposal route due to the regulatory constraints.

Consignment to waste broker for burial at an authorized site is usually reserved for long lived materials not suited for decay-in-storage, larger quantities of materials and, other forms not suited to available on-site methods. Use of this disposal method is limited by the high cost of these services and availability will be severely limited by state restrictions on access to burial sites which become effective July 1, 1994.

Records of disposal actions are maintained at all facilities.

Radiation exposure of VA staff who may receive an occupational radiation dose is monitored by personal dose measuring devices. Typically, exposure reports are reviewed monthly and permanent records or personnel exposure data are maintained. Exposure limits are established by regulation and there are no known instances of overexposure in connection with waste management.

Mr. SMITH of New Jersey. Okay. That would be helpful because we might not just be talking about the individual veterans but also the VA personnel who perhaps, maybe improperly, based on today's standards, may have handled some of these materials, and that is something we might want to look at in terms of casting a wider net in terms of people who may have been adversely affected.

Mr. Secretary, I know you know of my deep concern for Joan McCarthy, the widow of Thomas McCarthy, a Navy man who was killed or died as a result of a very rare lung disease which has been shown to be radiogenic.

A couple of years ago, I was poised to offer an amendment in this committee and was frankly persuaded that the process was best served by allowing the advisory committee to look at it. I then

recrafted my amendment, rather than forcing a presumptive disability for service connection, to a study and admonishing, again, the committee to look into it.

That report that we had asked for is now about 10 months late. It has not been made available to the Congress, to the best of my knowledge, and just recently you had found that there was no reason to provide service-connected disability compensation to those widows or men who suffer from that.

Could you perhaps elaborate on your reasoning and give any indication whether or not there is some additional thought being given?

This particular woman, Joan McCarthy, has gone through 14 years of trying to get service-connected compensation for his death. I became aware of it in the mid-1980's and have been working on it myself. So we have certainly exhausted, I think, she and now me as well, the due process of trying to get just compensation in this case. Her patience, in my view, is saint like, and, as you know, you met with her and were kind enough and gracious enough to give her over a half hour of your time.

She laid out her case, and if ever there was a case, I think, especially since he was a nonsmoker in this case, was on deck, and was sprayed with plutonium spray when that atomic test was detonated. Again, as you just said a moment ago, anyone who was harmed unfairly, with regard to the reason for this hearing, should have redress. This particular veteran and many others like him, I think, were harmed unfairly as well.

If you could respond.

Secretary BROWN. As you know, Mr. Smith, we have two basic approaches to resolving cases of individuals who have been exposed to radiation. One is what we refer to as our regulatory process, and the other one is our statutory process.

The regulatory process requires you to show cause and effect. By that I mean that you have to show that you were exposed to ionizing radiation, and you have to show the amount you were exposed to in order to be granted service connection for one of the radiogenic diseases listed in the regulation.

The other one is statutory. That is the "presumptive" list. There, all you have to do is to develop one of those diseases within a certain period of time if you were at a certain location.

As for the widow you talked about, I too was moved by her observations. As you know, that case was denied by the Board of Veterans' Appeals. After I met with you, I asked my personal staff to take a look at it. They have many, many years of experience. I sent that case back to our administrative review process to take another look. As it moved through, the experts decided and recommended that it could be best disposed of under the provisions presently in force. Those provisions, as I have mentioned, are regulation and statute.

VA would not oppose legislation to add this disease to the presumptive list, but we believe we have a criterion in place by which we can presently adjudicate it. But if you propose to add that disease to the presumptive list, you would not get any opposition from the Department of Veterans Affairs.

Mr. SMITH of New Jersey. I appreciate that, and hopefully that would also be translated into support.

Mrs. McCarthy has tried to adjudicate this for 14 years, and I would hope the committee would be sensitive to that, because I would look to try to amend the statute at the appropriate time, as I thought of doing a couple of years ago and was persuaded instead to go the regulatory route, which unfortunately has not yielded the desired effect.

I thank you, Mr. Chairman. I do have some questions with regard to the East Orange facility, which, if you have any information about over and above that which has been made public, I would ask that it be made a part of the record.

Secretary BROWN. Mr. Smith, we are doing things to be as cooperative as we possibly can. For those facilities we have identified as having radioisotope research activity, we are notifying the congressional member who has responsibility for that district and in addition, of course, the two Senators involved.

We want to try to get to the bottom of this, and just as another follow-up, I wrote to Secretary Perry and asked him to sit down with me so we can get a list of all military people who were involved in any type of experiment. We will write to them, find out how they are doing, and if they are sick or suffering from disabilities as a result of having participated in any research project, we want to offer them medical care and compensation benefits.

The CHAIRMAN. Dr. Rowland.

Mr. ROWLAND. Thank you, Mr. Chairman. I only have one question that I want to ask the Secretary.

In your testimony you described efforts to determine if VA ever conducted or sponsored inappropriate radiation-related research. Has the Department already made the determination about what constitutes inappropriate research, or will that decision be made by the advisory committee that has recently been established?

Secretary BROWN. No, sir, we have not drawn conclusions nor have we set up a definition.

It appears we will be working under standards of appropriateness to be defined by the interagency task force, and we will be working very closely with them.

Mr. ROWLAND. I have other questions I would like to submit for the record.

The CHAIRMAN. Without objection, and the Secretary said he would answer these questions.

Floyd Spence of South Carolina.

Mr. SPENCE. Thank you, Mr. Chairman.

Mr. Secretary, just one question. How is your VA hotline coming along? What are the results of it?

Secretary BROWN. We have had approximately 5,400 calls. Out of the 5,400, about 1,500 were pursued for additional information because they said something we thought would be helpful as we move forward and try to reconstruct exactly what happened between 1947 and 1980. So we think it is being very, very productive by giving us additional insight that may not be reflected in the official record.

I am always suspicious of the so-called official record. I want to hear from the people that were involved, and this hotline gives us

that avenue, and I am very, very happy that the veterans are participating and contacting us.

Mr. SPENCE. That is all, Mr. Chairman.

The CHAIRMAN. Thank you, Floyd Spence.

Chet Edwards of Texas.

OPENING STATEMENT OF HON. CHET EDWARDS

Mr. EDWARDS OF TEXAS. Thank you, Mr. Chairman.

Mr. Secretary, thank you for being here.

We all know that you did not create this problem, but we appreciate your commitment to getting to the bottom of it, because I think at risk is not only the unfairness to those individuals exposed in some of these experiments, but I am very much concerned about the integrity of the VA research program.

I think many Americans don't realize just how important of a role the VA has played in bringing about great advances in medical research, and I think it is a critical addition to justice to the individuals and their families that we need to see we get all the facts on the table so as to not further imperil the integrity of the VA research program, and I know nobody would be more committed to that goal and getting the facts on the table than you.

Regarding facts, I would like to ask you—Mr. Smith has referred to one report. I would like to ask about another report. It was due December 1st of 1993, that was required by Public Law 102–578, and I am not sure if you know the status. If not, if you could ask your staff to inform us, I would appreciate it. It dealt basically with this issue of a report on activities of active-duty service members that might have resulted in being exposed to ionizing radiation. Would you by any chance happen to know the status of that.

Secretary BROWN. No. I have Ed Scott here.

Are you familiar?

Mr. SCOTT. That report has been drafted, and it is in the clearance process. I am not certain whether it is at OMB yet or not.

Mr. EDWARDS OF TEXAS. Okay. What would be your estimate as to when that would be ready since it was due in December?

Mr. SCOTT. It could be any day. It was actually—when I saw it, it had been drafted around the beginning of December, and I would expect it would have been out by now.

Mr. EDWARDS OF TEXAS. Okay. Thank you very much.

The CHAIRMAN. Let the record show that Mr. Ed Scott of the Veterans' Department—Ed Scott.

Mr. EDWARDS OF TEXAS. One other question, Mr. Secretary. Again, we can't undo what has been done in the past. We can hopefully try to provide some compensation for those victims. But for the record can you say with certainty that today the VA has in place policies that are so clear that the American people can be confident and service personnel and veterans can be confident that there are no experiments that could go on that would use humans as guinea pigs in a dangerous situation?

Secretary BROWN. Yes, sir. I feel very confident in saying that the American people can be very proud of VA research, that it reflects the sensitivity, the creativity that is expected of this Department. I am not ready to say exactly how we behaved between 1947 and 1980, although I suspect we did very well there also. But I

want to be able to look at the records so we can go on record based on the facts and our analysis of those facts.

Mr. EDWARDS OF TEXAS. Thank you, Mr. Chairman.

Mr. Chairman, thank you.

The CHAIRMAN. Thank you, Chet.

Jill Long of Indiana.

Ms. LONG. Thank you, Mr. Chairman.

Mr. Secretary, I have a couple of questions that kind of follow on Mr. Evans' and Mr. Rowland's questions. In your testimony to us this morning, you have talked about legitimate experiments and conducted in an ethical way versus those that were not. Do you have confidence that you are going to be able to determine those that were legitimate experiments and those that were not?

And then I guess I have an additional question, which is, do you have confidence that you are going to be able to reconstruct the cases on the patients, on the veterans, to determine which ones were, given that the case data have been dealt with in different ways and so many years have passed since the experimentation?

Secretary BROWN. Ms. Long, you ask basically two questions. On the first question, at this point in time we have no evidence whatsoever that VA was engaged in unprofessional, unethical conduct—none whatsoever. However, we want to make sure that that is a fact, and we are going to examine the record to determine it. In that respect the record will stand for itself.

With respect to your other question on whether or not we will be able to reconstruct the record in a way that we will be able to make some sense out of it, I think, Ma'am, it will be determined by the findings. That is what we are involved in right now, a fact finding mission to pull together all the information we have available to us: information from our hospitals, our contractors, the medical schools we are involved in, and the individual researchers who are still with us. Three of them will be appearing before this committee later on.

So it remains to be seen what kind of picture we will piece together once we are able to assemble everything available to us.

Ms. LONG. And at this point it is really too early to determine that?

Secretary BROWN. Yes, Ma'am.

Ms. LONG. Okay.

I think I have some more time, so if I could ask an additional question, in your written statement you indicated that the Department of Veterans Affairs will take the necessary action to provide for the care of patients as well as addressing any other concerns they may have. And that may be just a general statement, but what actions would the Department of Veterans Affairs be able to take to address the other concerns that the veterans might have? And to do that, would the Department of Veterans Affairs need any additional authority?

Secretary BROWN. I am not quite sure at this point. The Department of Veterans Affairs is in a little bit different situation than the Department of Defense and the Department of Energy. For instance, we already have a criterion, a process, in place that will allow us to provide monetary payments. We already have a process in place that will allow us to provide medical care. We already have

a process in place that will allow us to provide educational benefits to children of veterans who may have died as a result of, let us say, unethical research. So we have to kind of piece that together. I am being a little vague because the interagency task force is going to have to consider compensation, and I want to be able to look at both and see which one is going to be in veterans' best interests. At the same time, I am not willing to relinquish the criteria we already have in place. It is very comprehensive, it is compassionate, it is very liberal, and I would not hesitate to use it if it fits the situation.

Ms. LONG. If in any individual case it is not clear that the health care needs of a veteran are solely related to an experiment, would you be inclined to give that veteran the benefit of the doubt—if there has been exposure but it is not clear that that is the cause?

Secretary BROWN. Well, you gave me a way out when you said "the benefit of the doubt."

Obviously, I have always been a veterans' advocate, and when representing veterans, I always closed my argument by saying, "We would hope that, based upon your review of the evidentiary record, that you resolve all reasonable doubt in favor of the veteran." We will certainly continue to do that since I am running VA now.

Ms. LONG. Good answer. Thank you.

The CHAIRMAN. Thank you.

Mr. Linder was here from Georgia and had to leave.

Mike Kreidler from the State of Washington.

OPENING STATEMENT OF HON. MIKE KREIDLER

Mr. KREIDLER. Thank you, Mr. Chairman, And I am very pleased to have the Secretary here with us, and thank you, Mr. Chairman, for holding this hearing.

One of the interesting parts about becoming Secretary of Veterans Affairs is that you automatically inherit all of the problems that preceded you. You thought you had problems just dealing with the future. Now you have to go backwards and carry that weight. Now you know what it is like to be a Member of Congress who has only served one year, and they keep saying, "you guys" and "you people." So there is some empathy here for you.

I am also on the Energy and Commerce Committee and on the Energy and Power Subcommittee, so I have had a chance to review these issues, and I have to say that I have a great deal of respect both for you, Mr. Secretary, and for Secretary O'Leary for your forthrightness in divulging this information. It is information that has been out there for a long time, but it is coming forward now, and I think that is the way government has to operate, and so I commend you for the directness in your approach to this issue.

I would like to ask you a question specifically about the focus of your investigation through the interagency working group on individuals involved in intentional exposure to ionizing radiation, excluding common and routine clinical practices.

I have noted that in the 1956 VA annual report there were studies that were taking place in Seattle and Houston dealing with coronary blood flow using radioactive tracer elements. Would you happen to know if this is going to be reviewed as something that is common and routine clinical practice, or is this going to be looked

at as something that would be more in the category of intentional exposure?

Secretary BROWN. We are going to look at everything, to include routine diagnostic procedures, routine research. I am very familiar with using radioisotopes in terms of blood volume, and that is legitimate. We now benefit from that research immensely. VA was in the forefront of it. But at the same time, it is not off the table. Even though it appears from what we know now that most of that research was very benign in terms of causing a pathogenic effect in the veterans that participated, I want to know that they fully understand what they were involved in.

I recognize that the rules were different, but we are going to look at those rules and at exactly what occurred. So nothing is off the table, sir.

Mr. KREIDLER. Good. I would certainly hope not, but I agree, you know, there is a whole different way of looking at the perspective from 1994 as opposed to 1956, but at the same time if there were people that were injured because of what we accepted at the time, I am certain we are going to want to know if they were and certainly want to take the right action with them.

Secretary BROWN. Yes, sir.

Mr. KREIDLER. Secondly, you are obviously involved right now in contacting medical schools that the VA had working relationships with, and I am curious, how is the VA going about the process of determining if they had a relationship with a medical school that was involved in this research?

Secretary BROWN. We will determine that primarily based upon our very detailed review of the records available to us. For instance, we came across the fact that we may have been involved in contracting out these projects. That led us to conclude that we need to look very, very carefully for additional sources of information.

We also have another problem we are looking at. Some hospitals participated in this radioisotope research but are no longer in existence, so we have to try to figure out where are those records and who were the players involved.

So, Mr. Kreidler, you can rest assured, and this committee can rest assured, and the American people can rest assured, that we are going to do everything we can to get all the information and make it public. There will not be any cover-up. There will not be any withholding of information. It will be made available to you.

Mr. EVANS. Would the gentleman yield?

Mr. KREIDLER. Surely.

Mr. EVANS. Mr. Secretary, could you make available a listing of those institutions that have been closed?

Secretary BROWN. Yes, I will do that, sir, for the committee. Yes, sir.

Mr. EVANS. My thanks to the gentleman for yielding.

(See 161.)

Mr. KREIDLER. Thank you.

The medical schools that are being contacted, what level of cooperation are you getting from them? They may have some real anxiety about the kind of exposure and publicity that is going to come about as they are recognized for their involvement in re-

search of this nature. Are you getting good cooperation from the medical schools?

Secretary BROWN. I am going do ask Dr. Mather to respond to that.

Dr. MATHER. At this point, that is occurring on a local level, and primarily our involvement with the medical schools has been because of shared staff, people who are part time at VA and part time at the university. There are Deans' Committees for all of those institutions. We will work through the Dean's Committee which meets regularly and members have conversations regularly. At this point we are not anticipating any problems.

Mr. KREIDLER. It is too early then?

Dr. MATHER. Yes.

Mr. KREIDLER. Thank you very much.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you.

Mr. Everett of Alabama was here and had to leave. He has some questions to be submitted to the Secretary.

Mr. Bachus of Alabama.

OPENING STATEMENT OF HON. SPENCER BACHUS

Mr. BACHUS. Thank you, Mr. Chairman.

First of all, Mr. Secretary, I want to commend you on what you have outlined as the steps you are taking, and I want to commend the Clinton administration. I think they have outlined a very good approach: I think most of our questions probably should be reserved until after you report back to us; I think you have described this search for the truth as an ambitious undertaking; I think that it is in fact because we are talking about things that happened 35 and 40 years ago; and you are going to be limited by that.

Many of the people that were involved are deceased. For others, you know, it is hard to remember what went on 40 years ago.

But I would stress that we do know some of the things that happened 35 and 40 years ago, and some of them were major advances in medical science from this program. The VA hospital was a leader in nuclear research, and, as a result of their efforts, I think we know and it is established and it is a scientific fact that these programs saved many lives, hundreds of thousands of lives.

We know from at least the testimony I have read that the dosages that were administered then and today are considered as very safe. We are conducting treatment today using dosages greater than these dosages in many cases, and we still don't have any evidence that these larger doses that are being administered today are not safe.

We also know something else. From the testimony that I have read, sometimes the consents were not written. In the legal system at that time, they were oral. Now there is a requirement that it all be written out.

But I have read Dr. Pittman's statement, I have read the statement of Dr. Rosalyn Yalow, who won the Nobel Prize for her work, and they have said that all the treatment of the patients was not done in a casual way, none of it was done in a callous way, and that there was care for the patients. Everyone that has testified or

submitted testimony that they were a part of this program has talked about their care and concern for the patient.

Yet I think sometimes, it is certainly not intentional, but I think sometimes the media account of this has been that there was no caring for these people, that these experiments were done maybe without proper regard for the people. I have not found that to be the case.

I did read Dr. Rothman's statement, and he says to condemn these practices is to invoke the standards of the 1990's in judgment on the 1950's, and then he goes on and he will testify to say that is probably not a valid defense.

But, you know, I am not so sure. How can we judge the 1950's by the 1990's? How can we do that? Now Dr. Rothman says that we can, and I think it is important to go back and see if there is anything that happened that can help us today. But many of the things that he says we ought to be doing today we are doing today and we have been doing since 1961. These informed consents have been in writing since 1961.

So I just want to say that in hindsight, there is an expression we have all used, "Hindsight is 20/20," and to say that we would have done things exactly as they were done in the 1950's and 1960's, we don't ever do things the way we would have done them, knowing what we know today.

But I will say that we did and I think Dr. Pittman is going to testify that he talked to these patients. He informed them of what was going on, and from what I know, the research at that time was done in a very caring way. You always have instances, and we may have instances, and we will know in a few months maybe where there was treatment that caused damage.

But I just want to conclude by saying that from what I have read so far, one reason that we have gone back and looked at this, I think, is to recognize again what fine work was done and how many people's lives were saved by this research and that we are much further along because of the work of the VA and of these researchers, I think, as much as anything, we ought to commend them for the fine work they did that resulted in so many advances in medical science.

Thank you very much.

Secretary BROWN. Mr. Bachus, I agree with you. As I have stated for the record, there is nothing in VA's history thus far that would suggest we were involved in anything other than honorable research.

But I must say for the record, I recognize there is a danger when you try to reimpose today's standards on yesteryear. However, some incidents are so hideous in their nature that it transcends generations. For instance, the situation involving exposing veterans to mustard gas without telling them, the situation of giving our veterans LSD, the situation where the Government allowed blacks in Alabama to continue to be exposed to syphilis. I think any reasonable person would agree, whether they lived in the 17th, 18th, 19th, or the 20th or 21st century, these things cannot be condoned and they must be made public so that they cannot continue to exist.

Mr. BACHUS. Let me say that I thoroughly agree with you and I thoroughly agree with the approach that we are taking here, and I think that it is a duty we owe our veterans.

I am simply saying that we need to be very careful not to paint the legitimate research that was done in an honorable way, with concern for the patients, with some of the instances that you have described. We need to make sure that we separate the good from the bad and that we don't assume that all of this research, because we are going to hear from some people on our next panel that research was done and with high standards, with informed consent, and whose research led to medical advances. We just need to be very careful as we look at this not to make blanket judgments over the overall advancements that were made, and what you are describing and some of this work is very, very different.

The CHAIRMAN. The time of the gentleman has expired.

Mr. Bishop of Georgia.

OPENING STATEMENT OF HON. SANFORD BISHOP

Mr. BISHOP. Thank you very much, Mr. Chairman.

I don't have any specific questions, but I would just like to make a couple of brief comments.

I certainly appreciate and commend you, Mr. Secretary, and Secretary O'Leary, and the interagency group for the openness with which you have approached this issue of the possible exposure and the reports that have come forth regarding the Government-sponsored experiments regarding radiation.

But I really think it is extremely important to note that you are conducting this investigation in a very open manner, because I believe very strongly that this type of approach is necessary to restore confidence and trust in our Government by our people as well as of course by veterans, and I certainly want to commend you for that.

I appreciate the fact that you are actively trying to ascertain what actually happened, what the facts are, and I exhort you to do that as soon as practicable, to analyze the data, which I know that you are doing and will do, and report the findings, make them public, respond quickly to any veterans and their families who may have suffered as a result of the experiments, the exposure, and follow that with the determination of the eligibility.

I think that that is the appropriate response. I think that it is the kind of response that the public will demand in the 1990's. We want confidence and trust in our Government and our elected officials and our public officials, and I commend you for that effort. And once the determinations are made, I join you in urging that veterans and their families be given the benefit of the doubt.

Thank you, sir.

The CHAIRMAN. I thank the gentleman from Georgia.

Ms. Waters of California.

Ms. WATERS. Thank you very much, Mr. Chairman.

I would ask unanimous consent to submit a statement for the record.

The CHAIRMAN. Without objection.

Ms. WATERS. And let me just say that I reserve comments, thoughts and certainly conclusions until I find out what really has happened here.

Thank you very much.

[The prepared statement of Congresswoman Waters follows:]

PREPARED STATEMENT OF HON. MAXINE WATERS

Mr. Chairman, I am pleased to be here to participate in these proceedings and I commend you for convening this hearing so that we can begin an open review of the radiation experiments that might have been conducted at VA medical centers and further examine the extent and effects these experiments have had on our veterans.

We have often heard the veterans community express disappointment with the services and care they receive from the VA. Their perception is that the VA often gives them "half truths" or "shades of the truth" rather than deal with them in an open and honest manner.

When we hear reports that veterans have been intentionally exposed to dangerous radioactive materials and literally used as human guinea pigs, it is easy to understand why our veterans express distrust in a system that was designed to care for their needs.

If we ever expect to restore the confidence of our veterans in the VA, we must have full disclosure and review of all activities that affect veterans. Mr. Chairman, I applaud your leadership in this effort.

I want to say to Secretary Brown that I am pleased by your willingness to participate in this hearing and to share with the Committee the Department's plan for addressing this issue. I look forward to hearing from all of the witnesses and I may have questions for you at the close of your testimony.

Thank you.

The CHAIRMAN. If there are no further requests of the chair, I would like to thank the Secretary for being here today and participating.

Mr. Secretary, you have got a lot of problems out there, and you are doing a good job.

I think when we get criticism of our veterans' hospitals that you have got to fight back and your public information office has got to fight back and let them know that it is not all bad out there.

I know that the President was approached last night in Shreveport, Louisiana, and made all the news programs by saying the veterans' hospital in Shreveport is, in effect, falling apart. I know you are looking into that, but we have done a lot of good for these veterans, and we have got to get our story out, and it is up to you and your public information office to get it out.

Secretary BROWN. Yes, sir. Mr. Chairman, as soon as we get some answers to this question, we will certainly share that information with you and this committee.

The CHAIRMAN. Counsel will ask one question here and see if we can get the record cleared up.

Mr. RYAN. Mr. Secretary, attached to your testimony is the request for information sent to all VA medical facilities directing them to search for records related to radiation research. It does not appear to require that VA facilities inquire about research conducted at affiliated medical schools.

Since we have produced some information about institutions that may have utilized veteran patients in some of their research, would you consider sending out an additional directive inquiring about the possibility that VA patients were subjects of research conducted by affiliated medical schools?

Secretary BROWN. Yes, we have already done that, but we will make it clear. I think a letter went out.

Mr. RYAN. Right. We have reviewed that, and it doesn't specifically direct each VA facility to make any inquiries to the affiliated medical schools about veteran patient involvement in research.

Secretary BROWN. Okay. I am going to ask our General Counsel to respond.

Ms. KEENER. The initial survey information that went out we recognized was deficient in that area, and there was an additional directive that was sent out that specifically referred to asking the kind of questions you have mentioned, and we could provide a copy of that for the record.

Mr. RYAN. Thank you very much.

The CHAIRMAN. Thank you, Mr. Secretary.

(See p. 68)

The CHAIRMAN. We will now move to our next panel. We would like our next panel to come forward: Dr. Rosalyn Yalow.

I might say to my committee members that Dr. Yalow is a recipient of the Nobel Prize back in the late seventies, I believe. We are very proud of her record in research.

It has been several years since we have seen you here at the committee, and we are glad to have you back.

Dr. Burrows, Chief of Nuclear Medicine, Department of Veterans Affairs, at the Boston Medical Center; Dr. Ervin Kaplan, former Chief of Nuclear Medicine Service at the Hines VA Medical Center; and Dr. James Pittman, who has testified before us many times, a distinguished professor and dean at the University of Alabama and Alabama School of Medicine.

We would appreciate it if the witnesses would hold their statements to 5 minutes. If you want to go longer, the chair will certainly be lenient.

Dr. Yalow, we will start with you.

STATEMENTS OF ROSALYN S. YALOW, Ph.D., SENIOR MEDICAL INVESTIGATOR EMERITUS, DEPARTMENT OF VETERANS AFFAIRS, BRONX VA MEDICAL CENTER; BELTON A. BURROWS, M.D., CHIEF OF NUCLEAR MEDICINE, DEPARTMENT OF VETERANS AFFAIRS, BOSTON MEDICAL CENTER; ERVIN KAPLAN, M.D., FORMER CHIEF, NUCLEAR MEDICINE SERVICE, HINES VA MEDICAL CENTER; AND JAMES A. PITTMAN, JR., M.D., DISTINGUISHED PROFESSOR AND DEAN EMERITUS, UNIVERSITY OF ALABAMA AT BIRMINGHAM, SCHOOL OF MEDICINE

STATEMENT OF ROSALYN S. YALOW, Ph.D.

Dr. YALOW. Okay. Nuclear medicine, the use of radioisotopes for medical purposes, now has an important role in diagnosis and therapy. My own background goes back to 1948 when I first joined the Bronx Veterans' Administration Hospital.

Nuclear medicine has three roles: Treatment with radioisotopes, diagnostic studies using radioisotopic techniques in vivo or in vitro, and medical research employing radioisotopes.

Probably the most common role of nuclear medicine in the therapy of a nonmalignant disease is in the treatment of

hyperthyroidism. Before he completed his role as our chief executive, both the President and Mrs. Bush were reported to have overactive thyroids. The public was informed that both were treated with radioiodine. No information was given about their dose, but typical doses for this nonmalignant disease is usually 5,000 to 10,000 microcuries of radioiodine. Their whole body dose was probably about 5,000 to 10,000 millirem. The dose to their thyroid was 1,000 times greater. Thus, after a half century of experience, the considered medical opinion is that radioiodine is the optimal treatment for the disease in the President and his wife and that those doses to the thyroid and to the whole body during the treatment are safe.

Patients with thyroid cancer have been successfully treated with radioiodine using doses a hundred times as large as those used for hyperthyroidism without evident deleterious effects.

In the 1950's, the diagnosis of an overactive or underactive thyroid was based on the 24-hour uptake of radioiodine by the thyroid. It has been estimated that in the United States alone at least a half million people were tested in this way in the 1950's and 1960's before the modern techniques of radioimmunoassay of thyroid-related hormones were introduced.

Since the dose for the diagnosis of thyroid disease is only a few percent of the doses used for the treatment of an overactive thyroid, no harmful effects could be expected. For the past 30 years, radioimmunoassay has been the method of choice for measuring in blood and tissue taken from the subjects a wide variety of hormones, including the thyroid-related hormone.

With radioimmunoassay, there are no concerns about the administration of radioisotopes to people; we work on their blood or tissue. Furthermore, those workers who use radioimmunoassay techniques need not experience even measurable amounts of radiation exposure.

I have not worked extensively with in vivo studies employing radioisotopes over the past quarter century. However, from what I note from the literature, the doses employed remain small compared to those used for the treatment of an overactive thyroid.

For the most part, the half lives of radioisotopes employed in nuclear medicine are short enough that the disposal of the radioisotope should not present a significant problem.

It is evident that the use of radioisotopes in nuclear medicine has had major advantages in our medical care. It should be noted that our paper in 1956 led to an appreciation that all diabetic subjects treated with insulin develop antibodies to insulin, to animal insulins, and led to the development of radioimmunoassay for which I received the Nobel Prize, and now some 30 years later, you know, human insulin is now available for treatment.

I will end by reminding you that the large doses of radioiodine received by the President for the treatment of his overactive thyroid is not considered a problem, and the doses used in research studies were generally, certainly in our hospital, a few percent of the dose used for the treatment of the President's overactive thyroid. I therefore wonder why the radiation exposure in experiments a half century ago is a cause for concern now. If you look at the numbers, there is no possible way that they could be of concern in

a country where we treat the President with a large dose for his overactive thyroid.

Thank you.

[The prepared statement of Dr. Yalow appears at p. 79.]

The CHAIRMAN. Thank you, Doctor, for that excellent testimony.

If you have no objections, I might mail this testimony to President Bush.

Dr. YALOW. I am sure his doctor told him about that.

The CHAIRMAN. All right.

Representative Joe Kennedy cannot be here this morning, but he extends his greetings to you, Dr. Burrows, and the chair recognizes Dr. Burrows, Department of Veterans Affairs at Boston Medical Center.

STATEMENT OF BELTON A. BURROWS, M.D.

Dr. BURROWS. I am pleased to contribute the enclosed material relevant to the topic of VA research involving the use of radionuclides and other forms of ionizing radiation.

Consistent with my previous training in internal medicine and my research experience in metabolic diseases which required laborious balanced studies before the more accurate radioactive tracer methods became available, I was attracted to the opportunities offered by the establishment of a radioisotope unit at the Framingham, then called Cushing, VA hospital in July 1950.

Initially, as you have heard, radioiodine was employed for the diagnosis and treatment of hyperthyroidism and cancer. Subsequently, radiosodium, and radiopotassium and radio sulphur were used to study body composition changes in a variety of chronic diseases such as hepatic cirrhosis, hypertension, cardiovascular disease, diabetes, and renal insufficiency, which were prevalent in the veteran patient population.

With the recruitment of additional staff and the support of a USPHS training grant in radionuclide techniques, the scope of our activities expanded to other medical subspecialties, endocrinology, hematology, gastroenterology, nephrology, and oncology, in which scanning devices were becoming useful.

In the early fifties, there was also a training program in the use of radiation survey monitors to detect areas that might be contaminated with radioactive materials as a result of industrial accidents or military action. In addition, the professional staff was trained in the clinical management of such exposures.

From its inception, the radioisotope unit, later called radioisotope service, and finally nuclear medicine service, was integrated with a similar service at the Massachusetts Memorial Hospital, later the University Hospital, and its staff held faculty appointments at the Boston University School of Medicine.

I was acting director of the Nuclear Medicine Office, VACO, when it was first established about 1967 for its first 5 years and helped establish training programs in other VA hospitals which materially assisted in the development of a separate and distinct specialty later to be certified by the American Board of Nuclear Medicine under the superb leadership of Dr. Joseph Ross. Hines VA Hospital was one of those hospitals that had a training grant.

There was a close working relationship between the VACO office and the AEC in the processing of applications for the authorized use of by-product material in the field, and the AEC would not consider an application until it had passed through this office which was established in Central Office in 1967.

Many of the published studies resulted from the retroactive compilation and analysis of diagnostic results and their correlation with other clinical and laboratory data. In other words, it was a retroactive compilation of data that was obtained during routine diagnostic procedures whereas others required the approval—that were not in that category—required the approval of the radioisotope committee locally to ensure that they complied with AEC, later the NRC, regulations.

The formal process of informed consent was signed forms approved by a local human studies committee and was not developed for several years, and you have heard the date from previous testimony, after radioisotope research had become an active pursuit in the majority of the radioisotope units.

The studies were conducted in an open clinical setting with the full understanding of the nature of the materials, the purpose of the studies, and the potential applicability of the results to the individual patient's problems.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Burrows appears at p. 81.]

The CHAIRMAN. Thank you, Doctor.

Dr. Kaplan at Hines VA Medical Center.

Dr. Kaplan.

STATEMENT OF ERVIN KAPLAN, M.D.

Dr. KAPLAN. Ladies and gentlemen, members of the committee, I feel it a privilege to have been able to serve the Federal Government for 43 years, and I would like to give my qualifications both as a veteran and as Chief of Nuclear Medicine at VA Hines.

The first five years of my Federal service was as an enlisted man in the United States Marine Corps during the entire duration of World War II. I served overseas in the Pacific with the Second Marine Raider Battalion, Colonel Evans F. Carlson, and participated in the Battle of Midway, the Guadalcanal Campaign, and the assault landing on the Island of Bougainville. The second and less peaceful half of my service was 38 years in the Veterans' Administration.

The CHAIRMAN. We only have one person, I believe, in the Congress that has served longer than you in the Federal Government, and that is Mr. Whitten. He has been over here about 53 years now.

Dr. KAPLAN. Yes.

The CHAIRMAN. You have been here 43 years with the Government?

Dr. KAPLAN. Forty-three years, and I am now retired for six years.

The CHAIRMAN. Good, sir.

Dr. KAPLAN. Having interrupted my education to so serve, I returned, went to medical school, did a residency at the VA, and

served for 36 more years in the Nuclear Medicine Service, most of that time as chief of the service.

I was affiliated with the University of Illinois College of Medicine as a full professor of internal medicine and of physiology. In addition, at the VA Hospital I participated in an active patient care service. Other activities included research and education, exemplified by residency training of physicians, clerkships for medical students and the training of nuclear medicine technologies and computer specialists.

I brought up my record of service because I have a great deal of respect for the dignity of the veteran, and I would never harm a veteran. They trusted me, and I had to trust them many times with my life.

I want to briefly review the organization of the hospital clinical care. Our school's professional policy was set by the deans of four medical schools, the bed services were specialty oriented, and the service chiefs were people of high regard and high competence. Supervision of patient care consisted of a descending hierarchy of medical school consultants, section chiefs, fulltime physicians and resident physicians. In nuclear medicine research the selection of research subjects was accomplished by interaction with the above clinical hierarchy and the development and subsequent approval of a research protocol.

The prospective studies were reviewed through various channels, the hospital safety committee, the hospital research committee. We went through the VA Central Office and the AEC for permission to obtain isotopes. Many were sent to the National Institute of Health for review and funding. We could not move a patient from the bed floors to our laboratories without the knowledge of the people who were taking care of that patient.

Patients were fully informed. They had every right to refuse to participate in any research program. In a 145 page document, "Evaluation of Medical Research, Specialty Research Report Review of Radioisotope Research" covering the period from the beginning of my service at the hospital to 1967, it deals with protocols, collaborators, universities. Copies have been sent to VA Central Office and to this committee.

We interacted with the bed services. When we developed a research project, these projects were applied in nature. We were trying to solve problems that dealt with the patient's complaints and with his disease. During the time that we worked on these patients, I would suspect that over the 36 years, counting the clinical and research patients, we probably performed in excess of several hundred thousand procedures. I don't know of one case in which a patient had side effects attributable to diagnostic studies or was injured or died. None were badly treated in any case. We did a good deal of follow-up.

I would simply like to conclude my initial statement by saying that I think it was virtually impossible considering our mind set, that of the veterans, and the relationship between our laboratory service in nuclear medicine and the patients that we were taking care of, for anything to be done that was harmful to these patients. I wouldn't harm people that were under my care. I would simply quote Hippocrates who, 2,500 years ago, said, "do no harm."

Thank you.

[The prepared statement of Dr. Kaplan appears at p. 83.]

The CHAIRMAN. Thank you very much for that very strong testimony, Dr. Kaplan.

Our last witness on this panel, Dr. Pittman, who is at the University of Alabama at Birmingham, School of Medicine.

Dr. Pittman, it is good to have you again before this committee.

STATEMENT OF JAMES A. PITTMAN, JR., M.D.

Dr. PITTMAN. Thank you, Mr. Chairman and committee members.

I worked with isotopes, radioactive isotopes, from about 1954 to 1971, first at the National Institutes of Health, then as chief of the radioisotope laboratory at Birmingham VA Hospital. From 1971 to 1973, I was ACMD for R and E in VA Central Office.

First, I believe nobody was harmed in this VA program and many were helped. Second, the patients and the subjects did have explanations given them when they were enlisted in research studies. The VA had a rigorous and detailed system of administrative oversight for the use of radioactive isotopes in patients and research subjects requiring, (a) prospective committee review of all research proposals using radioisotopes, and, (b) consents from the subjects, less formal than they are now but consents all the same.

Most of my own research done in the Birmingham VA hospital was aimed at understanding the physiology and diseases of the thyroid. For example, we attempted to devise new, quicker, and safer methods to measure the level of thyroid function in patients with I–132 instead of I–131.

Radiation doses received by patients with these tracer doses were small and often less than doses received from natural sources. Long-term follow-up of such patients in Sweden and elsewhere failed to disclose deleterious effects. Similar small tracer doses were typical of our other research studies.

As for consents, when we recruited subjects for the studies from among patients in the VA as well as hospital personnel, lab personnel, and others, we explained we were trying to develop a new test or understand a disease and would appreciate their help. Although we did not pay them for their participation, they knew the purpose of the research was to advance the cause of medical science.

The uses of radioactive isotopes in the VA were medical uses and as such were oriented toward understanding of human diseases. This orientation was completely different from that conducted for military weapons. In the VA, as in medicine generally, radioisotopes were used as a tool to probe the intricacies of the body just as chest x rays or any other diagnostic probe, to find disease otherwise undetectable and to eradicate it.

In the case of research, the investigators were interested in the biology and in tracing molecules or atoms through their courses in the body, and the emphasis was on using as little radioactivity as permitted detection.

There was a radioisotope committee in each VA facility using isotopes, and this committee considered each therapeutic use. We no longer have committees to consider each individual patient's treatment since it has become more routine and the prerogative of each

authorizing doctor, though probably there was committee discussion for President and Mrs. Bush.

The VA radioisotope committee also reviewed beforehand any and all proposals for using radioisotopes in patients or other human subjects for research, and each VA facility has an RSO—radiation safety officer—to monitor isotope use. So I don't think you will find any scandals in the VA in this area of inquiry.

I wish we had time to discuss the very positive accomplishments of the scientists working in the VA system using radioactive isotopes and the benefits they have brought mankind in general. In particular, one that hasn't been brought up here this morning was the development of scanning procedures around 1950 in the West Los Angeles VA, Wadsworth VA, where Benedict Cassen and Herbert Allen built the first rectilinear scanner and William Oldendorf did work in the same hospital, a neurologist, leading to CT scanners. Although Oldendorf didn't win a Nobel Prize, he was mentiond prominently in articles about the prize. That other VA employee, Dr. Oldendorf, who died last year, I believe, did some of the math and other work that helped lead to the CT scanners which are used in medicine every day now all over the world.

So I thank you and would be happy to answer questions.

[The prepared statement of Dr. Pittman appears at p. 87.]

Mr. ROWLAND (presiding). I want to thank all of you very much for your testimony, and Chairman Montgomery had to leave for another commitment, so he asked me if I would chair the remainder of this hearing.

Let me ask you in general, all of you, when you were going to conduct some kind of research where there was some radiation involved, what did you say to the individual that was going to be involved in this research, that was going to be the recipient of the radiation? How did you talk to them or explain to them what you were doing? Do you remember generally, Dr. Kaplan?

Dr. KAPLAN. Generally, we would delineate the problems. We would work as a group. There were people from the university who collaborated, that were on the ward. They had patients with specific problems or groups of patients with specific problems. Little point in naming any one of the problems, but some of these problems were extremely difficult of solution.

So we would have to devise means, both radioisotope means and other types of methodologies, to solve these problems, and what we would do is to define the type patient we needed for a specific study. We would generally have the man who was directly assigned to the patient speak to the patient and tell him that he had certain problems that we thought we could resolve more easily or better by certain means, and he was given time to think about this and asked if he was interested at all.

If he was, generally I would go down, or several of us would go down, and talk to him. We would indicate what we were going to do. We would indicate the risk versus the possible benefits, and we would make sure that we were not putting undue pressure on the person, and they were—they knew that they could not participate and nothing would be done to them or that they could drop out of the study if they wanted to, and we worked with disease-related situations.

Very often, all that was demanded was that we take some blood or urine or body fluid of some sort from them, and we would deal with them in vitro, which meant they never received any isotopes.

As the risk became greater or became invasive or dealt with high levels, or relatively high levels of activity, we would let the patients know, and we always made an evaluation of risk versus benefit: If we do this to you and it hurts you a little bit, or if we give you so much radiation—and we explained to them what it was—then they had time to think it over, and we then developed a group of patients who participated.

We have one group of people from the National Guard who come in every 10 years and we do a study on them for 24 hours to determine the Circadian rhythm of the changes in the test during night and day, and we have done three such studies 10 years apart on this same group of patients. And if you have to go into a hospital in the middle of the night, your laboratory values might be considerably different than at 11 o'clock in the morning, and we now know that, and we know it with advancing years, and these people are all very anxious to come back and participate in another 143 tests that we do around the clock.

So I don't think I need to say more than this. We talk to them as we talk to any person who would be involved in something that had some level of risk. That's it.

Mr. ROWLAND. Any other comments from others?

Yes, Dr. Pittman.

Dr. PITTMAN. Our procedure back in the fifties and sixties—early sixties, was first to go to the doctor. Many of the patients in the hospital were not under our direct care. I am an internist also, and I did have responsibility for patients in the hospital, but we sometimes needed other individuals. So the orthopedic ward was a good place to look.

In those days, patients stayed on the ward a long time, many days, and I think they got bored a lot of times with fractures and things. And we would first talk to the doctor, the patient's doctor, to see if it would interfere with the treatment or anything. If it was okay there, then we would go talk to the individual patient, and we either had the test we wanted to check out or we had—we wanted to try to understand a disease and we would like to administer this substance to them and follow it through their body or urine or whatever, and most patients were happy to participate.

A few would say, "No, I don't want to do that," or, "I don't want to be a guinea pig," and that was that, we went on to somebody else. But that was the procedure.

We didn't have written forms at first. The procedure then was to write in the record, the patient's chart, that we had talked with them and they were going to participate in the study. I have tried to find those charts in the VA hospital in Birmingham and can't find them.

I did find last week a notebook; the radiation safety officer now, Kathy Boyd, found a notebook in the back of an old cabinet which had the records of the radioisotope committee meetings from May of 1953, so we do have that record which is pretty complete, and that was where I got the information that each individual patient was discussed at those meetings before therapy.

With regard to the studies, we noticed in the isotope lab in 1968 that there was something wrong with the radioisotope uptakes. As Dr. Yalow mentioned, the standard test of thyroid function was the 24-hour thyroidal radioiodine update. Well, they were all confusing, they were too low, and so we thought maybe there was something wrong with the machine, and George Dailey and Richard Beschi and I studied the machine, then the patients.

We looked at the urine, and it was filled with iodine. The daily excretion used to be 100 micrograms a day, or 75 micrograms. In 1968, we found over 600 micrograms. Then we began to look for where it came from. We homogenized the food on the trays, and it was in the food, it was in the bread.

We then went to the bakeries, and they were very suspicious in Alabama, these Federal guys from the VA coming, but we found that the method of making bread in the United States changed around 1960. The change started in Connecticut and spread throughout the country, with adding big wafers of calcium iodate to the bread. So the bread was loaded—you were getting 150 micrograms of iodine in each slice of bread, and so that changed the uptake.

Well, we had to go through those procedures and do these tests again in the patients to find that, and I think it was helpful. It was published in the New England Journal of Medicine in 1969.

I would like to add one other comment. The term "radiation research" has been used here several times this morning. I don't think this was radiation research, this was biological research using isotopes. In fact, I would like to quote from the VA regulations of 1957, which I obtained from Dr. William Blahd in the UCLA West Los Angeles VA.

I obtained a copy of the manual that the VA used from 1957, June 7, 1957, on page 342, where paragraph 3.06d says, "Studies involving the effects of external radiation are not considered appropriate activities to the radioisotope program." That is the VA regulation. So if anybody did that sort of study, they were contravening the VA's own regulations.

So I think that we are not going to find anything here.

Dr. YALOW. I am not a physician, and therefore I did not do studies. Not infrequently they were done on me, because only physicians could administer radioisotopes to patients. On the other hand, I was a hospital physicist, and I want to point out to you that while you are talking about radioisotopes, you are not saying anything about x rays, and by and large the most exposure the patients got were not from radioisotope studies but were from x ray procedures.

Mr. ROWLAND. Let me ask you on that point, are you saying that the radiation coming from the radioisotopes may not have been as much as that which you would have gotten from ordinary x rays?

Dr. YALOW. Oh, of course it wasn't as much. I pointed out in my speech that there was a therapy that gave a big dose, but most of our studies were not therapy studies, they were studies on tracer tests where the amount of whole body exposure was trivial compared to what you would get in many of the x ray studies, and using the machines available in the forties and fifties, you got con-

siderably more radiation exposure than you were now getting with x ray studies as you modernize the techniques.

So if you are going to look at the radiation exposure of the patients, the amount they got from isotope studies in the hospital was trivial compared to the amount that they got in x ray studies.

I asked the other day whether it is still done, but in those days on entering a hospital, you had a chest x ray because tuberculosis was common, and there were studies that were automatically done on patients, not because you had a particular disease but because this was the kind of thing that was being done, and with the x ray machines then available and the kinds of films then available, the amount of exposure you got for the radioisotope work was absolutely trivial compared to the x ray exposure.

Mr. ROWLAND. Let me ask something, and I will come back to this. I am going to have to go to another Member because we have taken a good bit of time. You say you were the subject of some of the radioactive isotopes that were used. Did you receive informed consent, and did you sign a waiver during that time or not?

Dr. YALOW. I could have given informed consent. I was the one who knew about the doses that were being used and how the radiation doses would be in the various parts of the body. I probably knew more about this type thing than the physician. So.

Mr. ROWLAND. Well, let me ask you this. Did you sign a form?

Dr. YALOW. I joined the VA in 1947. There was no signing of forms about this, and not infrequently the way in which we got patients who would volunteer to have our various studies, I would sit down with them and I'd get the first dose, and I'd look around and I'd say, "Boys, I have had my dose. Do you want to join me?"

Mr. ROWLAND. Let me ask you this—let me ask the other gentlemen at the table there. You did not sign forms during that period of time as far as informed consent was concerned. Well, let me ask you this. Did you sign forms prior to surgery being done as informed consent?

But you didn't do it in reference to the radiation, but you did do it in reference to surgery. Is that right?

Dr. KAPLAN. That is correct.

Mr. ROWLAND. Why did you not have informed consent about radiation if you were going to do it with surgery?

Dr. YALOW. Because I would think that the size of the doses that were done were trivial compared to the x ray exposure you got when you had an x ray exam, and nobody signed informed consent to have an x ray taken, so why should you sign informed consent for an even lower radiation exposure with the use of radioisotopes?

Mr. ROWLAND. I will come back to this again. Let me do go to another Member at this point.

Mr. Evans.

Mr. EVANS. Thank you, Mr. Chairman.

First I want to thank this distinguished panel for testifying before us here. Their service to our country continues, and it is great to have not only a Nobel Prize winner but one of Carlson's Raiders right with us today, and we appreciate it very much.

What we are trying to get to is not only what exactly went on but where we can obtain records so that we can deal with full public disclosure and get information out to individuals who may be

concerned about treatment they received as a result of perhaps some form of illness, so let me ask a few general questions to the entire panel.

With regard to your own research, what records did you provide to the VA? Were these records simply research summaries or actually research records including detailed descriptions of the protocols used, subject's history, data, and analysis? Can you answer that as a panel?

Dr. Kaplan, we will start with you and go across.

Dr. KAPLAN. I have samples in this notebook which you have a copy of, and I have given sample protocols in this book for various procedures that we were doing at the time, and they include the specific problems, the specific aims, the methodologies, the participants.

It is the same type of program the National Institutes of Health uses in a prospective study, and the general outline of what we were doing was not especially different from what we use today, and I think that we planned everything we were going to do including how much money we had to get.

Dr. PITTMAN. I worked at the NIH—National Institutes of Health—before I worked in the VA. I think both were careful, but I think the VA was more careful than the NIH was in that regard, and as far as the records go, I think most of them are just gone. I looked the last couple of weeks and was unable to find very much.

Mr. EVANS. Doctor, in your case, were records after a period of 5 years given to the VA, or would you retain them?

Dr. PITTMAN. I retained some, I remember, but the VA—and I don't know that the VA had any mechanism for storing research records at that time. I think they were more generally considered part of the investigator's property, but I don't really know about the policies in this regard. I have not been able to find any in the last couple of weeks.

Could I make a comment about informed consent?

Mr. EVANS. Sure.

Dr. PITTMAN. There is a book by Ruth Faden who is now heading the President's panel on radiation—the investigation of the Government research, and she has a striking paragraph in there about the history of informed consent.

The Germans in 1931 apparently passed a very strict informed consent law requiring all patients and experimental subjects in research to sign forms and give explicit informed consent, and that law was on the books all during the Third Reich until the end of World War II. So I don't have much faith in these written forms. I think that you get a "good doctor," and this is the best you can do.

Mr. EVANS. Dr. Yalow?

Dr. YALOW. Well, there was no informed consent until probably 10, 12 years after we got started. In general, we informed the patients about the purpose of the study, but usually the purpose really related to their medical care.

In other words, when we did tracer tests, this was because somebody thought there was something wrong with their thyroid function. When we did blood volume determinations—for instance, pa-

tients with heart failure have low hermatocrits. Are they anemic? No. They have expanded blood volumes.

The important thing was that we weren't just doing research. In fact, I rather resent calling it research, it was developing more knowledge about medicine so as to improve patient care, and by and large, even those patients who were so-called normal volunteers like the patients in heart failure, we provided to their charts information that was important to their medical care.

So I am a little hostile to your saying that all this was investigation. We thought of it as adding knowledge to how we could take care of the patients better, and I provided our early publications, a list of them, to the committee.

Mr. EVANS. All right, Doctor, but in your own research records, what happened to the records of your own research?

Dr. YALOW. When I moved from the hospital nuclear medicine service to the research building, my guess is that some of the early records were lost. They didn't move with me.

Much of the records of what we did after we developed radio immunoassay I do have, but that did not involve giving isotopes to people, that involved taking samples from people, and that isn't the kind of information that you want. In radioimmunoassay, we don't give anything to people, we just take blood samples or other samples and measure the hormone concentrations or whatever it is in those samples.

Mr. EVANS. Dr. Burrows?

Dr. BURROWS. Well, I think there are two questions you are asking me, one is this question of informed consent, and I have the other one very closely in mind.

I have tried to indicate that informed consent required a form. It had to be approved by a committee and supervised by administrative authority; and that just wasn't developed or available.

As far as the patients being informed, it was our practice in all our clinical work, as well as anything involving any investigative work, to explain to the patient what was being done, and in fact even up to the present, if that hasn't succeeded when the doctor on the ward or when one of our staff has gone over it with the patient, when the patient shows up for study, the technologists run through a little litany about, did they know what was being done and not that they asked for their consent, but if they didn't approve, we certainly wouldn't have gone on with it.

A patient did come as an emergency in the middle of the night, say to the civilian hospital where I was working, and he was not able to understand because of his medical problem, we wouldn't proceed unless it was a dire emergency without finding a parent, a guardian or some person in authority that could give us permission to go ahead even with diagnostic studies.

So we were very sensitive to the fact that we didn't want anyone to say that anything had been done to them that they were opposed to or that perhaps someone responsible for them, like a parent or guardian, was opposed to.

Mr. EVANS. Doctor, in your own case with your own research, do you know what happened to the records?

Dr. BURROWS. Oh, yes. Well I find that we have about 150 ledgers with lab data that was accumulated since we were at Fra-

mingham and after we moved into Boston. I can't say that I am really up to date on what is in all those records, but they are there. They occupy about three five-foot shelves in addition to other notebooks that are around. So I will be interested to know what the logistics might be of surveying those records, and obviously we are quite anxious to proceed with it as soon as possible.

Mr. EVANS. Thank you.

Dr. Rowland, I may have another round of questions as we go through.

Dr. KAPLAN. I have a comment about records, if I may.

Mr. ROWLAND. Yes.

Dr. KAPLAN. At the time I retired in 1988, I was ill, and my administrative assistant cleaned out my desk for me. After 36 years, cleaning out my desk amounted to 50, 50-pound cartons and they were stored in the hospital up until about the beginning of September of 1993. The space they were stored in was required, and I was asked to remove my personal records.

So I have 50 boxes about yea big sitting in my garage, and it has research information in it, it has a lot of things in it, and I don't know what is in it because I haven't gone through it yet, but I informed the VA Central Office that I had these papers and I was perfectly willing for someone else to go through them for me. There are many things in there that I think are not interpretable at this time.

Mr. ROWLAND. Thank you.

Mr. Bachus.

Mr. BACHUS. Thank you, Dr. Rowland.

I want to say this to the panelists. I want to thank you for the work that you did, and Dr. Pittman is here from Birmingham. He did not say in his statement that he is dean of the medical school at the University of Alabama and of his fine work there. There is not a more respected physician in the city of Birmingham than Dr. Pittman, and in his statement he describes Dr. Yalow's research in the Bronx which you received the Nobel Prize for, and I want to tell you that every one of us who have had a blood test, you have had a major impact on every patient by your work there.

Dr. Pittman, in his statement, describes the result of this research by the VA hospital, and he talks about the fact that everyone who has a thyroid condition has been helped by the research of the VA hospital; every diabetic's medical treatment is far advanced because of that work. For everyone who has a blood test, the techniques developed by the VA have resulted in better blood tests; and, finally, in the detection and treatment of various forms of cancer, research done at the VA hospitals has resulted in benefit to cancer patients.

So I want to commend all of you for your work, and I think the record of the VA in this regard is a magnificent record.

I read some statements Dr. Pittman made earlier about the enthusiasm of the VA researchers at the time, knowing that they were advancing the cause of medicine and helping humanity, and the excitement that researchers had at that time.

I also want to say this. We have something called eyewitness testimony, and it is often better than what you may find on a record in that we have Dr. Pittman's statement that he was there and

that he talked to the patients, he informed them of the treatment and told them what the treatment would be, and I think the other panelists have described a real care and concern for the patient.

Dr. Kaplan, in describing his military service, really understated it in his oral testimony.

I am reading your written record, Doctor. I saw where you went on a 150-mile combat mission behind enemy lines for over 30 days. I want to commend you just on your service to the country during the war and after.

But all this testimony today indicates that we could have had a written consent at that time and we could have given it to every patient, not just told them what was in there, and they would have signed it.

I sign consent forms every day. Every time I have treatment, I sign consent forms, and sometimes they are not explained to me, they are just put in front of me and I sign them. Apparently what was done then was much more useful than what we find today when we sign these forms, really not knowing what we are signing. So I think some of the consent then was more informed than the consent that you find today.

Dr. Rowland, one question you asked about radiation, and in Dr. Pittman's statement he made the statement that radiation was not as feared then as it is now and was not considered dangerous, that the standards are different today and that the understanding was limited, and it is hard to convey to a patient a concern that medical science didn't have then. I think that might be some explanation.

I want to read a statement that Dr. Kaplan made in his written testimony. I think it really comes down to the essence of why we are here. It was his final statement, and I would like to ask the other panelists to answer that question too. He makes a statement, "During my 36 years of my tenure with the radioisotope service and as subsequently changed to the nuclear medical service, there is no evidence that a patient was injured as a consequence of participating in radioisotope research projects."

I would like to ask the other members of the panel, do you have any evidence that any patients treated at the VA were injured as a consequence of participating in these research projects?

Dr. PITTMAN. I know of none, no.

Mr. BACHUS. Dr. Yalow?

Dr. YALOW. There were no injuries.

Mr. BACHUS. All right.

Dr. Burrows?

Dr. BURROWS. Well, certainly none of a physical nature. I am concerned, though, when we have a population we are dealing with on whom we are rather dependent for compliance, that our veteran patients, as a result of the publicity that they have been exposed to at least locally in my area, that they might be alienated a bit from our hospital system, and I certainly welcome anything that the committee can do to provide real reassurance that things aren't as have been portrayed in some of the media, both written and video.

Mr. BACHUS. I see.

And if I could have one more minute, Dr. Rowland, finally, I have read the statement of Dr. Rothman where he talks about cer-

tain instances of early research or experimentation on human subjects. I don't know whether you all have reviewed his statement, but it is my understanding that none of the instances which he describes in his statement occurred at VA hospitals or were under the direction or control of the VA. For that matter, apparently the VA, from what I understand, had no knowledge of this research going on, it was conducted other places. So my final question is, are any of you all aware of any research at the VA on human subjects before 1972 which you consider inappropriate?

Dr. YALOW. I would like to point out that starting in 1947 there was an annual meeting of the chiefs of the radioisotope services in which they described the research and other work going on in their unit during that year. There were secrets in the work that the VA was doing, there were no secrets from the community or from their associates, and therefore it would have been impossible to have things that you describe going on in the VA radioisotope programs.

Mr. BACHUS. Okay.

Dr. PITTMAN. I think what we did either was for direct patient care, diagnosis, therapy, or research aimed at ultimate publication, and if it was not publishable, then it was a waste of time. So we tried not to do anything that was not publishable.

So I don't know of any, and it went through committee, locally, a radioisotope committee, so I doubt that there would be any that would even be condemned now.

There was one other point I wanted to make.

Dr. KAPLAN. While you are thinking, Jim, I want to make a comment that in the general license that workers in the field received from the Atomic Energy Commission for obtaining isotopes, the atomic numbers were 3 through 83, and this excluded every weapon type radioisotope that existed. So we were precluded from even obtaining them.

Dr. PITTMAN. The point I wanted to make was about the secrecy. I have heard this morning and I have read about secret work going on in the VA. Appended to my written testimony is a letter that I got from Dr. Blahd in California a couple of weeks ago written by Mr. A. Graham Mosley who wrote it in 1985. He died not too long after that. He was head in Washington, head of the radioisotope services all over the country, and that letter is about 5 pages long. It is a memoir, and he talks about how there were certain things they didn't want to publicize much because they thought it would stimulate claims which might not be valid.

So it wasn't really a secret so much as it was just something they didn't want to publicize, and that is in the letter that is appended.

Mr. BACHUS. Thank you.

Mr. ROWLAND. Thank you.

Mr. Penny.

Mr. PENNY. Thank you, Mr. Chairman.

Dr. Kaplan, I too was struck by the last paragraph of your statement in which you indicate that there was no evidence that a patient was injured as a consequence of participating in a radioisotope research project. It sounds as if at Hines you had better records of all patients involved in such tests than might have been true at other facilities.

Dr. KAPLAN. I can't speak to that really. We kept records that we thought were appropriate and that were in compliance with the then existing regulations and directives, and I assume that other hospitals did approximately the same.

I knew the people in most of the hospitals, and I believe the rest of us also knew these people, but I am not sure that we kept records any better or that we kept them any longer either.

Mr. PENNY. The records would be kept in two separate ways, I would think: One, the individual patient's record would indicate any treatment or tests that were conducted, and then the other record might be tied to the broader purpose of study and analysis?

Dr. KAPLAN. Yes, that is correct. I think that many of the patient records went to the depository in St. Louis. I don't have personal knowledge of that, but I have been told that some of those records were sent to the depository, and it might be useful to call up someone at the depository and ask them about that.

Mr. PENNY. In terms of your observation that no patients were injured by this testing, is that statement simply related to a reaction that may have resulted from the test at the time, or is this an observation that to your knowledge no subsequent ill health effects were a consequence of that particular medical procedure?

Dr. KAPLAN. Well, both essentially took place. There were people that we studied over a period of time, and there was then a number of follow-ups, and we didn't see anything of this sort, and others came back to the hospital, and we saw many of them.

There was a large group of patients who had small tracer doses, and we had no reason to follow them up, but we never received any complaint of any kind relevant to radiation.

Mr. PENNY. You would have other patients that would come back for other purposes throughout the course of time?

Dr. KAPLAN. We followed up some patients, and we didn't follow others. It depended on how major we thought the risk was to that individual. If we thought there was significant risk, we watched them for a significant period of time.

One group of patients that we followed were most interesting, and that is a group of patients who had metastatic carcinoma of the prostate to bone, and they had become fast to narcotics for the intractable bone pain that they had. They had the metastases in the pelvis and in the vertebral column, and these people hurt so badly that narcotics would not knock out the pain. These people couldn't sleep, they couldn't eat, and in a period of a couple of weeks they died, and we developed a material called polymetaphosphate. As a matter of fact, it is the number one article in volume 1, page 1, of the Journal of Nuclear Medicine, in which we reported some of this information and giving them this substance, it was incorporated in the regenerating bone around the lesions, and many of them within several days were free of pain.

Some of those patients went on, gained weight, felt better, had no pain, and lived for a number of months.

This same therapy is being done now by Dr. Ralph Robinson in Kansas City, KS.

With strontium. It is a different substance, but its localization is essentially the same, and his patients react in the same way, and we started this work in 1959.

So this was a group of patients that were going to die, and we knew it. They were incredibly uncomfortable, and we did palliative procedures on them that freed them of their pain.

Mr. PENNY. Dr. Pittman.

Dr. PITTMAN. I started to give a little more complicated answer to Mr. Bachus' question a few minutes ago when he asked if anybody was harmed. It depends on your definitions.

When radioactive iodine was introduced actually before World War II with Cylcotron-produced radioiodine, it began to be used for therapy of hyperthyroidism during World War II before Oak Ridge began distributing it in 1996. It is a very good treatment, as President Bush and Mrs. Bush got it.

The problem with it is—and we didn't know this until I suppose it was the sixties—it may have been the late fifties—is that most people, if you follow the curve of the people after treatment with radioiodine, probably all of them ultimately become hypothyroid. That is, the aim in treating a hyperthyroid patient is to bring the overactive gland down to the normal level but not under it, not underactive.

But radioiodine apparently has a continuing effect so that the curve just keeps ongoing in a cumulative curve. Probably if people live long enough, ultimately it reaches 100 percent. But the treatment is simple. You just take the thyroid. It is no big deal; you just take a thyroid every morning.

But if you call it harming the patients, then I suppose that is harming the patient. However, that is a pretty minimal price for getting rid of the hyperthyroidism, and it is still an excellent treatment.

Dr. YALOW. You probably have the same result if you operated on them.

Dr. PITTMAN. Probably a lower incidence later on.

Dr. YALOW. No.

Dr. PITTMAN. I don't know.

Dr. YALOW. No good reason to believe that. The radiation effect is essentially over in a fixed period of time, surgery is over in a fixed period of time, and you should follow these patients.

Dr. PITTMAN. One of the things I learned about 30 or 40 years ago is never argue with Dr. Yalow. (Laughter.)

Mr. PENNY. Mr. Chairman, if I might ask just one final question.

Patients who were subjected to certain tests or certain treatments at one point, if they came back into the system in later years for another ailment, was there any follow-up from your department, Dr. Kaplan, as to these patients and analyzing their later health problem in light of an earlier treatment or test to see if there might be some relationship or causal situation?

Dr. KAPLAN. Some were seen casually, and a few were scheduled to come back over a period of time, and I think that probably most of them came back that we saw were casual except for small groups of patients, and many of them came back a number of times.

Mr. PENNY. But no indication of any relationship between the testing or an earlier treatment in a future health problem?

Dr. KAPLAN. Other than what Dr. Pittman mentioned. We see that, but it is so easily treated with taking a pill a day that we don't consider this as a significant risk factor.

Mr. PENNY. Dr. Burrows?

Dr. BURROWS. At intervals we try to make a survey of patients who have received radioiodine for treatment of hyperthyroidism, and of course we do that primarily to pick up the hypothyroidism, that the patient himself had not complained about, easily taken care of. But, on the other hand, we also have a tumor registry and scan that. It has been a continuing thing at our hospital, and all patients are entered into that when they have the diagnosis of a tumor, and I have glanced through that, checking off the roster of patients that we have given radioiodine to and have not seen anything identifiable as possibly having any other tumor.

Mr. PENNY. So you don't see that—the incidence among that population group doesn't differ from the——

Dr. BURROWS. Well, I can't say that it is perhaps a valid study, but we have tried to pick up those patients. We just didn't have the interest earlier to pursue it along those lines. There could be an epidemiological study along those lines, but we haven't really done it systematically, we have just checked them off as they have come back for their annual studies.

Mr. PENNY. But in reviewing the list, nothing jumps out at you as a glaring——

Dr. BURROWS. That is right. Not at the moment could we say that there is anything in that population of over 100 patients that we could attribute to the radioiodine therapy they had received up to 30 or 40 years ago.

Mr. PENNY. Thank you, Mr. Chairman.

Mr. ROWLAND. Dr. Pittman, I wish it was so that you could just get a good doctor and you wouldn't have to worry about having to have a signed form, but you know, I don't have to tell you that it is important to have a signed form if you are going to be carried into court and defend yourself, because it is your word against the patient's word.

I wish Mr. Bachus hadn't left. I wanted to point out to him that the medical community was very much concerned, acutely aware, of the deleterious effects of radiation even when you were involved in the research that you were involved in. I guess Madam Curie pointed that out to us with her demise, which was x rays, and of course people who were painting luminous dials on watches with radium——

Dr. YALOW. Well, even Madam Curie died from aplastic anemia probably attributed to her radiation exposure. It is well known that the early radiation workers did get very large doses or exposure, but starting with World War II we have monitored radiation workers and we know more about the radiation effects, and there is no reason to believe in our country this happens.

The information that is coming out of the Soviet Union makes me careful to say that at least in our country and Western Europe there were no such problems. We cannot say what happened in the Soviet Union.

Mr. ROWLAND. I guess what we are investigating here is not people like Madam Curie who—I wonder if she really would have laid down her life had she known that that was going to take place with exposure to radiation. But that is another whole subject that I guess we could get off on.

Mr. Evans.

Mr. EVANS. Thank you, Mr. Chairman.

Dr. Kaplan, let me ask you some specific questions about your affiliation, but I might leave it open to comment from the others about affiliation issues. As director of nuclear medicine at Hines VAMC, you were also affiliated, I understand, with the University of Illinois. Is that correct?

Dr. KAPLAN. That is correct. I was Professor of Medicine for many years, and for quite a period of time I was also Professor of physiology. Other affiliations were an affiliation with the Argonne National Laboratories, which was under the aegis of the University of Chicago, and we worked with Dr. Austin Brues and several other people out there and did a lot of neutron activation analysis, which is an in vitro procedure, and some of that work—that work has been widely published.

Mr. EVANS. Are you aware, did the university conduct any radioisotope or other nuclear medicine research?

Dr. KAPLAN. Not in affiliation with us. We did work with Loyola University Medical School.

Mr. EVANS. What university? I am sorry.

Dr. KAPLAN. Loyola.

Mr. EVANS. Loyola, okay.

Dr. KAPLAN. And Chief of Medicine, and one of the professors of medicine over there worked with us in doing lean body mass by studying the natural radioactive potassium in people which does not reside in fatty tissue so we could tell their relative body density, and he was doing some of that work in affiliation with Purdue University in Lafayette, IN, and Dr. Oster, who was Chairman of the Department of Pharmacology, worked with us. He later was the head of research service at our hospital, and we had a lot of formal and informal affiliation with people that we worked with.

Mr. EVANS. Did any of these affiliations, Doctor, where veterans—were there veterans subject in any research?

Dr. KAPLAN. In the lean body mass studies, they were, and all you did is went into a big iron room that was made from the turret tops of the old USS Indiana, and they sat in a chair for a period of 5 or 10 minutes with the door closed, and then they came out, nothing ever touched them.

Mr. EVANS. All right.

So would there be records at the universities that you were affiliated with of this research involving that?

Dr. KAPLAN. I have a record of it in this notebook which you have a copy.

Mr. EVANS. All right. If we could obtain that, that would be useful.

Can I ask the other doctors here whether they were affiliated with other institutions and what, if any, records of any veterans that might have been subjects for research were kept?

Dr. PITTMAN. Yes. At UAB, University of Alabama at Birmingham, which is right across the street from the Birmingham VA hospital medical center and is joined by a five-story building, the first such building in the VA system, there is a clinical research center.

There are about 73 clinical research centers in various universities—university hospitals around the country which are bed units of five or ten beds funded by the National Institutes of Health for the purpose of clinical research—translating the basic research into clinically applicable diagnostic and therapeutic procedures. As I recall, there were times when we had a study going on in the CRC—clinical research center—in which a veteran would participate. I think that was not very frequent because usually we got other patients who were subjects, but there were probably some times when that occurred.

Those records do still exist. There are patient charts, and they are held by the university hospital.

Mr. EVANS. By the medical school at this point?

Dr. PITTMAN. What?

Mr. EVANS. They are held by the University of Alabama Medical School?

Dr. PITTMAN. Well, actually by the hospital, the University of Alabama Hospital, not the medical school which is not a patient care operation.

Mr. EVANS. All right.

Dr. Yalow?

Dr. YALOW. Since I have left the nuclear medicine service, it really isn't a research service any more, and since we described radioimmunoassay by 1959, our own research no longer involved giving radioisotopes to people because, using radioimmunoassay, we could measure their hormonal changes and all this sort of stuff. So that really since 1960, I have had no knowledge or involvement at our VA of research involving giving radioisotopes to people.

Mr. EVANS. Dr. Burrows.

Dr. BURROWS. Well, as I understand the question, there was no independent study conducted at an affiliated hospital or medical school on veteran patients under our supervision.

Mr. EVANS. Finally, do you believe the VA can obtain records necessary to get an accurate picture of its research activities during the forties and fifties, and would these records contain enough personal data to allow the agencies to help locate the individuals and help them come up with compensation if appropriate?

Dr. YALOW. I left the committee a list of all our publications through 1965. If they want any more information on any of it, it is available. From 1956 on, it didn't involve giving radioisotopes to patients.

Dr. PITTMAN. I think I would just say no. I am amazed at Dr. Kaplan's collection there. I think there may be some more of those around, and maybe the VA Central Office people could tell you. I believe most of the records are not retained from the forties and fifties, patient records or other records, in any systematic way.

Dr. KAPLAN. I believe there may be some in the garage collection that I have, but I am going to wait and see what we find in there. It may be surprising. But I don't think we are going to find any smoking gun or any gun or even any smoke.

Mr. EVANS. Or any of the individuals, Doctor?

Dr. KAPLAN. Pardon?

Mr. EVANS. I mean we are not necessarily looking for smoke, we are trying to get to these individuals that might have concerns

given the reports that they have heard. Maybe nothing has happened to them, per se, but do you think we are going to be able to obtain information about patients out of these records, Doctor?

Dr. KAPLAN. We may have some information that goes back a long way, but I can't really tell you what is in that collection because it is so huge that I haven't gone through it yet.

Mr. EVANS. Thank you, Mr. Chairman.

Mr. ROWLAND. Thank you very much.

We will have some additional questions that we would like to submit to you.

I want to thank all of you for being here. We do appreciate it.

The next panel: Dr. David Rothman, Columbia College of Physicians and Surgeons in New York City; Dr. Richard Setlow from Brookhaven National Laboratory; Dr. Charles R. McCarthy from Georgetown University; and Dr. William R. Hendee from the Medical College of Wisconsin.

Gentlemen, we thank all of you for being here. We would ask that you limit your oral statement to five minutes, and your entire statement will be made a part of the record.

Dr. Rothman.

STATEMENTS OF DAVID ROTHMAN, Ph.D., BERNARD SCHOENBERG PROFESSOR OF SOCIAL MEDICINE, DIRECTOR, CENTER FOR THE STUDY OF SOCIETY AND MEDICINE, COLUMBIA COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK CITY; RICHARD SETLOW, Ph.D., SENIOR BIOPHYSICIST AND ASSOCIATE DIRECTOR FOR LIFE SCIENCES, BROOKHAVEN NATIONAL LABORATORY; CHARLES R. McCARTHY, Ph.D., SENIOR RESEARCH FELLOW, KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY; AND WILLIAM R. HENDEE, Ph.D., SENIOR ASSOCIATE DEAN AND VICE PRESIDENT, PROFESSOR OF RADIOLOGY, RADIATION ONCOLOGY, BIOPHYSICS, AND BIOETHICS, MEDICAL COLLEGE OF WISCONSIN

STATEMENT OF DAVID ROTHMAN, Ph.D.

Dr. ROTHMAN. First, let me add my voice to those who have congratulated the committee on holding this hearing and the energy with which the committee is going about trying to ferret out the historical record. Both obviously for reasons of compensation, but let me say also for reasons of public education, I think the emphasis that you are placing on the issues in and around consent and how research is done has been of great importance to the public to hear, and so I think that the raising of these issues whatever the compensation points, remains terribly important in terms of public education.

The key questions that were raised this morning were your efforts to distinguish between legitimate and illegitimate research. I would remind you that the answer to that is not simply to figure out whether the research did make a contribution to science. One could have research that did make a contribution that we would still think of as illegitimate or as not necessarily ethical.

You know, and Congressman Bachus referred several times to my points about the fact that trying to decide in retrospect what

the ethical standards of the period were is not necessarily an easy task. My efforts extend what I will be able to say this morning.

The only thing I would like to urge the committee is that it be careful because it may well be hearing two things simultaneously, and I am not too sure those two things easily mesh.

On the first hand, we have heard a good deal this morning about the fact that without it necessarily being formal, all that we would think of substantively in terms of consent was followed. Patients apparently at the VA were told the risks, their consent was solicited, and it would all appear, if the record bears out what we heard this morning, that the standards carried on in the VA hospitals in the fifties were more or less identical to our standards with the exception of the signature.

On the other hand, I can assure you, not drawing from the VA, that there were many examples in the forties, fifties, sixties, and into the early seventies where those practices were not followed where, in fact, consent was not solicited, where indeed the subjects of the research were incompetent to give consent.

So that I would ask you to continue to ferret out the record. I think it is very important. You will not get a complete record, you can't this distance later, but you will still have a good deal to learn, and as you try to make the judgments, not to impugn any given individual, that is not so interesting, but to understand the process by which this kind of research went on.

You may be hearing these two strains, and they don't coexist altogether so easily and I think will make the process more complicated but yet more important.

I would urge the committee, were it possible—not that you don't have enough work to do with radioisotopes—were it possible for you to be able to extend the scope of the investigation so you would include not only that which went on in the world of radioisotopes but research that might have gone on in VA hospitals of a very different sort.

I do not know for a fact, I have not reviewed VA records, whether or not other research did go on, but I think it would be important to know whether or not VA patients were involved in the other kinds of research, whether it had to do with LSD or any of the other kinds of interventions that we have been hearing about.

This morning we have heard mostly about research that had a therapeutic intent. I would also want to know whether or not there was research that went on of a different sort that did not have a therapeutic intent. The record may show it, the record may not be able to show it, but I would urge your definition of purpose be as broad as possible.

Third, and perhaps most important, the VA hospitals today do still work with institutional review boards, and those of us who have been studying institutional review boards have a series of recommendations that we think might be helpful to improve their performance. The issue has not simply gone away.

Human experimentation, for all the reasons we have heard, has to continue, but I am among those who are not convinced that the present structure of the institutional review boards is as good as it might be. It is a very decentralized system. The level of audits conducted at Washington exist, but they could certainly be im-

proved. We could do a good deal more in the training of institutional review board members. There is a whole territory, I think, that requires attention as to strengthening the role of the institutional review board.

It is important to set up a national commission to look at broad ethical issues. But let me close by urging that you include in your agenda a very careful analysis of how research is going on now at the VA under institutional review boards and consider the kind of changes you could make to be altogether confident that when the Secretary says he knows of no research going on that is unethical, we are confident, altogether confident, that he is right.

[The prepared statement of Dr. Rothman appears at p. 127.]

Mr. ROWLAND. Thank you, Dr. Rothman.

Dr. McCarthy.

STATEMENT OF CHARLES R. McCARTHY, Ph.D.

Dr. MCCARTHY. Mr. Chairman I am Dr. Charles McCarthy. I served for 14 years as Director of the Office for Protection from Research Risks (OPRR) in the Department of Health and Human Services, and I retired from government service several years ago.

I am very pleased that the President and department heads have undertaken a retroactive study of possible abuses of radiation research. I hope that you can caution those involved in this study, (1) to make their best efforts, and you have already made that clear to Secretary Brown, to find out as much as possible; and (2) to identify and compensate any individuals who may have been injured in the course of that research. That is a very delicate process, because the process must avoid needless frightening of people who may have innocently and harmlessly participated in research. They may feel terribly frightened when they read about the occasional person who was damaged.

I have included about 10 pages of testimony on the historical development of protections for human subjects in the Government. The history begins with the Nuremberg Code in 1946; and includes NIH policy in 1953, the 1966 Public Health Service policy; the 1971 HEW policy, the 1981 policy revisions that came after the National Commission made recommendations; and finally, the most important step in 1991 all of the Federal departments and agencies that carry out research involving human subjects have come under the same rule.

That rule includes research conducted or supported by the Department of Veterans Affairs. The VA had its own policy through the 1980s that was different from many other departments and agencies, but in 1991 all Federal departments and agencies agreed on a common Federal rule which, if employed, ought to prevent damage to human subjects and unethical research.

Nevertheless, I agree with Dr. Rothman that we have gradually developed in this country the best system for protecting human subjects in the world. The IRB system is second to none, but at the Federal level, partly because of Federal downsizing over the last three administrations, at the Federal level we have diminished the oversight of that system. I can assure you that a system that is not enforced is a system that is likely to be abused.

I am not suggesting that we have a white coat crime wave in this country. I am merely suggesting that because the Federal Government is involved in supporting $14 billion worth of research, at least 25 percent of which involves human subjects, that major oversight efforts are needed.

We have had no new personnel positions in the Department of Health and Human Services since 1985, and have not been able to replace persons who retired. We have one MD on the OPRR staff who has returned several years after retirement and volunteers her time simply because she knows that there is a great deal of work to be done and not enough people to do it.

I can assure you that 10 years of prospective surveillance are less expensive for the Government than one major retrospective study like the one that is now being undertaken. It is penny wise and pound foolish to understaff the prospective oversight of research and then have to conduct retrospective investigations of the type that we are now considering.

In the Department of Veterans Affairs, you have one part-time official who looks after the implementation of the regulations in all of the VA hospitals. That man, Dr. Ted Lauri, is doing a magnificent job. He works nights, he works weekends, but that is not enough. He needs a staff.

There is no trained investigator in the Department of Veterans Affairs to investigate complaints. We have only two in the Department of Health and Human Services. I checked last week, and OPRR had a backlog of 56 allegations of noncompliance with regulations and only two investigators trying to check on these complaints.

I can assure you that the cost of carrying out one investigation often is more than the entire annual budget of the staff that carries out the oversight.

I would like to make two other recommendations: First, that we have a national oversight body, an ethics advisory board; Dr. Rothman already recommended that; Senator Hatfield has introduced legislation to create such a body. I am not aware that anyone in the House has endorsed the Hatfield legislation or introduced a similar bill on this side of the Congress. I think it is very important.

Secondly, Mr. Chairman, I think we must develop a system for compensating injured research subjects and not do it on an ad-hoc case-by-case basis. I think it is fine if the case mentioned earlier in the hearing of the McCarthy family—not related to me, by the way—should be compensated, but I think we ought to have a comprehensive system whereby anybody injured in research can be adequately compensated. You may be able to provide compensation to some veterans, but there are some 16 other departments and agencies in the Government that do not have any system for compensating research-related injuries. I would encourage you to work with the rest of the Government to have a comprehensive system for compensation.

Thank you, sir.

[The prepared statement of Dr. McCarthy appears at p. 131.]

Mr. ROWLAND. Thank you, Dr. McCarthy.

Dr. Setlow.

STATEMENT OF RICHARD SETLOW, Ph.D.

Dr. SETLOW. Thank you, Mr. Chairman.

I am going to summarize briefly for the committee the information about the risks of radiation and radioisotopes. You have to recognize that we live in a very hazardous world. There are hazards in all of our life-styles. One of the hazards is radiation, and the question is, how large is that hazard?

There is a lot of background radiation, that I have summarized in my written testimony, from cosmic rays. Denver, Colorado gets lots more than Long Island, from where I come. There is radiation from the rocks around us. There is radiation inside of us. Each of us has about a tenth of a microcurie of radiation made up of radioactive potassium and carbon, and it gives us 200,000 disintegrations per minute for your entire life. This sort of background radiation amounts to about 20,000 millirem, 300 millirem per year for 70 years. So just living, sitting here, on the average, we are accumulating damage.

The reason we are not dropping over dead is that we have very efficient repair systems for damage that occurs slowly. Damage that occurs rapidly can't be repaired easily.

It has been estimated from animal experiments and from the Japanese cancer data among bomb survivors—that is not a chronic irradiation, that is a quick bang for radiation—that approximately five percent of the cancer deaths in this country arise from this background radiation. The uncertainty in this number is pretty high, maybe 50 percent, because it is a big extrapolation. We cannot detect that five percent because it is buried in the noise of the other 95 percent. So we can't pick out a particular cancer and say, "Ha, that came from radiation," because there are cancers all around us that come from life-style, oxidative damage as we breathe, and many other things. So this five percent is not observable.

However, since we have no present way of detecting it, we have to recognize that there may be a future way, and the genome project that the Department of Energy started may be one of these ways. We may be able to pick out particular gene changes that give us this information.

This average of five percent obviously varies greatly over the population. Denver probably may have more from radiation than Long Island, but it has less from oxidative damage than Long Island. We have more oxygen than Denver. So there is a trade-off, and it is very difficult to look at the particular individual and say, "Ha, I know what happened to you."

On the average, over our entire population, medical procedures amount to about 50 millirem per year; that is about one-sixth of background. Now only the people that have the procedures get this radiation. Those of us that don't, don't get it. So it is a strange kind of an average. It means there is a big variation among people.

In nuclear medicine procedures using radioisotopes, originally developed as a result of the Atomic Energy Commission, we find a number of diagnostic procedures, and Dr. Yalow alluded to many of these. There are diagnostic procedures for the heart, for the lung, for the thyroid, for brain function, for liver function, for bones, numerous abnormalities. These procedures use isotopes,

that decay radioactively to give radiation. They have short half lives; they only exist for a short time, less than a day or maybe 10's or 20's of days at the most. So even though you may get a lot of radioactivity initially, it is all gone in a relatively short period of time compared to, remember, living your 70 years and getting your 300 millirem per year, year in, year out.

That doesn't mean it is harmless, it means it is relatively innocuous compared to this sea of radiation in which we live. That is what Dr. Yalow in a sense was saying.

At the present time, there are over 10 million diagnostic procedures using radioisotopes in this country. There are 100 million laboratory procedures that Dr. Yalow alluded to in this country, so they are being used all the time, mostly for diagnostic purposes, and almost all of them produce much less radiation than we would get if we sat in this room for a year or maybe two. That is the perspective I wanted to give you.

There is one other point I want to mention. It is a little off the subject, but not greatly. The estimation of cancer risk depends on the dose to which people have been exposed and of course the tissue involved. There are at least two National Research Council committees grappling with the problem of estimating doses to exposed individuals, exposed presumably inadvertently, and most of them were veterans. They were exposed at various bomb tests in various parts of the world, and the problem with estimating the compensation these individuals should receive, if any, is to get some estimate of the dose and therefore some estimate of the risk. These are difficult problems that we hope will be solved within several years. Obviously, the level of compensation, once having estimated the risk, is an ethical and political problem that my colleagues have already addressed.

Thank you.

[The prepared statement of Dr. Setlow appears at p. 149.]

Mr. ROWLAND. Thank you very much, Dr. Setlow.

Dr. Hendee.

STATEMENT OF WILLIAM R. HENDEE, Ph.D.

Dr. HENDEE. Thank you, Mr. Chairman.

I wish to discuss four concepts that I hope will provide a historical and scientific perspective on experiments involving exposure of human subjects to ionizing radiation that were conducted in past years.

Concept one is the knowledge of long-term effects of ionizing radiation. The scientific understanding of the effects of exposure to radiation is much more sophisticated today than it was a few decades ago. Although it had been known since shortly after the turn of the century that radiation can cause cancer, it was thought for many years that large amounts of radiation were required to cause the disease and that the onset occurred relatively soon after exposure.

It was not until survivors of the atomic bomb blasts at Hiroshima and Nagasaki had been studied for many years that data began to reveal increased cases of leukemia and later increased numbers of other forms of cancers in the population.

The appearance of increased numbers of cancers in a population of individuals several years or even decades after exposure is known as a long-term effect of exposure. This effect was not appreciated until the late 1950's. Before that time, individuals exposed to radiation were not thought to be at increased risk provided that the doses were kept low enough to prevent short-term effects. This concept is familiar to us all. None of us believes that an aspirin now and then does not increase our risk of injury even though aspirin in large doses can be lethal.

The concept was even embodied in earlier expressions for radiation and protection standards such as tolerance dose and later maximum permissible dose that implied that doses of radiation are innocuous if they are small enough that they do not produce short-term effects.

Concept two is the estimation of radiation effects of low doses of ionizing radiation. Survivors of Hiroshima and Nagasaki have been followed for almost 50 years. All of these survivors were exposed to relatively large amounts of radiation. Once the greater numbers of cancers were discovered in the survivors, the question arose of how to estimate the risk of radiation-induced cancer at much lower exposures, in the range of those that might be received by a radiation worker. This question was very important to setting protection standards for radiation workers at levels low enough to ensure safe working conditions. The preferred model for making this estimate was to assume that there is no amount of radiation below which the risk is zero and that the level of risk increases in a straight line fashion with the amount of radiation received. This model is known as the no-threshold linear model of radiation damage.

It is important to point out that we have very little direct data on the health effects of exposure of humans or animals to small amounts of radiation and that the limited data that we do have is inconsistent. For example, some data even suggest that there is a beneficial effect of small exposures, a phenomenon known as radiation hormesis, analogous to the scientific finding that an aspirin or two each day decreases the risk of a heart attack.

The important point is that risk estimates of radiation exposure in small doses are just that, they are estimates obtained from a hypothetical model of radiation injury that extrapolates from measured effects in humans at much larger amounts of radiation.

Concept three is the purposes of early experiments employing ionizing radiation. Many of the experiments referred to as radiation experiments in the press employed radiation not as a causal agent but as a means to collect data about human health and disease, as you have heard this morning from many of the witnesses. For example, in the study at the Fernald State School, adolescent boys received a very small, less than one microcurie amount of radioactive calcium in milk in order to study the metabolism of calcium. The radioactivity was used as a tracer so that the metabolism study could be performed and not for the purpose of studying the effects of radiation on the body. At that time, the amount of radioactive calcium was thought to be innocuous. That conclusion is still true today because the amount of radioactivity used in the study

is so small as to constitute an insignificant although theoretically not zero risk to the 19 boys studied.

As you have heard, many studies were performed on individuals in the years after World War II in an effort to develop procedures employing radiation that would benefit patients. Such studies continue today and constitute the research aspect of disciplines such as diagnostic radiology, nuclear medicine, and radiation oncology.

The payoff of these studies has been spectacular, Mr. Chairman. For example, 500,000 cancer patients in the United States underwent radiation treatments last year, and, as Dr. Settlow mentioned, over 10 million nuclear medicine procedures were also performed.

My fourth point involves the ethical considerations of human experimentation with radiation. Just as our knowledge of the health effects of radiation exposures has evolved over the years, so has our appreciation of the rights of individuals involved in human experiments. Today a physician is required to provide enough information about a medical procedure to permit a reasonable patient to make a decision about participating and to ensure that the patient fully understands the risks of the procedure and the option to decline or withdraw from participating.

In the 1940's and 1950's, the process required for an experimental procedure was whether it was customary among physicians to seek consent from patients participating in similar procedures. Since for many of the radiation experiments the risk was thought to be nonexistent or negligible, one can easily appreciate how individuals may have unknowingly participated in experiments that involved exposure to radiation. Understanding how this may have happened is not equivalent to condoning the practice from the perspective of today's ethical standards. It is simply a recognition that the standards are different today from those in place in years past.

Mr. Chairman, in my written testimony I make several recommendations regarding the concerns that are being addressed at this hearing today. I want to just emphasize one of those recommendations. I hope very much that the concerns we are addressing here today not be allowed to imperil in any way biomedical research in VA hospitals across the country, for it is from those hospitals that many of the advances have come in the medical applications of ionizing radiation that have resulted in the alleviation of human illness and suffering.

Thank you very much for this opportunity.

[The prepared statement of Dr. Hendee appears at p. 154.]

Mr. ROWLAND. Thank you.

Dr. Rothman, much of the difficulty that we have on this committee arises from the classified or confidential Department of Defense record. For example, we have only recently learned that during World War II some service members were intentionally exposed to mustard gas. What can we do about the apparent set of standards for research conducted for, I guess you would say, military purposes?

Dr. ROTHMAN. I think in a variety of ways it is very important. But just to clarify the question, are you looking now as we look back to judge compensation, or are you looking to the future to make certain it doesn't recur?

Mr. ROWLAND. Well, I am looking in both directions.

Dr. ROTHMAN. In both directions.

Well, I think in the first instance it is going to be terribly important for the record to become clear, and your question about turning to the Department of Defense, extending it beyond the subject matter of today, is one that I completely concur with and would urge you to do.

I think it is true, looking back, that research ethics fashioned during the hot war, World War II, seemed to justify violating rights of patients for the sake of the war effort. In a world of draft, it didn't seem to make a lot of sense to have consent of subjects necessarily, and what we did in the hot war we then did in the Cold War, and in some instances that I know of, not involving the VA, we did it in the war against disease. So I think it terribly important for you to tease out the record so we will understand the process that went on.

By way of the present, I do think, as Dr. McCarthy also said, I do think that for the most part the IRB's do a wonderful job, but I would want much more national investigation or audit—let me use the word "audit"—over the research that is being conducted or sponsored by the Department of Defense, by other agencies of Government, so that we know that it is not only those inside the agency who are getting ultimately to decide what is an acceptable risk and what is not an acceptable risk, what should somebody know about the research protocol, what don't they have to know.

Mr. ROWLAND. Does anybody else have a comment?

Dr. MCCARTHY. I would simply concur in that and suggest that since 1991, Department of Defense, just as the Department of Veterans Affairs, now comes under the common Federal rule. The Executive Branch has an oversight committee that covers research across the entire Government. That committee is understaffed and not very effective at the present time, but we have an instrument there that could be developed to accomplish adequate oversight.

For many years in my job at HHS, I had security clearance to review research in the CIA and in the Defense Department, as did some of my colleagues. Thus, we were able, even though we were from a different agency, to bring in outside influence and to bring any concerns we had to the highest levels of Government. That experience illustrates that there are ways to handle oversight without breaching confidentiality. You can have outside people come in, check them for security, and then let them do an audit. We are not doing very much of that because it is costly, but I would suggest that preventing one scandalous situation or one situation that may lead to compensation for injuries sustained in the course of research is much less costly than subsequent remedies.

So I encourage you again to support audits of the system and not to be penny-wise by cutting down our auditing now and pound foolish by perhaps in the year 2004 or 2014 or 2024 having a massive retrospective look at research going on today. I would encourage you to get the preventive kinds of structures in place now. We know how to do it after 30 years experience. What we need are the personnel and the dollars to carry it out.

Mr. ROWLAND. From the testimony we have heard here this morning regarding the kinds of radioactive material that were used

in research in the VA, let me ask you this: Should the VA, I guess as a matter of science or of ethics, have done some follow-up studies on the people that were involved in that research?

Dr. MCCARTHY. I think it is ethically required that investigators establish a way of following up. I don't think it is always incumbent on the investigator himself or herself to follow up, but there ought to be some kind of arrangement with attending physicians or others who carry out the medical care of those subjects to report back any untoward results that may appear at some later date.

So, yes, I think there is an obligation. I don't think it always falls on the investigator himself or herself. Otherwise, they would not be able to engage in new research. But I think follow-up structures can be readily established.

Mr. ROWLAND. We heard from the panel before you that the amount of exposure was insignificant insofar as any health-related after effects were concerned. So I guess from your standpoint, even in view of that, do you think that there should have been some follow-up?

Dr. ROTHMAN. Well, there is also the issue though of did the panelists who spoke this morning have knowledge of the entire record? And I have no doubt that the entire record is not going to be able to be reconstructed, but I am not certain that four individuals who seem to have been mostly involved in research that was of a more therapeutic than nontherapeutic sort represent for us the universe of what went on. I would certainly want more investigation before deciding, you know, where and what it is necessary to do.

Dr. SETLOW. It was pointed out that the effects of radiation are often long-term effects that only show up many, many years later even though they may only show up with a low probability. Nevertheless, if you are to find any effects, there have to be long-term follow-ups, and the statements that no effects were observed in the first few years really add nothing to the scientific base.

In the Japanese experience, we are still following these people, and more cancers are appearing. That doesn't mean that you are going to get some tremendous result, but if you don't follow these people now, you will never have any data at all in the future. They must be followed.

Mr. ROWLAND. Do you think that the radiation—I won't use the words "radiation-related experiments"—research with radioactive material that was conducted by the VA ignored some of the principles that were set forth at Nuremburg?

Dr. ROTHMAN. It is too soon, I think, to be able to know the answer to that question. No one has combed the records. What we have heard this morning does not suggest gross violations, but I would not want to prejudge that.

The whole point of your investigation and the whole point of the energy that you are committing to this is to get that record out, and I can't encourage you enough to do that. Once that record is out, I would hope that we could be able to answer your question and to say no, there were not violations that rose to that level. But at the moment, prior to the effort, I would say we have got to keep that question in mind, it is one of those questions that is going to impel us forward, and we hope we get the answer that we want to hear, but we have got to go through the effort first.

Dr. MCCARTHY. I would endorse what Dr. Rothman just said. I have no inside information, but I have looked at some of the press accounts of whole body radiation carried out in part by the then Veterans' Administration back in the 1960s. Certainly that research came in for severe criticism from an ethical standpoint by the press.

That does not mean that somebody was guilty of doing something wrong, but it does raise some questions. Let's look at that study along with some other experiments very carefully, and see what information can be found. I am not in a position to level any accusation, but if I were looking, that is the one I would start with because at least the press accounts suggest that there was inadequate or perhaps no informed consent and that the risks were not justified by expected benefits.

Again, I don't have inside information on that study. I have never seen the protocol or a single patient record, nor have I seen the consent documents. I have merely seen the press accounts.

Mr. ROWLAND. Dr. Rothman, you have called for an independent review of the full record of Government research. Who ought to do that?

Dr. ROTHMAN. I think it has got to be done under HHS auspices of one or another sort. We could establish a committee. Dr. McCarthy has said—has talked about the downsizing of the regulatory apparatus already, so it makes me all the more eager to suggest that HHS, through one or another of the mechanisms. The office that he once headed would not be a logical place where one would begin an audit process. One might, in the process of sampling from local IRB's, actually take the step of speaking to the subjects in the experiments, get their vision of what the consent process was like and what the research process was like.

Obviously, given the enormous amount of money expended on investigations, on clinical investigations, human experimentation today, we are not going to be able to do it for everyone, but we do know how to sample, and it has got to come out—I mean from a regulatory standpoint, but also from a very logical standpoint—it has got to come out of Washington, and so I would hope that HHS would take it upon itself to begin to devise the administrative mechanisms, the sampling procedures, so that we could know better what these local boards are up to.

I serve on one of those local boards at my medical school. I am confident that we do the right thing. I am not suggesting that I think we are going to discover rampant abuse out there, but I would certainly be far more comfortable if I knew that local boards were being somewhere along the line checked, and we should also remember that local boards are not only university boards, private companies have their own boards, for-profit corporations have their own boards, the Government agencies have their own boards.

I really do want to see somebody reviewing the reviewers, and I think it does have to come out of Washington, and HHS would be the logical place for it to emerge.

Dr. MCCARTHY. I would agree with that, and I think it is not going to be a whole lot more difficult to look at the whole spectrum of research, not just at radiation research.

I suspect that some worse things occurred in other forms of research than in radiation research, and as long as we are going to make this enormous effort, I think it is not much more difficult to look at all the research conducted in a time period and then, even more important, in my judgment, to establish an audit oversight system for ongoing research.

In 1944, the National Institutes of Health spent about $180,000 in extramural research. Last year the Federal Government spent close to $14 billion on biomedical research. The enterprise has grown enormously. But the oversight of the enterprise is no bigger now than it was in 1985.

Mr. ROWLAND. Thank you.

Dr. Setlow, you note that isotopes that are commonly used today have a half life of about 6 hours and consequently there is almost negligible risk to individuals even in large doses, but what can you tell us about the half life of isotopes that were commonly used back in the 1950's and 1960's, and maybe compare that risk then with what the risk is today.

Dr. SETLOW. I couldn't really answer offhand without looking at the particular ones, I am sorry to say, but I can research it and give you an answer. Maybe my colleagues——

Mr. ROWLAND. Maybe Dr. Hendee can answer.

Dr. HENDEE. Yes, Mr. Chairman, the most commonly used isotope back in the fifties was Iodine 131 for a variety of nuclear medicine procedures. That has been largely replaced by Technetium 99m and other radioisotopes which have a much shorter half life.

However, the relationship of risk has not changed with the relationship of half lives. Iodine has a half life of eight days. What has happened is that we have been able, while keeping the radiation dose in the same ballpark for the patient, to greatly increase the amount of activity that we can administer because it decays away much more rapidly, and therefore greatly improve the quality of the studies.

So if I look at the quality of the studies today compared to 20 years ago, they are much better. When I look at the radiation dose administered to the patients, it is roughly within the same ballpark. Therefore, the short-lived isotopes have not resulted in a tremendous reduction in dose and a tremendous reduction in estimated risk. But we are able to obtain much better studies.

Mr. ROWLAND. Gentlemen, I would like to ask some more questions here. I find this very interesting, but I note it is the noon hour now, and you have been here a long time, and you have been very patient.

We will have some questions that we will submit to you and ask that you answer those.

Mr. ROWLAND. I want to thank all of you very much for being here this morning, and we stand adjourned.

[Whereupon, at 12:03 p.m., the committee was adjourned.]

APPENDIX

PREPARED STATEMENT OF HON. BOB STUMP

Thank you, Mr. Chairman. I commend you for calling this timely hearing on a subject that's been very much in the news lately. Questions have been raised about government radiation research back in the 1940s and 1950s. Our focus is of course on the VA and whether veterans were the subjects of any improper research.

Also, I want to join you, Mr. Chairman, in a warm welcome to Secretary Brown this morning.

I am confident that the VA under the Secretary's direction is losing no time in its conduct of an exhaustive, Department-wide investigation into its early radiation research activities on human subjects. We owe nothing less to veterans and the general public.

Mr. Chairman, if mistakes were made, whether through ignorance or malfeasance, they should be revealed and corrected as best we can. I look forward to hearing from Secretary Brown and from our panels of distinguished witnesses.

Mostly what we're going to find out today, I believe, is that the VA's role as pioneer in nuclear medicine is not well known and that in yet another way modern medicine in this country owes the VA much more than most people realize.

Thank you, Mr. Chairman.

PREPARED STATEMENT OF HON. CHRIS SMITH

Thank you, Mr. Chairman, for holding this very important hearing to examine the Veterans Affairs Department's role in human radiation experiments conducted over the past five decades.

The preliminary findings of the VA's survey of their hospitals raise more questions than they answer. The findings indicate that we must investigate further the issue of whether harmful experiments were conducted in VA hospitals and whether patients were unknowingly exposed to radiation. According to the findings I have received, 54 VA hospitals, out of 168, have reported that they had a radioisotope/nuclear medicine program in place by 1961. This number includes the East Orange Medical Facility in my home state of New Jersey. East Orange and others have conducted a preliminary search and report that they have few or no records from the time frame in question and thus reason that human radiation experimentation were probably not done without the patients' consent. In reality, Mr. Chairman, most of the hospitals in question have no records of protocols used for radioisotope research during that time period and are short on providing names of participants in any experiments at all.

I do not think this is good enough and believe we need to search more. Saying "we have no record," rather than "the record is clear" on human radiation experimentation will not satisfy the many veterans who are today wondering about past trips to VA hospitals. We must assure our veterans that they were not guinea pigs in questionable experiments. Should we find that some vets were not informed, appropriate compensation should be considered. I look forward to hearing the testimony of the members of our panels, who I am sure will be able to shed more light on this issue for us.

On a related matter, I will be questioning Secretary Brown on the matter of bronchioalveolar carcinoma. As you know, Mr. Chairman, I have been working to ensure that this type of cancer is included as a presumed service-connected illness.

On November 17, 1991, the VA Advisory Committee on Environmental Hazards discussed and agreed to the following statement:

> Bronchio-alveolar carcinoma is a type of lung cancer. Lung cancer is on the list of cancers which the Committee has accepted to be radiogenic. Recent evidence . . . strengthens the connection between radiation and lung cancer, including bronchio-alveolar carcinoma . . .

Despite this statement, and the findings of many other doctors and scientists, I received a letter last month from Secretary Brown informing me that he would not propose that "service connection be granted for this disease on a presumptive basis . . ."

To me, the findings of the Veterans' Advisory Committee on Environmental Hazards, as well as studies in the medical journals *Experimental Lung Research, Annals of Surgery, American Journal of Clinical Oncology, and Cancer: A Journal of the American Cancer Society*, are more than enough to warrant that bronchio-alveolar carcinoma be included in diseases which are presumed to be service-connected.

I was first made aware of this issue in 1986 by Joan McCarthy, a widow whose husband Thomas died of the disease in 1981. Mrs. McCarthy, you may recall, has testified before our committee about her husband Thomas, who was a non-smoker and only 44 years old at the time of his death. Thomas was serving on the *USS McKinley* in May 1955 when a plutonium bomb was exploded in the Pacific Ocean and the plutonium-filled ocean spray came in contact with him. Mrs. McCarthy has layed out for us point by point the 14-year process she has engaged in with the VA. This process has found that there is a connection between bronchio-alveolar carcinoma and service-connected radiation exposure, but now the VA refuses Mr. McCarthy and his widow their due compensation.

Through years of frustration, Joan has been patient with the process, and through the process, a presumption was found. Why, then, was no action taken? In 1992, I inserted an amendment into legislation eventually signed into law which required the Advisory Committee to issue a report by April 1, 1993. While a statement has been agreed to, the Committee has yet to release a report. Congress has yet to see that report, which is over 10 months late.

Secretary Brown wrote that this issue will be decided by Congress. We cannot continue to pass the buck. It has been proven that this illness is radiogenic and that Thomas McCarthy died as a direct result of an incident which occurred during his service to his country. It has been 13 years since Thomas McCarthy's death. Let's right this injustice, and do it quickly.

Thank you, Mr. Chairman.

Statement Before the Veterans Affairs Committee on Human Radiation Experimentation by the Department of Veterans Affairs

Congressman Lane Evans
February 8, 1994

Mr. Chairman:

Let me begin, by sharing Congressman Gutierrez apologies for not being here this morning, but he was detained in Chicago on another matter. VA's Hines Medical Center in Chicago, which serves his veterans, was one of the facilities that conducted radiation experimentation. This matter is of great importance to him and he looks forward to fully participating with the Committee's investigation.

While I thank you for convening this hearing, I feel there is no excuse for the actions that led up to today. How many times will we hear about the abuses that the own government heaped upon its citizens and in particular, the very men and women who defended this nation? National defense should never be an excuse to experiment on or endanger a single individual.

It appears as if VA may not have participated in the type of research that our colleague, Ed Markey, first uncovered, but we cannot be sure. VA has not been able to, and may never be able to, assemble the records necessary to paint a complete picture of its own research, let alone the projects conducted by its affiliates.

Nevertheless, we cannot allow anybody to continue to suffer simply because their records are incomplete. If veterans were injured by government sponsored experimentation, restitution will have to be made.

And we cannot forget about the atomic veterans. These men and women are also victims of government experimentation.

During the past 50 years, thousands of service personnel were exposed to ionizing radiation while on active duty. While the majority of service personnel were exposed during U.S. nuclear weapons tests, some were exposed during other activities such as the occupation of Nagasaki and Hiroshima and guarding U.S. nuclear weapon production facilities. These men and women were typically under orders to participate and not properly informed of the potential dangers of exposure to ionizing radiation.

Recently, 28 of our colleagues, including 12 members of this Committee, joined me in requesting that President Clinton include these men and women in the ongoing investigation. I would like to have a copy of this letter included in the record.

I am disappointed to report that the President has chosen not to give these veterans the consideration that they deserve.

The plight of atomic veterans has not been adequately addressed. The existing statutes and regulations do not go far enough and the Administration continues to drag its feet on the issue. In fact, VA has yet to deliver two reports dealing with atomic veterans to this Committee although they were due last April and December.

Atomic veterans were not adequately informed of the dangers of ionizing radiation and many were injured as a result. There can be no doubt that some veterans have paid for their dedication and bravery with their health and in some cases, their lives.

For this reason, I intend to introduce legislation in the near future that would finally treat atomic veterans with the fairness and respect that they have earned.

The government has begun an important process by revealing information pertaining to radiation experimentation and promising to care for those individuals injured by the research, but more still needs to be done. And we must also do everything possible to ensure that this type of experimentation never happens again.

Congress of the United States
House of Representatives
Washington, DC 20515

January 7, 1994

The Honorable William J. Clinton
President of the United States
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Dear Mr. President:

We would like to commend you for quickly addressing the questions raised by recent accounts of U.S. government human radiation experiments on American citizens from the 1940s through the 1970s.

We are concerned, however, that the task force's investigation might focus solely upon civilians who were exposed to radiation without their consent. Any government investigation or initiative on radiation experimentation must include consideration of those individuals who were exposed to ionizing radiation while serving in the U.S. Armed Forces as well as the adequacy of the relevant statutes and regulations.

During the past 50 years, thousands of service personnel were exposed to ionizing radiation while on active duty. While the majority of service personnel were exposed during U.S. nuclear weapons tests, some were exposed during other activities such as the occupation of Nagasaki and Hiroshima and guarding U.S. nuclear weapon production facilities. These men and women were typically under orders to participate and not properly informed of the potential dangers of exposure to ionizing radiation. Similarly, some Persian Gulf War veterans believe that they were exposed to depleted uranium in Southwest Asia from our own munitions and equipment without being adequately informed of the potential radiation risk by the Department of Defense.

The government has begun an important process by revealing information pertaining to radiation experimentation and promising to care for those individuals injured by the research, but more still needs to be done.

We respectfully request that you direct the task force to include those Americans who were exposed to ionizing radiation as they defended their nation. Like the civilians who were exposed, these men and women were not adequately informed of the dangers of ionizing radiation and may have been injured as a result. There can be no doubt that some veterans have paid for their dedication and bravery with their health. We must ensure that these veterans are not forgotten and that they receive every consideration.

Thank you.

Sincerely,

Lane Evans
Member of Congress

Don Edwards
Member of Congress

Patricia Schroeder
Member of Congress

Joseph P. Kennedy II
Member of Congress

George E. Brown, Jr.
Member of Congress

Mike Synar
Member of Congress

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Ted Strickland
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Mike Kreidler
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Corrine Brown
Member of Congress

Karen Shepherd
Member of Congress

Bob Filner
Member of Congress

Bob Clement
Member of Congress

CONGRESSMAN J. ROY ROWLAND
VETERANS AFFAIRS COMMITTEE HEARING
ON GOVERNMENT SPONSORED RESEARCH INVOLVING
RADIOACTIVE MATERIALS CONDUCTED IN VA MEDICAL CENTERS
FEBRUARY 8, 1994

I want to thank the Chairman for holding this very important hearing on the issue of human radiation experiments involving intentional exposure to ionizing radiation. I am pleased that Secretary Brown will testify today to update us on the progress by the VA in determining the use of radiation in human subjects in VA hospitals. In order for trust to be established, this process must be open and accessible for all veterans and their families.

I am pleased by the quick actions of the Department to review the circumstances under which VA nuclear medicine research was conducted in the 1940's and 1950's. I, like the other members of this committee, am concerned that veterans may have been subjected to improper or inappropriate research. Additionally, I am troubled that research which might otherwise have been sound may have been tainted by researchers' failure to fully inform and obtain the consent of research subjects. Undoubtedly, we are all committed to finding out the truth.

As a sponsor of legislation pertaining to atomic veterans, I am very interested in radiation health-effects and learning more about the nature of these experiments. I realize that the search undertaken by the VA and other agencies and departments is extensive and time-consuming. Until all of the necessary data is collected and analyzed, it is difficult to gauge the appropriate response. In the meantime, it is important that the Department keeps us advised of the progress of their review.

Our priority is to take care of those who served our country in the armed forces. This hearing will help us better understand this complex issue so that we can take the necessary action to provide for their care. Again, I thank the Chairman for holding this hearing and I look forward to hearing the testimony from our witnesses today.

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Congress of the United States
House of Representatives
Washington, DC 20515

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February 7, 1994

STATEMENT BY CONGRESSWOMAN CORRINE BROWN
HOUSE VETERAN AFFAIRS COMMITTEE
HEARING ON HUMAN RADIATION EXPERIMENTS

Like many Americans I was shocked and outraged to hear about radioactive experimentation on innocent people. The idea that various Federal departments over the last fifty years were intentionally exposing American citizens and American soldiers to ionizing radiation is sickening.

I am glad to know that this administration -- and Secretary Brown's department -- plans to conduct a thorough investigation, and I expect that the Interagency Working Group appointed to oversee the inquiry will make any and all its findings open to the public. In addition, you may rest assured that I will follow the progress and developments in the Group's investigation with close scrutiny.

Finally, once the details of the investigation are known, and if the findings conclude that any public servant acted illegally, I want those in charge of the experiments to be held accountable. This is absolutely necessary if trust is to be restored to the government.

STATEMENT OF JOSEPH P. KENNEDY II
THE VA'S ROLE IN HUMAN RADIATION EXPERIMENTS
FEBRUARY 8, 1994

Good Morning. I would like to begin by thanking Chairman Montgomery for convening this important hearing.

In recent weeks, the watchful eyes of the American people have been opened to a troubling chapter in our nation's history – an era where humans were sometimes the unwitting guinea pigs of radiation experiments. Many already deemed to have been participants in government-sponsored radiation tests were among those who traditionally turn to our government for care. By preying upon an essentially captive audience of subjects ranging from the infirm and the elderly to those on active duty military and others seeking care at veterans hospitals, medical ethics standards are put to the test.

Now, it is time for our government to acknowledge this Cold War legacy and make amends. We can accept no less than a comprehensive investigation and a full, independent review demanded of a free society.

Secretary Jesse Brown is to be commended for acting quickly and openly to investigate the Department of Veterans Affairs' role in human radiation experimentation. The VA is no stranger to the concerns of radiation exposure. The plight of our atomic veterans is well known and must not be forgotten today. The VA's interest in uncovering radiation exposure does not stop with possible radiation testing at VA hospitals but includes any exposure that may have occurred to our veterans while on DOD's watch.

The investigation ahead will be challenging, as VA's radiation research program appears to have been widescale. Of the 17,000 calls placed to the government's radiation hotline, about 40% were from veterans. And according to Secretary Brown's testimony, the VA "pioneered" nuclear medicine in this country. In fact, a full 10% of VA research was radiation-related during this era. VA established radioisotope units nationwide with 48 in place by 1958. Further review of VA's Annual Reports shows the VA had 70 such units in place by 1970.

I am deeply distressed by the fact that the VA set up a secret Atomic Medicine Division, due to mounting fears built by the armed services' growing atomic energy activities. Keeping this division confidential due to concerns about paying service-connected compensation is particularly reprehensible and suspect.

Several unsettling experiments involving veterans have recently come to my attention. Reports of full-body irradiation experiments involving veterans in connection with the University of Cincinnati are alarming. Several Boston-area veterans have detailed accounts that radium tubes were inserted in their noses to treat eardrum damage. Now, these veterans wonder if the DOD's treatment for popping ears and equilibrium problems that surfaced as they manned submarines during the 1960's threatens their lives. I ask Secretary Brown for his assistance in investigating these and other cases, and urge the VA to seek full DOD cooperation and disclosure of information relating to our veterans.

I look forward to the the testimony of Secretary Brown and our other distinguished witnesses. In particular, I would like to welcome Dr. Belton Burrows, Chief of Nuclear Medicine at the Boston VA Medical Center.

STATEMENT OF
THE HONORABLE JESSE BROWN
SECRETARY OF VETERANS AFFAIRS
BEFORE THE
HOUSE COMMITTEE ON VETERANS' AFFAIRS

February 8, 1994

Mr. Chairman and Members of the Committee, I am pleased to appear before you today to discuss the role of the Department of Veterans Affairs (VA) in connection with the Administration's commitment to a full and open examination of the nature, extent and effects of human radiation experiments involving intentional exposure to ionizing radiation.

Before reviewing with you the steps we are taking to determine if inappropriate radiation-related experiments have ever occurred at any facilities for which the Department of Veterans Affairs (VA) has responsibility, I think it may be worthwhile to to review for the Committee the major initiatives now underway by the Clinton Administration to provide full public disclosure and an independent review of the ethical and scientific propriety of government-conducted or sponsored human radiation experiments.

This Administration recognizes that public trust can only be achieved if American citizens believe that their government is open, candid, and accountable. President Clinton is publicly committed to open and responsive government.

In response to recent reports that government-sponsored experiments involving radioactive materials may have been conducted in an inappropriate manner many years ago, the President established a Human Radiation Interagency Working Group. VA has been an active, full-time partner in the Interagency Working Group since the inception of that group on January 3, 1994. Together with the Departments of Energy, Defense, Justice, and Health and Human Services, and the National Aeronautics and Space Administration, the Central Intelligence Agency, and the Office of Management and Budget, the VA shares a commitment to a full and public accounting of the government's role in human radiation experiments during the past fifty years.

The Interagency Working Group will conduct an extensive review of human radiation experiments. The focus of the investigation will be on individuals involving intentional exposure to ionizing radiation (excluding common and routine clinical practices) and experiments involving intentional environmental releases of radiation that were designed to test human health effects of, or the extent of human exposure to, ionizing radiation. Further inquiry into other radiation experiments may be undertaken if warranted.

Mr. Chairman, the task of the Interagency Working Group is to ovrsee an open and thorough investigation of government sponsored human radiation experiments. The group will coordinate a government-wide effort to uncover the nature and extent of such experiments, to seek answers to questions of whether medical follow-up of the experiments is warranted, and whether compensation or other assistance to those subjected to the experiments may be appropriate.

The Interagency Working Group has established five subcommittees to address specific issues: Public Information and Communications; Records Retrieval and Review; Ethical and Scientific Standards; Congressional Relations; and Legal Issues. VA representatives have participated in the work of these subcommittees to begin the arduous task of documenting, analyzing, and making public the details of experiments conducted since the mid-40's.

In the relatively brief period since the Interagency Working Group undertook its task, substantial progress has been made in developing mechanisms to gather maximum information from outside and within the Government on the nature and extent of governmental human radiation experiments, to preserve that information for deliberate and thorough investigation, and to make the information public to the fullest extent possible.

Through its Public Information and Communications Subcommittee, the Interagency Working Group has developed guidelines for collection of information from the general public concerning incidents and details of human radiation experiments. Information collected through these efforts will be pursued by the Interagency Working Group and compared with information in the files and records of Federal agencies to capture the greatest amount of information on the extent of human radiation experiments.

In consultation with the Records Retrieval and Review Subcommittee, each of the Federal agencies that have conducted or sponsored human radiation experiments has already taken steps to notify its components, as well as outside entities that conducted such experiments under contract or grant, to locate and preserve records of human radiation experiments and to coordinate the retrieval and inventory of such records for further review and investigation. The Interagency Working Group is working with individual departments and agencies to ensure that consistent procedures are employed and that the scope of these record searches will be comprehensive.

The review of human radiation experiments will not be limited to the Government's internal resources. The Interagency Working Group's Ethical and Scientific Standards Subcommittee, on which VA participates, offered advise and counsel to the working group on the establishment of a body of citizens from outside the Government to assist the working group through independent review of the ethical and scientific standards by which the experiments will be evaluated. To that end, on January 18, 1994, the President signed an Executive Order forming an Advisory Committee on Human Radiation Experiments, to be made up of private citizens, including experts in ethics, science, medicine, and law, that will afford independent advice and recommendations to the Interagency Working Group concerning human radiation experiments. The Advisory Committee will determine the ethical and scientific standards and criteria by which it will evaluate the experiments and the extent to which the experiments were consistent with applicable standards. If required to protect the health of individuals who were subjects of experiments or their descendants, the Advisory Committee may recommend that particular subjects, or their descendants, be notified of any potential health risks or the need for medical follow-up. The Advisory Committee may recommend further policies, as needed, to ensure compliance with recommended ethical and scientific standards for human radiation experiments.

In compliance with the Federal Advisory Committee Act, the meetings of the Advisory Committee on Human Radiation Experiments will be open to the public except as to discussions of individual subjects or their records. Such discussions will be closed to protect personal privacy interests. Six months from the filing date of the Advisory Committee's charter, the Advisory Committee will issue an interim report stating whether it anticipates fulfilling its duties within a one-year time frame.

These measures constitute a major initiative on the part of the Administration to develop a clear and credible record concerning the nature, extent, and effects of human

radiation experiments, and to answer questions as to whether the experiments comported with applicable ethical and scientific standards. We have given great attention to ensuring that the review entrusted to the Interagency Working Group is comprehensive, that the integrity of records of experiments will be preserved, and that all of the facts will be developed without predisposition as to where the facts should lead us.

Once the details of what happened have been made public and judgements can be made on the propriety of these experiments, we will join with our colleagues on the Interagency Working Group in making any necessary recommendations to the President and Congress.

Throughout all of this activity, the Administration will continue active consultations with the Congress. However, I want to emphasize that until the information is collected and analyzed, it would be premature to predict the form of response which will be most appropriate. The Administration has demonstrated its commitment to the subjects of human radiation experimentation, and I would urge the Congress to give us an opportunity to complete the review and analysis process so that any recommendations or legislative proposals can be structured on the basis of the fullest information possible.

Regarding the Department of Veterans Affairs' own efforts to determine if VA ever conducted or sponsored inappropriate radiation-related experiments on humans, I have pledged to veterans, their families and the American people that VA will initiate a full and comprehensive review of its activities and records. At my direction, a review to assess the conduct of human radiation experiments research at any VA facility is now underway. I have established an internal coordinating committee, chaired by the General Counsel, to oversee these efforts. If evidence indicates that any abuses associated with radiation experiments have occurred, VA is fully prepared to take whatever action is necessary to address the possible health care and other needs of veterans who may have suffered adversely from the effects of such experimentation.

I wish to assure you at the outset that every possible action is now being taken by VA to determine whether experimental abuses have occurred. We are determined to learn whether any radiation-related experiments of dubious merit or means were ever performed under our aegis, and to share our findings with the Congress and the American people.

Our search for the truth is an ambitious undertaking. During the early years of the Nuclear Age, VA was a pioneer in nuclear medicine and a great deal of research, with major benefits for patient care, was carried out in VA facilities using radioisotopes. A review of centrally held research and nuclear medicine records has revealed no information on specific research projects, protocols, or human subjects. Therefore, I found it necessary to require each VA medical center to conduct a search of its research and other files to determine if that information exists locally. Attached to my testimony are copies of the documents directing this undertaking. All VA facilities are now engaged in this effort, which includes any research that VA conducted in conjunction with our affiliated medical schools and any research that VA, as some documentation indicates, contracted out to other entities. We are compiling and analyzing these reports as received in order to ascertain the level of VA participation in any human-related radiation experiments. A summary of our survey, to date, is attached.

As part of our outreach to veterans, we have asked veterans service organizations to help us locate veterans who might have been subjects of these experiments. We have also invited veterans to contact us on our toll-free line (1-800-827-1000) if they have concerns about their possible participation.

Mr. Chairman, we share your concern for the protection of human subjects in any research, radiation-related or otherwise. Clinical research directed toward improvement in disease prevention, diagnosis and treatment often requires the participation of patients in carefully designed studies. It is VA policy, and this policy is rigorously enforced, that all participants in research studies be fully informed, consenting subjects and that they must be protected by all legal and ethical safeguards pertaining to human subject research. In addition to human rights reviews conducted at local VA medical centers, there are two additional reviews undertaken routinely as part of the national VA peer review process involving any proposed human research. These reviews are designed to resolve any potential problems and assure compliance of the proposed research with appropriate human rights standards before any research is undertaken. VA was a key player in the development of current federal policies in this area. We believe that our regulations and procedures meet appropriate ethical, scientific and medical standards, and still permit us to maintain an excellent program of research.

Mr. Chairman, as I previously noted, VA has led the way in the development of the modern nuclear medicine discipline. Historical documents show that in 1947 VA

established a program employing radioisotopes for the purpose of medical research, clinical diagnosis and medical treatment of patients. VA medical centers were required to comply fully with standards established by the Atomic Energy Commission for health protection of patients receiving isotopes as well as for individuals working with them, and we are aware of nothing to indicate that these standards were not strictly observed from the beginning. By December 31, 1953, there were 33 radioisotope units either established or in the process of activation in VA hospitals. By 1958, the number had risen to 48. VA pioneered the medical use of radioisotopes and for many years VA researchers led the field in such research in this country.

All projects were to be reviewed at the local level by a Radioisotope Committee that included individuals from outside the VA and also had access to one of three radiation experts of international stature appointed by the then Chief Medical Director to serve as consultants to a Central Advisory Committee and to individual hospital programs. Research projects were not reviewed at the Central Office level until the 1960s. A separate review by a human subjects committee probably did not occur at the time of the early studies as that did not become a practice until about 1962. However, currently we have no evidence to suggest that VA ever engaged in radioisotope studies that were not medically sound and designed to benefit patients.

VA also had an "Atomic Medicine Division." According to a 1952 Bulletin of the Committee on Veterans' Medical Problems, which was a component of the National Academy of Sciences, in 1947, VA's Chief Medical Director became deeply concerned about the problems that atomic energy might create for the Veterans Administration due to the fact that the Armed Services were so actively engaged in matters of atomic energy. The Director, out of concern for problems VA might have in connection with alleged service-connected disability claims, classified the existence of VA's Atomic Medicine Division as "confidential." Mr. Chairman, it is extremely upsetting to me that VA apparently did not reveal for an undetermined length of time the existence of this Atomic Medicine Division, and I have directed a thorough review of the records to attempt to piece together why this was done; what, if any, secret activities it engaged in; and the consequences of those activities.

We do know that one purpose of the Atomic Medicine Program was to teach techniques of nuclear preparedness to the nation. VA was named the lead agency in that endeavor. The employment of radiation scientists allowed VA to conduct this training mission in connection with the Civil Defense program and at the same time launch an

important pioneering program on the medical use of isotopes. Information on VA's role in civilian defense is outlined in a December 15, 1950, "Brief of Training Plan, U.S. Veterans Administration: Medical Aspects of Atomic Warfare, Medical Aspects of Radiological Defense, Radiological Defense (Monitors)."

At the local VA hospital level, radiation specialists held courses in their communities on atomic preparedness and taught fire and police personnel how to use radiation monitoring devices like the Geiger counter. The Atomic Medicine Program also produced a Training Guide for a Course in Radiobiological Defense that was used extensively in the Civil Defense program of the 1950s.

Mr. Chairman, as you can see, this is a very complex issue made more difficult to some degree by the passage of time. However, let me again assure you that I will leave no stone unturned in our review of any VA involvement in the radiation-related experiments in question. Should the final evidence indicate that there were radiation-related experiments detrimental to the health and welfare of veterans, we will take the necessary action to provide for their care as well as addressing any other concerns they may have.

Mr. Chairman, this concludes my remarks. I will be glad to answer any questions which you or Members of this committee may have.

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DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration

Initial Report on Identification of Radiation
Research Records (1947-1961)

Purpose: This paper is the first report of the efforts of the Department of Veterans Affairs (VA) to identify records related to radiation and nuclear medicine research funded by VA between 1947 and 1961.

Background: On January 7, 1994, the Acting Under Secretary for Health issued a request for all VHA facilities to search local research and nuclear medicine records for information about radioisotope, nuclear medicine or radiation research between 1947, the year the radioisotope/nuclear medicine program was begun in VA, and 1979, when institutional review procedures for the protection of human subjects was well established. This is part of a government-wide investigation into federally funded or sponsored radiation experimentation involving human subjects and represents the first phase of the effort, i.e., locating records of human radiation experiments.

The individual VA medical centers efforts to identify existing research documents were reported through the use of automated reporting forms (attachment A) for two time periods, 1947-1961 and 1961-1979. The results of the search for records dealing with the 1947-61 time frame were received and an initial analysis accomplished by February 4, 1994. (Attachment B)

168 responses were received, reflecting all facilities recognized in 1994. Additional information on the Cushing VA Hospital at Framingham was also received. Summaries of search efforts have also been submitted. These will be assembled in a notebook format and analyzed.

Findings: Of the 168 facilities, 42 do not have Nuclear Medicine Services at this time. 54 facilities had radioisotope units (as they were called in the early days) or Nuclear Medicine Services during the 1947-61 time frame. Of these facilities:

- 20 have located some protocols used during that period for radioisotope research,

- 7 have names of patients who participated in at least some research projects,

- 31 have some publications available on specific research projects done during that period.

Future Actions: The next step in the process will be retrieval and inventory of these records prior to in-house review. A rigorous "chain-of-custody" in accordance with the interagency committee direction must also be established. Copies of all records eventually will be made available to the Advisory Committee on Human Radiation Experiments for their review.

116
2/3/94

THE SECRETARY OF VETERANS AFFAIRS
WASHINGTON

January 6, 1994

TO ALL VA MEDICAL CENTER DIRECTORS:

In response to recent reports that government-sponsored research involving radioactive materials may have been conducted in an inappropriate manner many years ago, I have pledged to our veterans and the American people that the Department of Veterans Affairs will commence a full and comprehensive review of its nuclear medicine activities and records. The attached directive from the Acting Under Secretary for Health provides instructions for executing the preliminary phase of this inquiry.

Underscoring my commitment is the belief I hold, and which I trust you share, that we must be seen as acting in the total best interests of anyone who has ever been treated or examined at a VA facility. Our review must be thorough, it must be accurate and it must be energetic. If our efforts are seen as anything less than a determined search for the truth, we not only will have failed those who placed their trust in us, but squandered this important opportunity to demonstrate our compassion and concern.

I recognize this task impacts on the daily pressures of our health-care mission and that it comes as an unexpected administrative burden. Nevertheless, we must respond not only to the public's expectations, but because it is the right and moral thing to do. Let us all work together so that the results of this review reflect our total acceptance of those principles.

Jesse Brown

Putting Veterans First

Department of Veterans Affairs

Memorandum

Date: January 7, 1994

From: Acting Under Secretary for Health (10)

Subj: Request for Information on VA Radioisotope/Nuclear Medicine Research Records

To: Directors (00) - All VHA Facilities

1. On December 31, 1993, Secretary of Veterans Affairs Jesse Brown, announced that VA would immediately look into nuclear medicine research conducted at VA facilities during the 40's and 50's. This is a part of a government-wide investigation into federally funded or sponsored radiation experimentation involving human subjects during that era.

2. A review of centrally held research and nuclear medicine records has revealed no information on specific research projects, protocols, or human subjects. However, it is known that as early as 1947 VA was encouraging the use of radioisotope techniques in biomedical and medical investigation and that VAMC Bronx was active with Rosalyn Yalow, Ph.D., Nobel laureate, and Bernard Roswit, M.D., at that time. The following year, eight radioisotope laboratories were functioning. By 1951, fourteen laboratories were in place; and by 1958, this number had risen to 48. The 1957 Administrator's Annual Report notes that 399 radioisotope studies or research projects were carried out in 1955 and 560 in 1956. This accounted for approximately 10% of all the VA research projects supported during those years.

3. I am requesting that you search your local research and nuclear medicine records for information about radioisotope, nuclear medicine or radiation research that was going on in your facility between the years 1947 and 1979. The following should be reviewed:

a. Radioisotope Committee minutes

b. Radiation Safety Committee minutes

c. Nuclear Regulatory Commission (NRC)/Atomic Energy Commission (AEC) licensing files

d. Research files

4. The earliest information is needed most urgently. Please provide information on the following for the **period 1947 to 1960 by COB 1/21/94.** Please provide the same information for **1961 to 1980 by COB 2/7/94.** Negative replies are required for each category.

a. Year the Radioisotope Unit or Nuclear Medicine Service was established at your facility (earliest date)

b. Amounts and types of radionucleotides used between 1947 and 1960 (chemical and/or biological form, dose ranges and dose units if available)

c. Existence of Protocols or Research Reports from individual studies (List the available documents but dc not send copies at this time.)

d. Citations of staff publications related to nuclear medicine research done between 1947 and 1960

e. Contract research activities in this area (This probably would have been in the period 1947-55.)

f. Year the Institutional Review Board (IRB) and Human Subjects Subcommittee were established at your facility

g. Did your facility ever receive or use plutonium in research?

h. A general statement (or white paper, if appropriate) summarizing what is known about the involvement of your facility in this area of research. Please include a statement about the type of informed consent that was obtained for any studies.

5. We will need any information which may be available on individual veteran patients who were involved as subjects in this research. Please indicate whether such information is available at your facility and the number of veterans you can identify. If there are individually identifiable subjects, please begin to develop a log which includes:

a. Veterans name

b. Social Security and accession number if the record has been archived

c. Follow-up information, if available

Do not submit the logs until requested.

6. We realize that this required report will be time-consuming. The necessary information may not be readily available because the reports control system does not require the retention of minutes and nonpatient specific information for thirty plus years. However, this report is essential to understanding VA's role in earlier radiation related research.

7. Please provide the above information to 116/13_ by COB 1/21/94. Use of the attached summary form which can be faxed directly to a computer in VACO will facilitate in the display and analysis of the information you provide.

John T. Farrar

John T. Farrar, M.D.

Attachments

Survey of Nuclear Medicine/Radioisotope Research in VA Faciliti

Between 1961 and 1979

Please provide the requested information by COB February 4, 1994. Fill out this survey even if most of your answers are "no" or "0" as appropriate.

VAMC Name:

VAMC Number: Region: O1 O2 O3 O4

Person Completing Form:

TELEPHONE NUMBER: (Commercial not FTS)

Extension:

1. Does your facility have a Nuclear Medicine Service? O yes O no

   If yes, indicate year the Radioisotope Lab or Nuclear Medicine Service was established (earliest date).

2. Do you know the amounts and types of radioisotopes used between 1961 and 1979 at this facility? O yes O no

3. Do research protocols or research reports from individual studies conducted at this facility exist for the time period 1961 to 1979? O yes O no

4. Can you provide information on scientific publications related to nuclear medicine research done between 1961 and 1979? O yes O no

5. Do you have any names of individual veterans who were research subjects during the period between 1961 and 1979? O yes O no

6. Did your facility contract out any nuclear medicine research? O yes O no

7. Did your facility receive or use plutonium in research? O yes O no

Thank you for completing this form. Please FAX this form to 202-523-3529 AND send a hard c to Dr. Robert E. Allen; (116); 810 Vermont Avenue, NW; Washington, D.C. 20420. Questions cc be addressed to Dr. Susan Mather, 202-535-7182.

Survey of Nuclear Medicine/Radioisotope Research in VA Facilities

Between 1947 and 1960

Please provide the requested information by COB January 21, 1994. Fill out this survey even if most of your answers are "no" or "0" as appropriate.

VAMC Name:

VAMC Number: Region: ○1 ○2 ○3 ○4

Person Completing Form:

TELEPHONE NUMBER: (Commercial not FTS) Extension:

1. Does your facility have a Nuclear Medicine Service? ○ yes ○ no

   If yes, indicate year the Radioisotope Lab or Nuclear Medicine Service was established (earliest date).

2. Do you know the amounts and types of radioisotopes used between 1947 and 1960 at this facility? ○ yes ○ no

3. Do research protocols or research reports from individual studies conducted at this facility exist for the time period 1947 to 1960? ○ yes ○ no

4. Can you provide information on scientific publications related to nuclear medicine research done between 1947 and 1960? ○ yes ○ no

5. Do you have any names of individual veterans who were research subjects during the period between 1947 and 1960? ○ yes ○ no

6. Did your facility contract out any nuclear medicine research? ○ yes ○ no

7. Did your facility receive or use plutonium in research? ○ yes ○ no

Thank you for completing this form. Please FAX this form to 202-523-3529 AND send a hard copy to Dr. Robert E. Allen; (116); 810 Vermont Avenue, NW; Washington, D.C. 20420. Questions can be addressed to Dr. Susan Mather, 202-535-7182.

GENERAL COUNSEL'S OPINION, VETERANS ADMINISTRATION - OP. G. C. 28-58

Chief Medical Director 4-8

General Counsel June 25, 1958

Legal aspects of medical research

1. This has reference to your recent memoranda raising a number of legal questions with respect to two proposed research projects. One memorandum, on the subject of 'Research Project entitled 'Tubeless Measurement of Gastrointestinal Motility' (M31-256)", concerns The R Institute for Medical Research in connection with the VA Hospital, Manhattan, New York. The other memorandum, on the subject "Research Grant Funds", concerns The W Laboratories of Chicago and the VA Hospital, Chicago, with respect to a study of the "Physiology of Intrinsic Factor", as further defined in the memorandum.

2. The file contains the following data relating to the proposed project in New York City:

> "Preliminary discussions have been carried out with Dr. _____ of Corporation _____ and The R Institute, on the subject of the possibility of making a pressure-sensitive device which would record intraluminal pressures without an attached tube. This capsule-shaped device would be approximately 1 cm. in diameter and 1.5 cm. in length, coated with plastic. The device is swallowed by the patient and subsequently passes through the gastrointestinal tract. During its course through the stomach, small intestine and colon intraluminal pressures are detected by microphones in the wall of the capsule. This signal is transmitted to an external receiver and recorder by means of an amplifier and oscillator, powered by a tiny battery. Such subminiaturization is accomplished through the use of the transitor principle.
>
> "Dr. _____ has stated that the construction of such a device is entirely possible, and has further stated that The R Institute and _____ Corporation _____ will undertake to build and test a prototype.
>
> "It is proposed that, if laboratory and animal tests are satisfactory, this device be used to study motility of patients at this hospital."

3. The capsules have now been developed by The R Institute for Medical Research. In letter of October 30, 1957, its President writes to the VA as follows:

> "We propose to lend to you upon the terms stated in this letter five devices known as 'radio pills,' which are designed to transmit a radio signal while within the human body, for the purpose of measuring digestive system functions. The devices to be loaned are more fully identified in the attached schedule. The terms of this loan are as follows:
>
> "1. We will receive no consideration from you for the loan of the devices, and reserve the right at any time to request you to return them, and upon such request you will return them promptly and in good condition subject to ordinary wear and tear.
>
> "2. The devices will at all times be in your possession and it is understood that they will be used only for experimental purposes and under the supervision of qualified Veterans Administration personnel. These devices have not yet been fully tested human subjects, but we have concluded that the following procedures should be observed in the course of any experimentation involving a human subject who has taken the device internally, for the protection of the subject and the success of the experiment:
>
> "a. Care should be taken to be sure that the intestinal tract of the human subject is sufficiently unobstructed to permit clear passage of the device.

"b. Care should be taken to avoid damage to the device through dropping or jarring it or through the subject's inadvertently biting the device in the course of swallowing it.

"c. The device should be kept tightly sealed at all times.

"d. The subject should not be in close proximity to a radio transmitter while the device is within his body.

"e. The subject should not be given diathermy treatment while the device is within his body.

"3. While the procedures listed should be followed in using the devices, we cannot make any representation or warranty that injury to the human subject will necessarily be avoided in every instance if these procedures are followed or that there are not other factors which might under some circumstances cause injury. For this reason it must be clearly understood that The R Institute for Medical Research assumes no liability or responsibility of any kind to the Veterans Administration or to any human subject who may be used in the course of experimentation performed by the Veterans Administration, whether or not the procedures listed above are followed.

"If this arrangement is acceptable to you, would you kindly so indicate by signing and returning the enclosed carbon copy of this letter."

4. It is indicated that the research if approved would be conducted on patients at the VA Hospital who volunteer for the purpose. The correspondence does not state whether they will be paid. The legal conclusions herein are the same whether the volunteers are paid or not.

5. The other project, the study of the "Physiology of Intrinsic Factor," was the subject of a letter from The W Laboratories of Chicago to the Veterans Administration of January 14, 1958, as follows:

"This letter, in triplicate, is written to you following our conference of January 8th.

"The W Laboratories would like to make a grant in the amount of $5,000.00 for the calendar year 1958 to support a study on the 'Physiology of Intrinsic Factor.' This project is to be under the direction of yourself and Dr. _____, Chief of the Radioisotope Service, and is to be carried out at the Veterans Administration West Side Hospital.

"The basis for this study is the following -

"In a pilot study with cirrhotic and normal patients, your group has observed that the addition of Intrinsic Factor of porcine origin inhibits the absorption of Co58 labelled cyanocobalamin. This confirms reports in the literature, 'Vitamin B_{12} and Intrinsic Factor,' edited by H. C. Heinrich, published by Ferdinand Enke Verlag, Stuttergart, 1957, p. 250. The cause of this phenomenon is not clear, and needs to be explored. Possible reasons for this may be:

"1. The presence of a biological agent in the Intrinsic Factor Concentrate which inhibits absorption. This appears unlikely in view of the effectiveness, of the same preparations in treating pernicious anemia patients.

"2. The inhibition of endogenously secreted Intrinsic Factor in non-pernicious anemia patients, as a result of the exogenous porcine Intrinsic Factor.

"3. Anatogism of non-pernicious anemia patients to heterologous Intrinsic Factor Concentrate

"The proposed study will test these hypotheses in a series of normal volunteers and patients with various diseases.

"The effect of porcine Intrinsic Factor Concentrate will be quantitatively compared with that of human gastric juice using pernicious anemia patients and the Co58 labelled cyanocobalamin technique. The W Laboratories will supply a number of chemically fractionated Intrinsic Factor Concentrate preparations to be tested for their Intrinsic Factor potency and also for their inhibitory effects. This will be designed to investigate the first hypothesis described above.

"It is contemplated that this study will involve approximately 20 or more normal volunteers and 20 or more pernicious anemia patients.

"If you are agreeable to carrying out this work, and it acceptable to the Veterans Administration West Side Hospital, we will issue a check to the Veterans Administration West Side Hospital for $1250.00, representing the first quarterly payment. The balance will be paid quarterly during 1958.

"In addition, we will include a check for $500.00 to be used as a fund for paying volunteers necessitated by this study. It is understood that where payment is necessary, the volunteer will receive either $10.00 or $20.00, depending upon the type of experiment. Disposal as of December 1958 of any unexpended or unallocated portion of the fund of $500.00 will rest with The W Laboratories.

"You will inform us from time to time and at the conclusion of the study as to results obtained.

"We are enclosing herewith three signed copies of this agreement. If it is acceptable to you and the Hospital, will you kindly sign one and return it to us? You may retain the other two for your own files and that of the Hospital."

le correspondence shows that volunteers would take weekly doses of Co58 Cyanocoamin, 0.5 microcuries per dose, for three consecutive weeks. They will be paid om funds provided by The W Laboratories. Twenty or more volunteers will be ected from pernicious anemia patients in the VA hospital. The other twenty volunteers ll be university students who, in connection with their studies, would devote part of eir time to various duties at the hospital.

. The basic question presented is whether the VA may enter into the research proed in each case, and if so, under what conditions. It is further asked whether the VA ll be responsible for any adverse effects upon the volunteers.

. The VA has authority to undertake research and enter into contracts for research rposes, wherein the objective is the health and welfare of veteran-patients or domiciliies. The current appropriation act, Public Law 85-69 provides that $10,344,000 all be available for medical research. Section 1716, Public Law 85-56, 38 USC 16, continues the authority formerly contained in section 1500 of Public Law 346, 78th ngress, as amended, 38 USC 697, granting the Administrator the power to enter into ntracts for research purposes.--86 Sol 349; 90 Sol 624, 627. Section 215, Public Law 5-56, 38 USC 2215, expressly provides for research in certain limited fields.

310

continuing the provisions formerly contained in Public Law 729, 80th Congress, 38 USC 253, 254. It has been held further that funds contributed to the General Fund may be utilized for research in accordance with the terms of the contributions, if the research is for the benefit of VA patients or domiciliaries. --Opinion of March 22, 1951, to the Assistant Administrator for Legislation (not published).

8. There appears to be no doubt that the VA can undertake research for the medical purposes here proposed if it is administratively determined that the research is for the benefit of its veteran-patients or domiciliaries.

9. While there is authority to accept a grant from The W Laboratories or any other source for a particular research program, such grant to be deposited in the Post Fund and earmarked for such research, there is no legal authority to enter into a contract to conduct research or study for any outside organization including The W Laboratories.

10. A number of legal questions will arise primarily with respect to the volunteers. Louis J. Regan in his work "Doctor and Patient and the Law", Third Edition, page 371, sets forth the following criteria with respect to research involving human beings:

> "It is clear that certain types of medical experiments on human beings, when kept within well-defined bounds, conform to the ethics of the medical profession. All agree, however, that certain basic principles must be observed to satisfy ethical, legal and moral concepts.
>
> "Thus there must be consent, [of the volunteer] given with understanding of all the hazards. There must be reasonable hope that the experiment will yield fruitful results, and in this regard supporting animal research must indicate reasonable safety, potentiality of minimal physical or mental suffering, etc., so that the risks do not exceed anticipated gain.
>
> "Further, it must always be permitted that the subject may terminate the procedure at any time; and that the scientist in charge may do so if it appears that continuation is likely to result in injury, disability or death. And no experiment should be conducted where there is on a priori reason to believe that death or disabling injury will result; except, perhaps, where the experimental physicians also serve as the subjects."

The persons who participate must voluntarily consent to the experiment on themselves. Such consent must rest upon an understanding of the hazards involved. The volunteer may withdraw from the experiment at any time. Moreover, before the experiment, steps to reduce the hazard, as for example indicated research on animals, must be made.

11. Compliance with the foregoing general criteria respecting the volunteers does not eliminate the possibility of injury or alleged injury to a volunteer, attributable to the experiment. Such possibility exists both with respect to the "radio pills" and the doses of cyanocobalamin.

12. In the event of any such injury to a volunteer, there will be no liability if the criteria set forth above are followed, except perhaps for negligence in administering the experiment. The applicable rule of law is set forth by William L. Prosser in his "Law of Torts", 2nd Ed., section 18, as follows:

> "The consent of the person damaged will ordinarily avoid liability for intentional interference with person or property. It is not, strictly speaking, a privilege, or even a defense, but goes to negative the existence of any tort in the first instance. It is a fundamental principle of the common law that volenti non fit injuria -- to one who consents, no wrong is done. . . ."

And in section 55, it is said:

> "The defense of assumption of risk rests upon the plaintiff's consent to relieve the defendant of an obligation of conduct toward him, and to take his chances of harm from a particular risk. Such consent may be found:

a. By express agreement. Such agreements are upheld, in general, except where one party is at an obvious disadvantage in bargaining power.

b. By implication from the conduct of the parties. When the plaintiff enters voluntarily into a relation or situation involving obvious danger, he may be taken to assume the risk, and to relieve the defendant of responsibility. Such implied assumption of risk requires knowledge and appreciation of the risk, and a voluntary choice to encounter it."

similar conclusion is set forth in the "Restatement of the Law" of the American Law stitute on the subject "Torts", sections 49, 892, and 893; 86 Corpus Juris Secundum on Torts", section 12; and 52 American Jurisprudence on "Torts", section 94.

3. In line with the foregoing, if the research is to be undertaken, it would be necessary at the VA obtain from each volunteer a written consent, whether the volunteer will be aid or not. The volunteers must be competent to give consent. A form should be prepared for signature by each one, setting forth the objects of the research and the risk volved, and containing further a statement substantially as follows:

"I understand that this research is for experimental purposes, and results cannot be fully foreseen. Preliminary tests have been made, and indicated precautions to protect volunteeers have been taken. The VA does not represent that any injury will necessarily be avoided in every instance even when these precautions are followed. Nevertheless, I voluntarily assume the risk involved, in order to advance medical knowledge. I will carefully follow instructions given by the VA for the conduct of the experiment. I will not make any claim or demand upon the VA or its personnel for injury, if any arises from the experiment. This does not relieve the VA of negligence in the performance of the experiment.

"I understand that I am to observe the following instructions (or the instructions attached hereto), subject to such further instructions as the VA may give: . . . ."

4. It would be appropriate that there then follow a paragraph relating to release of information, which could read as follows:

"I agree that data obtained by the VA from this experiment may be used for medical or other scientific purposes, including publication, but my identity will not be revealed unless I expressly consent thereto."

5. The agreement drafted by The R Institute contains the following language in paragraph 3 thereof:

". . . The R Institute for Medical Research assumes no liability or responsibility of any kind to the Veterans Administration or to any human subject who may be used in the course of experimentation. . . ."

he foregoing is on the premise that the VA and not The R Institute is conducting the search. This premise is correct. However, it does not relieve The R Institute of gligence in the preparation of the "radio pills".

6. In summary, the VA may conduct the research projects proposed in conjunction with he R Institute for Medical Research and with The W Laboratories, respectively, subject o the foregoing.

GUY H. BIRDSALL

Distribution:

A.'s, R.O. & Centers
with R.O. activities 2
Veterans Benefits Office 311
Director, Compensation & Pension Service 30
Director, Compensation & Pension Supervision 27
Adjudication Officers 5
Managers - all Field Stations,
Attn: Medical 2
Manager all Field Stations 2

5 -

VA-DC-177888

TESTIMONY BY DR. ROSALYN S. YALOW

Nuclear medicine, the use of radioisotopes for medical purposes, now has an important role in medical diagnosis and therapy. My own background in the field goes back to 1948 when I first joined the Bronx Veterans Administration Hospital.

Nuclear Medicine has three roles: treatment with radioisotopes, diagnostic studies using radioisotopic techniques in vivo or in vitro, and medical research employing radioisotopes. Probably the most common role of Nuclear Medicine in the therapy of a nonmalignant disease is in the treatment of hyperthyroidism. Before he completed his role as our Chief Executive Officer both the President and Mrs. Bush were reported to have overactive thyroids. The public was informed that both were treated with radioiodine (^{131}I). No information was given about their dose but typical doses for this nonmalignant disease is usually 5,000 - 10,000 microcuries of radioiodine. Their whole body dose was probably about 5,000 - 10,000 mrem. The dose to their thyroid was about 1,000 times greater. Thus, after a half century of experience the considered medical opinion is that radioiodine is the optimal treatment for the disease in the President and his wife and that those doses to the thyroid and to the whole body during the treatment are safe. Patients with thyroid cancer have been successfully treated with radioiodine using doses a hundred times as large as for hyperthyroidism without obvious deleterious effects.

In the 1950s the diagnosis of an overactive or underactive thyroid was based on the 24 hour uptake of radioiodine by the thyroid. It has been estimated that in the United States at least a half million people were tested in this way in the 1950s and 1960s before the modern techniques of radioimmunoassay of thyroid related hormones were introduced. Since the doses for the diagnosis of thyroid disease were only a few percent of the doses used for treatment of an overactive thyroid no harmful effects could be expected.

For the past 30 years radioimmunoassay has been the method of choice for measuring in blood and tissue taken from the subjects a wide variety of hormones, including the thyroid related hormones. With radioimmunoassay there are no concerns about the administration of radioisotopes to people. Furthermore, those workers who use radioimmunoassay techniques need not experience even measurable amounts of radiation exposure.

I have not worked extensively with in vivo studies employing radioisotopes over the past quarter century. However from what I note from the literature the doses employed remain small compared to those used for the treatment of an overactive thyroid. For the most part the halflives of the radioisotopes employed in nuclear medicine are short enough that the disposal of the radioisotope should not be a significant problem. The disposal of C14 and H3 used in biomedical investigation does require further description but is not particularly relevant to the hearing today.

It is evident that the use of radioisotopes in nuclear medicine has had major advantages to our medical care. It should be noted that our paper in 1956 (J. Clin. Invest. 35:170-190) led to an appreciation that all diabetic subjects treated with insulin developed antibodies to insulin and led to the development of radioimmunoassay, for which I received the Nobel Prize, which permits the measurement of hormones and other substances in the blood and other body fluids and has had major impact on the medical care of all subjects. I will end by reminding you that the large dose of radioiodine received by the President for the treatment of his overactive thyroid is not considered a problem.

I therefore wonder why the radiation exposure in experiments a half century ago, which resulted in radiation exposure less than the President received now for a benign disease, is a matter of current concern.

STATEMENT OF
DR. BELTON A. BURROWS
BEFORE THE
HOUSE COMMITTEE ON VETERANS' AFFAIRS

I am pleased to appear before you today to dicuss VA research involving the use of radionuclides and other forms of ionizing radiation.

Consistent with my previous training in internal medicine and my research experience in metabolic diseases requiring laborious balance studies before the more accurate radioactive tracer methods became available, I was attracted to the opportunities offered by the establishment of a Radioisotope Unit at the Framingham (Cushing) VA Hospital in July 1950.

Initially, radioiodine was employed for the diagnosis and treatment of hyperthyroidism and cancer. Subsequently, radiosodium, radiopotassium and radio sulfur were used to study body composition changes in a variety of chronic diseases, such as hepatic cirrhosis, hypertension, cardiovascular disease, diabetes and renal insufficiency prevalent in the veteran patient population. With the recruitment of additional staff and the support of a United States Public Health Service training program in radionuclide techniques, the scope of our activities expanded to other medical subspecialties: endocrinology, hematology, gastroenterology, nephrology and oncology, in which scanning devices were becoming useful.

In the early fifties, there was also a training program in the use of radiation survey monitors to detect areas that might be contaminated with radioactive materials as a result of industrial accidents or military action. In addition, the professional staff was trained in the clinical management of such exposures. From its inception the Radioisotope Unit (later Radioisotope Service and finally Nuclear Medicine Service) was integrated with the similar service at the Massachusetts Memorial Hospital, later the University Hospital) and its staff held faculty appointments at the Boston University Schoolf of Medicine. The Chief was Acting Director of Nuclear Medicine at VACO for its first five years and helped establish training programs in other VA hospitals which materially assisted

in the development of a separate and distinct specialty later to be certified by the American Board of Nuclear Medicine under the superb leadership of Dr. Joseph Ross. There was a close working relationship between the VACO office and the Atomic Energy Commission (AEC) in the processing of applications for the authorized use of by-product material in the field.

Many of the published studies resulted from the retroactive compilation and analysis of diagnostic results and their correlation with other clinical and laboratory data, whereas others required the approval of the radioisotope committee to ensure that they complied with AEC, later NRC (Nuclear Regulatory Commission) regulations.

The formal process of "informed consent", with signed forms approved by local human studies committees, was not developed for several years after radioisotope research had become an active pursuit in the majority of the Radioisotope Units. The studies were conducted in an open clinical setting with the full understanding of the nature of the materials, the purpose of the studies, and the potential applicability of the results to the individual patient's problems.

REMARKS CONCERNING SERVICE OF ERVIN KAPLAN, M.D.,
IN THE FEDERAL GOVERNMENT

I feel it a privilege to have served the Federal Government for a period of 43 years. The first five years as an enlisted man in the United States Marine Corps throughout the duration of World War II. My overseas service in the Pacific theater was with the Second Marine Raider Battalion, under the command of Col. Evans F. Carlson. I participated in the Battle of Midway, the Guadalcanal Campaign where I was part of a 150 mile combat patrol of 30 days duration behind the Japanese lines and in the assault landing at Empress Augusta Bay, Bougainville, Solomon Islands and subsequent engagements of that battle.

Having interrupted my education to so serve, I returned after World War II to complete my medical education. I completed my residency training at Hines and was subsequently certified in Internal Medicine and Nuclear Medicine. I served at Hines for a total of 38 years from July 1950 until retirement in 1988. I served for many years as Chief of Nuclear Medicine Service. I was a Professor of Medicine and Physiology at an affiliated medical school, University of Illinois, Chicago. I was very active in patient care, training of physician, medical students, technologists and computer specialists in nuclear medicine. I also had a very active research career. My rapport with veteran patients was immeasurably enhanced by my background. They trusted me as in the past I had often entrusted them with my life. To quote Hippocrates, ". . . to do no harm," was a creed I found easy not to violate.

A Statement to the Veterans Affairs Committee of the
United States House of Representatives
ERVIN KAPLAN, M.D.

I preface my statement to the House of Representatives Veterans Affairs Committee, by stating that we owe an incalculable debt to the veterans of our country; in fact, we owe them the very existence of the United States. To treat the veteran population other than with dignity and respect is contrary to the principles upon which this country exists. To violate their trust in us, at a time when they are ill and hospitalized, by using them as experimental subjects without their knowledge or concurrence in random indulgence of our curiosity is an anathema. On the other hand to apply new and promising methodologies to better understand the nature and treatment of their complaints and clinical findings, when these methods are non-invasive and of acceptable, minimum or no risk, and when approved by the veteran, and a highly qualified hierarchy of medical supervision and peer review is highly justified and is often highly beneficial to the patient.

VA Hospital, Hines, Illinois, had a professional policy originating with a Deans Committee consisting of the Deans of the University of Illinois, College of Medicine, Northwestern University, School of Medicine, Loyola University School of Medicine and Chicago Medical School. We interacted and collaborated with the University of Chicago by affiliation with the Argonne National Laboratories which was jointly sponsored by the University and the Atomic Energy Commission. The bed services were specialty oriented, consisting of Medical Service, Surgical Service, Neurology Service, Psychiatry Service. Non-bed services were Diagnostic Radiology Service, Therapeutic Radiology Service, Laboratory Service, Nuclear Medicine Service and Research Service. Each service was headed by a chief of service of professional stature and were faculty members of the affiliated medical schools. Medicine and Surgery were divided into subspecialty sections. Section Chiefs were well trained in their subspecialty and mostly had faculty appointments. The subspecialties were staffed with full time and resident physicians. Subspecialty sections were supplied with consulting and attending physicians mostly from the affiliated schools' faculty. They made patient rounds with the full time and resident physicians. Referrals were made to other services and sections as indicated. Participation in research was encouraged. Grand rounds and special lectures were very well attended, morale and esprit were high. Patient consents for procedures were obtained and signed for invasive procedures and were not written for non-invasive procedures. In the case of research procedures, the patient was informed and participation was voluntary and only made in writing if the risk so indicated. Competent nurses and aids were present in all bed services. Resident physicians were graded on competence and served a formidable hierarchy of supervisors and were directly responsible for assigned patients.

The internal organization of Radioisotope Service:

The service was responsible for performing clinical diagnostic and therapeutic procedures for patients using radioisotope methodology. It also had a research and development mission mandated by the VA to define and solve problems applicable to the continuing and growing needs of the field. These investigations were accomplished by a variety of chemical and physical means, among which radioisotope methodology has been prominent. It had been necessary, when seeking answers to specific problems, to deal with the theoretical and fundamental aspects involved; to apply a variety of physical principals and methodology; to develop and modify equipment. The purpose of these varied approaches had been, the definition of specific human anatomy and physiology, delineation and diagnosis of disease states, and in some instances development of specific therapy. To accomplish these ends the broadest and most diverse interdisciplinary team approach had been used. The contributions of biochemists, physicists, physicians in various subspecialties, engineers and physical chemists and others, had stimulated the solution of many difficult problems. My function was to encourage and integrate that work and to correlate it with the clinical and scientific work in the hospital and affiliated institutions.

To best serve the hospital patients, it was necessary to interact with the various bed services. It became necessary to know the professional staff, to make rounds with various physicians, to attend meetings at the hospital and medical schools, to formally and informally discuss problems and to stimulate participation of the staff in collaborative research. The professional staff of the Radioisotope Service had to keep current in all aspects of the specialty, by reading the literature, attending and participating in local, national and international meetings and having great familiarity with others in the field and the details of their work.

The development of a research project required a broad knowledge of the frontiers of the investigators specialty and a perspective of those problems which needed investigation and those solvable by the available state of knowledge and technology. Once a research area had been identified by any members of the collaborating group relevant background information had to be obtained, the significance of the study determined and the problem or hypothesis to be proven required precise identification. The methodology and experimental design to deal with the problem required constant interaction with the multidisciplinary staff. In those instances involving human subjects, those patients fulfilling the study requirements were identified and were entered into the study on a voluntary basis after informing them in all detail of the purpose, the nature of the participation, how they would personally benefit from the information derived and the types and severity of the risk, if any, that might be encountered. In no instance was a patient required to participate. In instances of no risk, such as obtaining urine, blood specimens or if radioactivity were not administered in procedures which were performed in vitro, the patient interaction was minimal. If interaction was invasive and had definable risk the patient was informed in great detail and may have signed an informed consent

form. Often, standard and required procedures which were widely accepted as routine were performed on patients and the goal was to evaluate newer instrumentation or methodology patient consent was irrelevant.

A prospective protocol was prepared, discussed, and reviewed and often rewritten several times. When acceptable to the collaborators it was submitted to the institutional Radiation Safety Committee and the institutional Research Committee. If revisions were requested, they were made. If collaborating with an affiliated institution, the protocol was examined at that institution. The VA Director of Nuclear Medicine in VA Central Office maintained a research office which passed upon projects for the purpose of approval. The new users of radioisotopes were reviewed for approval by VACO and the Atomic Energy Commission (AEC) on approval, issued a specific license. A general license was issued by the AEC for routine clinical use of radioisotopes. The general license permitted accepted uses of radioisotope of elements of atomic number 3 through 83 which excluded all nuclear weapon type radioisotopes and all alpha particle emitters.

Some projects were submitted to the National Institute of Health for approval and funding. This then was another and higher level of peer review and required a protocol of exceptional quality. To my knowledge, we were in compliance with the then existing protocols and regulations covering human research.

The determination of risk to the patient when a dose of radioisotope is administered:

The Radioisotope Service at VA Hospital, Hines, Illinois, employed a full time health physicist who was to safely receive, store, quantify and dispense radioisotopes. He was aware of the physical and chemical properties of the isotope. This included the physical form, the nature of the radiation, its penetrability, the amount of radiation exposure to the tissue and its distribution when administered. He possessed adequate instrumentation to monitor the patient and his environment, including a whole body monitoring room. He was also aware of the physical and biologic half life and the routes of excretion. With the above information, he could accurately reference documents and knew his legal responsibilities. Detailed records were kept by the health physicist.

Patients were often subject to follow-up if the experimental design so indicated. During the 36 years of my tenure with the Radioisotope Service and as subsequently changed to the Nuclear Medicine Service, there is no evidence that a patient was injured as a consequence of participating in a radioisotope research project.

TESTIMONY BEFORE HOUSE VETERANS AFFAIRS COMMITTEE
8 FEBRUARY 1994
Tuesday 9:00 AM
Room 334 Cannon House Office Bldg.

Mr. Chairman and Members of the Committee, my name is James A. Pittman, Jr., M.D. I was called to testify because in 1958, having very briefly run the NIH's diagnostic radioisotope laboratory in 1955 at the Clinical Center, I was appointed Director of the Radioisotope Unit* in the Birmingham VA Hospital. In 1956 I had also taken a course in the use of radioactive isotopes in biology and medicine at the Oak Ridge Institute for Nuclear Studies in Tennessee, where material for the first atomic bomb was produced and which at that time remained a center for nuclear physics, as well as a source for medically useful radioactive isotopes. I remained Director of Nuclear Medicine at the Birmingham VA Hospital for thirteen years (1958-1971). Most of this time, till the late 1960s, these activities in the VA were financed as a research activity by funds from VA Central Office, even though the work consisted increasingly of routine clinical diagnosis and treatment, especially after the development of scanning procedures. I believe that at one time we had in the Birmingham VA Hospital the largest training program in the nation, or world, for nuclear medicine technologists. Then from 1971 to 1973 I worked in VA Central Office as Assistant Chief Medical Director for Research and Education. As such I had oversight of the Research Service, which was almost entirely "medical research," and of the Education Service, which was chiefly financing physician residencies and allied health training throughout the nation. I have not been directly involved to any great extent in work with radioisotopes since 1971 or with VA research since 1973, when I was appointed Dean of the University of Alabama School of Medicine, UAB. I am also a practicing physician certified by the American Board of Nuclear Medicine, the Board of Endocrinology, and the Board of Internal Medicine.

As I prepared this material for the Committee, particularly the little chronology at the end of this written testimony[1], I began to relive something of the excitement of those days in the early 1950s and '60s, when we felt we were making great discoveries for humanity and helping advance medical understanding, diagnosis, and treatment. That chronology demonstrates how very recent our knowledge of these matters is and how strenuously the scientists and physicians struggled to gain that knowledge.

The modern VA medical care system was created just after World War II, when on January third 1946 President Harry Truman signed Public Law 293[2]. When P.L. 293 was signed it created the legal obligation for the VA to provide "medical care second to none" for this nation's veterans. The United States was not only the most powerful, but also the richest, nation in the world. As late as 1950 and after, our country had the highest per capita GNP in the world and consumed 50 percent of the energy produced in the world. In 1950 the U.S. also had 54.5 percent of the steel production and 81.6 percent of the passenger vehicle production in the world.[3]

The United Nations promoted a program of "Atoms for Peace," largely through applications to energy production, medicine, and biology,[4] and the new VA medical care system took the lead in developing radioisotopes in medicine. The VA channeled substantial amounts of administrative, financial, and scientific support to its new radioisotope program and played a crucial role in the development of new diagnostic and therapeutic uses of radioactive isotopes, including immunoassays[5] and the first radioisotope scanners,[6] then the technology leading to CT scanners.[7] The VA was thus a major factor in the establishment of nuclear medicine as a recognized medical specialty and much of the technology on which modern medicine throughout the world depends today.

Most, probably all or nearly all, of the medical work with radioactive isotopes in the VA in those days was done in hospitals with close connections with medical schools and universities, "Dean's Committee hospitals" established in accord with P.L. 293. This meant that the VA's physicians held faculty appointments in the affiliated medical schools. Therefore, the objective of the research (and I believe this would be all the VA research) was aimed at ultimate publication. From the standpoint of those investigators, if it proved unpublishable it was a waste of time, money, and effort. The basic motivation and rationale for the work was the improvement of medicine and the care of individual patients.

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*The unit may have been officially a "Radioisotope Service" by that time in Central Office documents. The units gained administrative status both locally and in Central Office as they grew more useful clinically with the development of new diagnostic and therapeutic procedures. In each hospital the operation went through a series of designations, usually "Radioisotope Laboratory," then "Radioisotope Unit," later "Radioisotope Service," and finally "Nuclear Medicine Service," theoretically equal to a urology service or neurology service, or perhaps even a surgical or medical service, though usually all the smaller services reported to either the medical or surgical service. Most of the radioisotope units were initially headed by internists, though a few had chiefs who were surgeons or even pediatricians. Increasingly they came under the aegis of the radiologists.

I shall append to this written testimony some references to my own work with radioisotopes in which veterans were given radioactive substances, particularly I-131.[8] In all cases the protocol for the research project was reviewed by the local Radioisotope Committee and approval was given before the study was permitted. These prospective reviews included careful attention to the radiation dosimetry and the amounts of radiation the patients would receive - generally only a few microcuries of the isotope concerned.[b] Further, the investigators involved had to document for the Radioisotope Committee that they had completed certified training and experience in the use of radioisotopes. In the early days these certifications were carried out by the AEC, the U.S. Atomic Energy Commission. Later such radiation safety activities were delegated by the federal government to the individual states, but the state requirements had to satisfy the federal requirements in order to be acceptable to the latter.

The VA remained under the aegis of the AEC until the advent of the NRC (Nuclear Regulatory Commission). The AEC formerly, and now the NRC, conduct periodic inspections of each VA facility using radioisotopes to monitor the adequacy of safety procedures and appropriateness of isotope use.

I shall append copies of the recommendations and requirements of the Veterans Administration as stated in the VA's **Manual**, M-3, Part III, "Chapter 3. Radioisotope Program," dated June 7, 1957. I shall also append the AEC regulations and recommendations of the mid-1950s generally applicable to medical uses outside the government.[9] I have also obtained from Dr. William H. Blahd, a pioneer in the field of nuclear medicine at the West Los Angeles VA Medical Center, a most interesting memoir written in 1985 by Mr. A. Graham Moseley, M.S., who was VACO's Director of Radioisotope Laboratories in the 1950s and '60s. Mr. Moseley, now deceased, provides a most interesting and detailed account of those early days of medical uses of radioisotopes in the VA. So I have appended that also to this testimony.

Use in our VA was also guided by Handbook 52 from the National Bureau of Standards[10] and other handbooks distributed commercially[11].

In general I think the system worked well. The VA did lead in "atomic medicine," and important discoveries were made in the VA. The prime example is the development of radioimmunoassay from 1956-on as a method of measuring solutes in solutions, particularly biological solutions such as blood. This led to recognition by a Nobel Prize awarded to Dr. Rosalyn Yalow in 1977. That initial work was done **entirely within the confines of the Bronx VA Hospital**. It has led to a major revolution in laboratory diagnosis in medicine, such that many, many measurements of constituents of body fluids are now available for clinical purposes. Without this technique such knowledge about the physiology and pathology of sick people would simply not be available to doctors trying to help their patients. These tests have not only speeded diagnosis and made it more accurate; they have also made it cheaper.

Studies involving administration of radioactive isotopes to veteran patients might be exemplified by my work, with George Dailey and Richard Beschi, which showed that the thyroidal radioactive iodine uptake, a standard and frequently used test of thyroid function, was changing between 1958 and 1968 because of a change in the way bread was manufactured in the United States. That test itself -- the thyroidal radioiodine uptake -- gives information on thyroid function that can be determined no other way. As the scene continues to change, more modern techniques, such as chemiluminescence assays, have made it possible to dispense with the use of radioisotopes in many immunoassays, and thyroid function tests (using immunoassays in most cases) have reduced reliance on thyroidal radioiodine uptakes. In the larger world outside the VA radioisotopes have also led to dramatic advances. John B. Stanbury, the world's leading authority on genetic abnormalities of the thyroid, says simply, "Radioiodine has permitted the study of the dynamics of iodine metabolism in ways that would be quite impossible otherwise."[12]

There have been statements in the media suggesting that physicians of the times (1950s) were casual and callous in their administration of radioactive isotopes to patients, but I think this was absolutely not the case in the VA. Just last week we located in the Birmingham VAMC a notebook containing minutes of the meetings of the Hospital Radioisotope Committee from the beginning May 6, 1953. For nearly two decades the chief topics of discussions in those meetings were the cases of individual VA patients, presented for consideration of administration of radioisotopes, particularly therapeutic doses. The committee was composed chiefly of physicians and surgeons from the affiliated medical school and community, as well as the VA's RSO (Radiation Safety Officer) and sometimes others. Those discussions were far from perfunctory and considered first and foremost the welfare of the individual patient.

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[b] The recent change in units of radioactivity from Curies to Becquerels may have made sense to the physicists, who wanted a more neat system with round numbers and decimal symmetry, but it was unfortunate for public relations in clinical medicine. Since the latter units are much smaller than the Curie/millicurie/microcurie system, an ordinary therapeutic dose of 5 mCie (or $5 \times 3.7 \times 10^7$ dps) of ^{32}P is now reported as 185 MBq (or "185 megabecquerels" = 185 million Becquerels), which makes it sound as if the doctors are dropping a hydrogen bomb on the patient.

There are two questions which occur to me as probably your primary concerns: (1) whether the VA patients always understood they were the subjects of research studies; and (2) whether VA research ever harmed anybody. These questions probably cannot be answered definitively; but I can offer some opinions.

With regard to the first, which we would now call "informed consent," most of the doctors I have known subscribe in practice as well as precept to the Hippocratic Oath and the principle "First do no harm." It was certainly the practice in all the VA facilities and personnel that I know of to follow those guides in all cases. However, in the earliest days there were usually no written consents for such research and no formal bodies we now call "IRBs," or "Institutional Review Boards," created for the sole purpose of evaluating the ethics of the experiments proposed and to review any proposed written consent forms. In my study of iodine intake and thyroidal radioiodine uptakes mentioned above, we went to hospitalized veterans, usually not our patients, after talking with their doctors to see if it would disturb them or their treatment in any way, and explained to them that we were trying to learn why these clinical tests had changed, and that we would appreciate their help by serving as subjects to whom we would administer a tracer dose of radioactive iodine, then make some measurements. Most patients agreed, usually readily; but a few refused, and if they refused, that was that; we had to find somebody else. There were undoubtedly sometimes problems, but I think they were rare, and I can remember none in the VA.

At first we used no written consent forms signed by the subjects, and I do not know exactly when we started using them, perhaps around 1961.* Informed consent is not a simple thing.[13] First of all, no physician, no matter how conscientious and diligent, having spent much of his life doing little except studying human beings in body, mind, and soul, can ever expect to impart in a few minutes that same understanding to a patient, particularly one of limited education and capacity; that is, there are often very narrow limits to how "informed" a consent can be. I have had the experience of trying diligently to get across to a patient that we want to do a research study to learn more about his or her disease, that this study is not expected to help them but that it may help others with the disease, that it is experimental, and that to participate he or she must sign this form indicating they understand this. I have sometimes gone through this whole discourse and discussion only to have the patient say a few days later, perhaps as we are about to inject the isotope when I explain again that we are starting the study, "O.K., Doc, anything as long as it might help me."[14]

There is one other point important for lawmakers: A legal requirement for informed consent does not guarantee anything if those charged with implementation are scoundrels. There is a fascinating discussion of this in the book by Faden, Beauchamp, and King,[15] which I shall quote here:

> "The extreme disregard of ethics in the Nazi's exploitation and abuse of subjects is all the more remarkable in the light of the fact that in 1931 Germany had enacted, on moral grounds, strict 'Richtlinien' (regulations or guidelines) to control both human experimentation and the use of innovative therapies in medicine. Issued by the Reich's Health Department, these regulations remained binding law throughout the period of the Third Reich. Consent requirements formed two of fourteen major provisions in the guidelines, one dealing with 'New Therapy' and the other with 'Human Experimentation.' It was demanded in both cases that consent (first party or proxy consent, as appropriate) must always be given 'in a clear and undebatable manner.'"

There is no substitute for a good doctor.

As to the second question, whether patients or normal subjects, or perhaps the physicians and technical people chronically exposed in the workplace, have ever been harmed by such work, this is also problematic. I've already noted some of the safeguards that were put in place in the VA very early to protect such individuals, and of course accidents must have occurred at times. However, our attitudes are limited and determined by the state of our knowledge at the moment, and even more by the state of our ignorance. As evident from the attached chronology, in the 1940s, '50s, and '60s we were just beginning to gain experience with these new phenomena and new tools and sometimes did not appreciate the hazards. For example, in the 1930s it was common medical practice to use external irradiation to reduce enlarged tonsils or to treat acne. Only years later did it become evident to careful and knowledgeable observers that such radiation probably causes an increased incidence of cancer, especially cancer of the thyroid gland.[16]

In 1941 Joseph F. Ross, M.D., repeatedly gave himself radioactive iron from the Harvard/MIT cyclotron while working under the OSRD (Office of Scientific Research & Development), 1941-45. It was a mixture of Fe-59 with

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*Last week I discussed this with Mrs. Frances N. Kontzen, whom I hired into my radioisotope lab in 1961 as a GS-1 and who worked as a truly exemplary nuclear medicine technologist in the VA for many years, finally retiring in 1987 as a GS-11. She recalls that we were using written patient consent forms when she started; i.e., in 1961. I would have guessed that the transition from verbal consents to more formal written consents occurred somewhat later, perhaps in 1964 or '65.

some Fe-55. He would give himself the radioiron, permit a long enough time to elapse to label his red blood cells, then give blood for storage in various kinds of containers, with different solutions, under a variety of conditions, etc., Aliquots of these were later transfused into human recipients to determine the red cell survival. Who were the recipients? "Residents and technicians from around the lab and hospital; and they were well informed enough to know exactly what was going on and all the risks, even though we did not obtain 'informed consents' on written forms."[17] Later Dr. Ross was cited by President Harry Truman for so improving human blood preservation that it made possible transport of 400,000 units of blood overseas. This was said to have kept at least one full regiment of soldiers in battle rather than on the sidelines because of blood loss and anemia. Now 84 years old and "feeling fine," Dr. Ross has "five very normal children and fifteen normal grandchildren."[18]

In 1948 physicians gave radioiodine to pregnant women who had difficult pregnancies not expected to go to term in order to determine how early the human fetal thyroid begins to accumulate iodine[19]. (The fetal thyroid begins to accumulate iodine at about 10 weeks of gestation.) These results were published, but we do not know for certain whether there were some women whose pregnancies did not terminate with spontaneous abortions but went on to normal delivery instead. Obviously, that work was not done in the VA; but it illustrates the more limited understanding and different standards of the time. Radiation was not as feared then as it is now, and these more casual uses were not considered dangerous. I myself remember going with my mother in the 1930s to buy new shoes and looking -- often staring fascinated for perhaps several minutes at a time -- through a fluoroscope which showed the outlines of my bones and feet within those of the shoes. So, although I know of no specific instances of harm resulting from radioisotope use in the VA, I would not be surprised to find a few instances which might now in 1994 be judged as at least possible causes of harm. However, to jump from such a judgment to condemnation of the "perpetrators" requires another step, a step which calls into question our own morality.

There are two other points I would like to discuss briefly before concluding. The first is that every diagnostic test and therapeutic procedure we use in medicine today, and every drug or surgical procedure or psychotherapy, all these had to be tried on somebody <u>first</u> at one time. I do not know the nature of any "informed consent" Edward Jenner may have had from James Phipps, the 8-year-old Gloucestershire boy he injected with pus from the milkmaid Sarah Nelmes in 1796, thus performing the first vaccination in history against smallpox, a once fatal disease and terrible public health problem which decimated whole populations and is now essentially gone from the face of the earth. He completed the experiment by purposely exposing the boy to real smallpox, deliberately injecting smallpox pus into small cuts on his arm. Soon he encountered criticism from colleagues and authorities. Jenner had conducted 18 years of clinical observations and inquiries before vaccinating Phipps. But regardless of the background and animal tests, one never knows exactly how it will go in human beings. In order to develop these diagnostic and therapeutic measures, we must first understand as much physiology and pathophysiology as possible, then just try it, and getting the physiological understanding may require use of human subjects. For example, until it was determined by clinical studies on normal subjects, no one knew how much carrier iodine-127 should be added to a tracer dose of I-131 in order to interfere with the thyroidal radioiodine uptake; and we know that I-131 is a major fission product resulting from atomic explosions and nuclear accidents. Chapman and Saxena therefore gave I-131 with varying amounts of carrier I-127 to normal subjects in order to find out.[20] This information was used by Nauman in Poland after the 1986 Chernobyl accident, when the Polish physicians were able to distribute some eighteen million doses of stable iodide within 96 hours (most within 72 hours) and thus avoid excessive thyroid radiation and possible later thyroid problems from the fallout.[21] Work like that of Saxena <u>et al</u> made possible the estimation of the amounts of iodide needed for this important public health prophylaxis. The proposal urged by two Princeton University physicists, nationwide distribution of potassium iodide to prevent thyroid damage from ^{131}I, while controversial because it seems to imply that atomic energy is unsafe, is probably a prudent measure and has been endorsed by Russell Peterson, "former Dupont R & D administrator and governor of Delaware who chaired CEQ under Presidents Nixon and Ford."[22]

The second point is that radioactivity is here with us to stay. Not only is it a natural day-to-day encounter in the environment, but atomic energy will increase in the future as a proportion of all energy production. We all have radioactive atoms within our bodies naturally, right now. The amounts can be counted in any of us who sit around this room, provided we use sufficiently sensitive detection and counting equipment. We are also exposed to radiation from external sources, and this is increased by flying across the country at high altitude or by living in Denver.[23] The amounts of radiation received by patients in some published studies are <u>less than</u> the amounts received from the radioactive fallout from atomic bomb tests of the past.

Two other recent studies should be mentioned in connection with possible damage from radiation received from levels of radiation to patients receiving diagnostic doses of radioactive isotopes. In 1988 Holm et al of Sweden published a long-term follow-up of 35,074 patients who had received diagnostic thyroid tests using I-131, but they found no convincing evidence that the usual small diagnostic doses of radioiodine induced cancer in the

recipients.[24] And Shore published similar findings in 1992.[25]

American veterans will continue to be bothered by these problems, because American service men will continue to be exposed to ionizing radiations such as those from nuclear-powered ships. There may also be nuclear power from other military sources. Nuclear power is not only here to stay, but, barring unforseen breakthroughs in solar power, human dependence on atomic energy will only increase in the years and decades ahead. The Thirtieth Activity Report of the OECD's[4] Nuclear Energy Agency **NEA Activities in 1984**,[26] states that "the OECD countries currently produce about 80 percent of the world's nuclear generating capacity, and in 1984 the nuclear share of total electricity generated in the OECD area surpassed the percentage supplied by oil."

We had better keep learning all we can about these subjects, particularly their effects on human beings.

Perhaps the best way to close this testimony is with a quote from J. Robert Oppenheimer, recounted to an audience shortly after World War II, about his thoughts as he watched "Trinity," the test of the plutonium bomb in the early morning of 16 July 1945, the first atomic blast in history:

"When it went off, in the New Mexico dawn, that first atomic bomb, we thought of Alfred Nobel, and his hope, his vain hope, that dynamite would put an end to wars. We thought of the legend of Prometheus, of that deep sense of guilt in man's new powers, that reflects his recognition of evil, and his long knowledge of it. We knew that it was a new world, but even more we knew that novelty itself was a very old thing in human life, that all our ways are rooted in it."[27]

CHRONOLOGY OF RADIATION
Selected Items With Special Reference to Radioactivity

1895, December	- Roentgen discovers x-rays
1896, Feb-March	- Becquerel discovers radioactivity
1897	- J.J. Thompson discovers electron, named by Stoney in 1891 (intended then for elementary natural unit of electricity)
1898	- Radium discovered by P.& M. Curie & G. Bemont
1901	- Roentgen receives first Nobel Prize in Physics
1901	- Becquerel reports skin burns from radium in vest; inspires research leading to med. use
1902	- R. Abbe cures thyrotox. by sewing radium into goiter
1903	- Third Nobel Prize in Physics to P. Curie, M. Curie, & A. H. Becquerel
1913	- Hevesy & Paneth first use radioisotope as tracer
1920 & before	- Means & Holmes use x-ray Rx for Graves' disease
1923	- Hevesy first uses radioisotope as biological tracer, or "radioactive indicator"
1934	- Curie & Joliot, artificial production of radio-isotopes
1934	- Fermi, artificial production of radioisotopes; discovers radioactive iodine
1936, November	- Saul Hertz suggests use of radioiodine-128 in thyroid studies
1937-42	- Hertz, Means, Evans, et al develop radioiodine for medicine & physiology
1938	- Hahn & Strassman discover nuclear fission
1939, 11 Feb.	- Meitner & Frisch correctly interpret Hahn & Strassman's findings
1939, August	- A. Einstein signs letter to Roosevelt suggesting atomic bombs may be developed by Germany
1940, 7 March	- Einstein writes FDR second letter warning of Germany's increasing interest in uranium & presumably atomic bombs
1942, December	- First nuclear chain reaction in Chicago pile
1943	- Hevesy receives Nobel Prize in chemistry for radioactive tracers
1944	- O. Hahn receives Nobel Prize in chemistry for fission of heavy nuclei
1945, 16 July	- "Trinity", first atomic bomb test explosion
6 August	- Hiroshima bomb ("Little Boy;" uranium)
9 August	- Nagasaki bomb ("Fat Man;" plutonium)
1946, 3 January	- Truman signs law creating modern VA medical system

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[4]Organization for Economic Co-operation and Development, organized at a convention in Paris & signed by most western governments 14 December 1960. The original 20 signatory governments were later joined by 4 others (Japan, Finland, Australia, and New Zealand) to bring the total to 24 by 1984.

1946, 25 July - Bikini becomes test site for atomic weapons
1946, 24 Sept. - Study finds food still radioactive at Bikini
1946 - Radioactive isotopes become available in abundance from Oak Ridge labs
1947 - Gen. Paul Hawley orders creation of "radioisotope laboratories" in VA hospitals to promote "atoms for peace." VA assumes a leading role in development of radioisotopes in medicine & biomedical research
1949, 23 Sept. - Truman learns Soviets have exploded atom bomb
Early 1950s - Berson & Yalow in Bronx VA Hospital use I-131 to study thyroid physiology and disease
1950 - Automated scintiscanning of thyroid invented by Benedict Cassen and Herbert C. Allen, with Reed & Curtis; 1st clinical scanner is made in LA VAH. Wm. Oldendorf later develops precursor of CT scanning for human brain at same VA hospital.
1949-52 - U.S. develops thermonuclear (hydrogen) bomb
1952, 1 Novem. - U.S. explodes first hydrogen device, Eniwetok
1953 - U.S.S.R. explodes hydrogen bomb
1953 - Pres. Eisenhower proposes "Atoms for Peace" program
1954 - Eisenhower signs Atomic Energy Act; private development of atomic energy
1955, August - 1st International Conference on Peaceful Uses of Atomic Energy, Geneva
1956 - Berson & Yalow publish basis of radioimmunoassay, later developed in their Bronx VA labs;
1956 - Photoscanning developed by David Kuhl
1957 - Britain explodes hydrogen bomb
1957, October - Sputnik, U.S.S.R., 1st artificial earth satellite
- (Stimulates U.S. Nat'l. Defense Education Act)
Late 1950s - Intercontinental missiles developed
1958 - 2nd Internat. Conf. on Peaceful Uses Atomic En.
1950s & '60s - Worldwide fallout from nuclear weapons testing
1963, 10 Oct. - Nuclear Test-Ban Treaty becomes effective (U.S., U.S.S.R., & U.K. only)
1977 - Rosalyn Yalow receives Nobel Prize for development of radioimmunoassay (entirely within VA labs & VA support; Nobel also to A. Schally that year for research in New Orleans VAH)
1979, 29 March - Three Mile Island nuclear reactor accident
1986, 26 April - Chernobyl reactor explosion

VA TESTIMONY - Specific Questions from Committee

A. Background on nature & duration of [my] work in VA relative to Hearing:

a) Positions & titles:

1. M.D., Harvard Medical School, 1952.
2. Temporary Director, NIH Clinical Radioisotope Lab., 1955
3. Chief, Radioisotope Lab, Birmingham VA Hosp., 1958-71
4. ACMD for R&E, DM&S, U.S. Veterans Adm. Central Office, 1971-73
5. Dean, UAB School of Medicine, 1973-92.
6. Distinguished Professor, UAB, 1992-present.

b) Educational experiences, certifications, society memberships, etc.

1. American Thyroid Association, 1956
2. Endocrine Society, 1956
3. ORINS (Oak Ridge Inst. for Nuclear Studies) course, 1956
4. American Board of Internal Medicine, 1959 (recert. 1974)
5. Society of Nuclear Medicine, 1959
6. American Board of Nuclear Medicine, 1972
7. American Board of Endocrinology & Metabolism, 1972
8. Health Physics Society, 1969-71
9. Radiological Health Committee, State of Alabama 1969-71
10. State (Ala.) Committee of Public Health, 1978-92

c) Publications, presentations at meetings, etc.

1. Approx. 125 papers, chapters, books, etc., & 50+ abstracts, notes, etc. Bibliography available on request.
2. Presentations at meetings re. above; cf. abstracts

B. Recollections of VA units which handled radioisotopes, their nature, purpose, responsibilities, where [I] worked:

a) Birmingham VA Hospital (1958-71).

1. Nature - ordered, received, handled, identified, monitored, calibrated, etc., all radioactive isotopes for whole medical center, including all investigators (except radium, handled by radiotherapy/radiology); did "wet work" lab. examinations in routine care of patients; organized, managed, and carried out routine diagnostic and therapeutic procedures on inpatients and

outpatients; did research experiments involving radioactive isotopes for other investigators; did our own research, both basic tissue & animal work and patient/human clinical research.

2. Purpose - threefold: routine diagnostic procedures on patients; routine therapeutic procedures on patients; and research to improve diagnosis and treatment for VA patients and all patients everywhere, including understanding normal and abnormal physiology.

3. Responsibilities - to do the above with care & excellence, but first of all with care for the individual patient. Also to train others to do these things, especially younger technical people and physicians.

4. Kinds of "diagnostic, treatment, and research endeavors in which such unit(s) were employed:

1) Thyroid studies (thyroidal I-131 uptakes, PBI-131, I-132 uptakes, thyroid scintiscans with I-131, I-132, I-125, Tc-99m, determination of PII with I-131, turnover rates of T4 and its analogues, metabolism of T4 and analogues, assessment of congenital defects in these by pharmacologic manipulations, assessment of acquired abnormalities including those from drugs used clinically), treatment of Graves' disease and other forms of hyperthyroidism, treatment of thyroid cancers, improvement of thyroid tests used clinically [e.g., TSH stimulation tests], RBC T3 uptakes, etc.)

2) Schilling tests for Dx of pernicious anemia (Co-60)

3) RISA (radioiodinates serum albumin) tests of blood volume & for brain tumor localization, cardiac output, circulation times, radiocardiography, detection of gallbladder disease)

4) Radioactive phosphorus (P-32) Rx of polycythemia vera and leukemia & for bone scans to locate metastases

5) Radioactive gold (Au-198) for Rx pleural effusions from carcinoma of lung, mesotheliomas, etc.

6) Radioactive chromium (Cr-51) red cell turnover studies in patients with hemolytic anemias & to localize GI bleeding

7) Radioact. iron (Fe-55 and Fe-59) for Dx and study of anemias and iron overload diseases & GI absorption

8) Radioact. bromine (Br-82) to understand iodine metabolism in body

9) Radiocarbon (C-14) in vitro tissue studies of thyroid and other tissues, esp. intermediary metabolism

10) Tritium (H-3) for animal & in vitro metabolic studies

11) Radioact. mercury (Hg-203) for brain tumor localization

12) Radioact. potassium (K-42) to study body potassium stores

13) Radioiodinated hippuran, etc., to determine renal blood flow & urinary retention &/or residual

14) Radiocalcium (Ca-45) to study bone metabolism in chicks & other animals

15) Radioxenon (Xe-133) for diagnostic studies of pulmonary function

& probably others.

5. Relation to affiliated medical schools, VA Central Office, & external groups such as the AEC:

The Birmingham VA Hospital was affiliated with the University of Alabama School of Medicine (now of UAB) from the outset, as the founding Dean of the four-year medical school, Roy Kracke, M.D., was on an advisory committee to General Hawley just after the war and arranged to have land supplied to the VA for construction of the VA Hospital, completed in 1953, immediately across the street from the University Hospital. In 1967 a VA research building was completed spanning the street and providing the first building in the nation to link physically the VA Hospital with the University Hospital. The first Chief of the Radioisotope Unit was William L. Hawley, M.D., who had worked as a house officer in Boston with Dr. Joseph Aub (where he administered P-32 to a patient with a pleural effusion in 1939 or '40) and after the war had worked as a physician with Hempelman at Los Alamos. After establishing the radioisotope lab at the VA in 1953, Dr. Hawley did so in the University Hospital across the street. However, these remained relatively minor and primitive operations by today's standards, doing chiefly clinical thyroidal I-131 uptakes and a few Schilling tests, until scanning procedures came along in the late '50s and '60s, when major growth occurred with the expanded clinical applicability.

The activities of the two hospitals and the medical school/university were highly coordinated, but everyone understood, I think, that the VA was an autonomous institution with its own federal laws, regulations, procedural requirements, and reporting channels. One example of this in the segregated city and state of the times (the Birmingham VA was racially integrated from the outset) was that Alabama State troupers were required to remove their pistols when they entered the federal property of the VA, a symbol of who was boss. Nevertheless, physicians on the VA Hospital staff were appointed only after recommendation by the Dean's Committee, and this required that they obtain medical school faculty appointments. There were interdigitating committees and coordination of use of isotopes, sharing of isotopes and equipment, and the like.

Relations with VACO were through a physicist, Mr. A. Graham Moseley, M.S., head of the radioisotope "service" in Washington during those times. Mr. Moseley was a kindly and upright gentleman who would not even let you buy him lunch for fear of a conflict of interest. He, in turn, made sure we abided by applicable regulations of the AEC (Atomic Energy Commission), which retained control over isotope use until that authority was delegated to the

individual states, in the 1960s as I recall. While the states took over authority and responsibility for radiation safety, federal agencies remained under federal jurisdiction (especially in the 1960s). Thus, the NRC (federal Nuclear Regulatory Commission) assumed control of such activities in VA hospitals/medical centers. I do not recall any difficulties in these relations.

c. Human subjects:

1. Kinds of studies (I) participated in as PI (Principle Investigator): These were chiefly studies of thyroid physiology and disease and of diagnostic and therapeutic procedures used for patients suffering from diseases of the thyroid. My lab was devoted especially to trying to understand the control of thyroid function and how this has gone awry in patients with Graves' disease, which is usually characterized by hyperthyroidism. If you really want detailed data on this question, I can send you a complete collection of my published work from those times, including effects of pituitary TSH on thyroidal glycogen metabolism, effects of TSH on thyroidal glucose oxidation (done with bovine and porcine thyroids as well as human thyroid tissue excised in the course of thyroid operations), effects of cobalt on thyroid metabolism, effects of thyroxine analogues (esp. rT3) on thyroxine metabolism and action (chiefly in rats, but some in humans), effects of commercially available drugs on thyroid function (in rats, dogs, and humans), changes in thyroidal I-131 uptake tests consequent upon changes in bread-making processes in the United States, standardization of TSH testing in human beings, effectiveness of TRH (thyrotropin releasing hormone) in humans, effect of a triazine on adrenal and thyroid function in humans, detection and publication of the first case of hypothalamic hypothyroidism, and similar work.

2. Relationship of those studies to patients' clinical care: In studies of diagnostic or therapeutic procedures, these were often simply collected as those regular clinical procedures occurred in the normal hospital fashion, but usually with controls or additional studies, either in the same or other patients or normal subjects. Regulations permitted the use of non-veterans in such studies, even when done in the VA facilities; so some non-veterans were occasionally included, especially since thyroid diseases preferentially affect females, and there were few females among the patients. In many studies the patients used were in the hospital for non-thyroidal illnesses, especially patients on the orthopedic service, since they were generally healthy except for their fracture or other orthopedic problem, and in those days they tended to stay in the hospital for prolonged periods and often became bored. Often they seemed to welcome the research as a break from the otherwise tediously dull daily routine. In some cases (e.g., the study of thyroidal radioiodine uptakes as affected by diet), we simply did the routine procedure, collected urine, analyzed patients' diets (i.e., identical trays of food), but otherwise did not disturb the patients. In others, though I recall none done in the VA*, we sometimes administered molecules tagged with a radioactive isotope in order to follow that molecule's metabolism through the body. In most of the normal subjects, there was no relation between their medical care and the research studies done. In some instances we used ourselves, as I did when I took the first dose of TRH we had synthesized locally, thus escaping FDA regulations and laws, and my colleague Jerome M. Hershman, M.D., took the second dose. As I joked in some talks I gave shortly after that, "Then we began giving it to our friends." The purpose of that particular study in 1969 was to learn the effect of the synthetic TRH (thyrotrophin releasing hormone) on the pituitary and its secretion of TSH (thyroid stimulating hormone, or thyrotrophin). In some cases VA or university staff served as normal volunteer subjects. In two other cases I was the first to take newly synthesized drugs, and in another I was the first (and maybe only) human subject to take a labeled molecule (rT3) intravenously to study the disappearance rate.

3. Procedures used for review & approval of the research projects: Prior to sometime in the 1960s, probably around the time of the Helsinki Declaration about 1964 or 65, there was no requirement to obtain written consents. However, we probably started using them in the Birmingham VA about the same time the CRC (General Clinical Research Center, or GCRC) opened in the affiliated University Hospital, which was about 1962. Prior to that time the consents were simply written into the regular hospital record by the doctors with no signature or note from the patients. However, we always obtained verbal consent from the patients or subjects, and this required explaining to them the nature and purpose of the research, what we expected to learn, and some assessment of the risks. Since miniscule quantities of radioactivity or labeled molecules were used, there was generally assumed to be only a very small risk or essentially none at all. Mostly such studies were just an inconvenience to the subjects or patients, and as I mentioned, many did not consider the special attention undesirable. On the other hand, how much the patients actually understood is uncertain. Probably it was quite variable and dependent upon the patient's educational level and native intelligence. I think we recognized that at the time and tried to make adjustments for it, like using the simplest language possible consistent with understanding.

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*As members of the medical school faculty we also conducted such studies in the affiliated University Hospital's CRC (Clinical Research Center), supported by money from the NIH (National Institutes of Health).

4. Radiation levels used in those studies and then-current understanding of radiation risks from those levels: The radiation levels were in the range of those of common diagnostic procedures; e.g., 1 to 100-200 microcuries of I-131 for radioiodide (same as for scans then), or less. The current understanding of radiation risks limited exposures to 500 mr (milliroentgens, or millirems, for "roentgen equivalents man" [or "mammal]) a year or 125 mr/quarter; but these were the limits for occupational exposure and were lower than for diagnostic uses of isotopes. Nevertheless, the latter were judged to be safe for routine clinical use, so we considered them reasonable and safe for research subjects as well.

5. The then-applicable standards, & those used by [us], in research regarding enrolling patients and eliciting their understanding of, and agreement to participate in, the research: See #3 above.

6. Existence of follow-up studies on subjects/patients: Basically there were no follow-ups on these patients/subjects specifically for these studies. Last week I attempted to find medical records or research records for these patients, and they are all gone from the hospital and probably destroyed. For many years I had a bound book I had kept with the names, medical record numbers, diagnoses, ages, sexes, etc., for research patients; but last week I could not locate it. In any case, there were no organized follow-ups.

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Clinical Use of Radioisotopes

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Chapter 1

Certain Preliminaries

WHO SHOULD TRAIN?

WHO SHOULD receive training to diagnose and treat patients with radioactive isotopes? When in the physician's career should this training be acquired? How should one acquire this training?

On February 7 and 8, 1954, a Conference on Training in the Use of Radioactive Isotopes, sponsored by Northwestern University Medical School and Argonne National Laboratory, was held in Chicago to urge certain interested persons to crystallize their thinking on these problems. Our opinions coincide with the conclusions derived from this conference.

1. **The Medical Student.** The medical student is required to take chemistry and physics in undergraduate school. When he enters medical school, a separate course on radiation biology or clinical techniques should not be taught, both because of curriculum difficulties and because this material can be pertinently presented in relation to material included in existing courses. On the other hand, coverage of certain fundamental topics in this field should not be left to chance. Inclusion of such topics in specific courses should be recommended by the curriculum committees.

Instruction should be given in the freshman year on properties of radiation, principles of radiation detection and measurement, and interaction of radiation and matter. This material, presented in lecture and demonstration, should be included in either biological chemistry or physiology, depending upon which subject is presented first in the curriculum. As students are now taught to think in chemical terms of the structure and interrelationships of matter, they should also be encouraged to regard structure and function from a physical point of view. The effect of radiation on tissue might be taught in the second year in pharmacology or pathology. Instruction on radiation hazards and protection should be included in the curriculum, possibly in the junior year, as a part of the course work either in radiology or in public health and preventive medicine. The application of radioisotopes in diagnosis and therapy would be left entirely to the clinical departments as to what and how much to include.

2. **The Intern and Resident.** Current opinion agrees that radioactive isotopes should be a tool for the use of the skilled clinician in diag-

osis and treatment. It is suggested, therefore, that the period of radioisotope training might best be presented at the end of two or three ears of specialty training. The major quantity of radioisotopes used in linical medicine today are administered by internists, radiologists and urgeons. Pathology may soon include training in radioisotopes as part f clinical laboratory pathology. We have made rotation through the linical Radioisotope Unit available to all residents in University Hospital to give them a broader knowledge of modern medicine, to prepare hem to be relatively well informed members of their community in espect to questions of atomic warfare, civil defense programs and hazrds which might arise or be alleged to arise from industrial use of rtificial radioactivity, and, most important, to equip them for the possibility that they may be needed to head a clinical radioisotope laboratory in a university hospital or a leading hospital in a large community.

3. **The Postgraduate in Private Practice.** Physicians in private ractice generally request training in a clinical isotope unit for one of wo reasons. The specialist usually wants to learn how to handle a cerain radioactive isotope in his practice as a specialized tool in his daily ork. The general practitioner, on the other hand, desires information n the indications for the use of all clinical radioisotopes in his patients, ow to prepare his patients for these isotopes, and how to handle his atients after the isotopes have been administered to his patients. This atter type of instruction should be available to any physician to keep im informed on the utility of this new development in modern edicine.

RECOMMENDATIONS AND REQUIREMENTS BY THE ATOMIC ENERGY COMMISSION

The Atomic Energy Commission has made several specific recommendations and requirements to be met by the person who wishes to se radioisotopes in clinical medicine. These statements are reproduced *n toto* as follows.

THE MEDICAL USE OF RADIOISOTOPES

Recommendations and Requirements by the Atomic Energy Commission

I. INTRODUCTION

The present procedures of the Atomic Energy Commission for the llocation of radioisotopes for medical research, diagnosis and herapy are set forth in this announcement. The recommendations for inimum clinical radioisotope training and experience for use of adioisotopes in human subjects have been established in advisement ith the Subcommittee on Human Applications of the Atomic Energy ommission's General Advisory Committee on Isotope Distribution.

These recommendations are designed to provide guidelines for hysicians and typify the nature rather than the precise extent of he desirable clinical radioisotope experience. For special situations, other experience may serve in lieu of the particular recommendations set forth in this announcement.

II. ADMINISTRATIVE PROCEDURE FOR RADIOISOTOPE PROCUREMENT

A. APPLICATION

A medical institution or a physician in an individual medical practice desiring to obtain radioisotopes, forwards to the Isotopes Extension*, Form AEC-313, "Application for Byproduct Material Licensee," and Supplement A, (Form AEC-313-a). If the radioisotopes are to be obtained as sealed sources (such as Cobalt 60 for teletherapy units or Strontium 90 for medical eye applicator), the applicant should complete the basic form (Form AEC-313) and Supplement B (Form AEC-313-b). These forms should be completed in accordance with the instructions attached thereto. Applications for use of radioisotopes in human subjects in an INSTITUTIONAL MEDICAL PROGRAM should be supported by the special information described under Section III, Page 4, Section IV, Page 6 and Section V, Page 7 of this announcement. For such use by a physician in his INDIVIDUAL MEDICAL PRACTICE the application should be supported by the special information described under Section III, Page 4, Section VI, Page 11 and Section VII, Page 13.

In considering such applications, the Atomic Energy Commission is concerned primarily with matters of radiological health safety. Toward this end the Commission seeks to determine if the applicant has equipment and facilities appropriate to the proposed use and whether the physician is trained in basic principles of radioactivity and has specific experience in the use of radioisotopes in the clinical situations being proposed. The information is indicated by the applicant on his application form and the supplementary sheets attached thereto.

B. LICENSE

Upon favorable review of the application (See NOTE below), Form AEC-374, "Byproduct Material License," is issued. This license permits the holder to procure radioisotopes in accordance with the conditions stated on the application and license forms and in Title 10 of the Code of Federal Regulations.

NOTE. The Isotopes Extension normally reviews applications proposing new or nonroutine medical uses of radioisotopes in collaboration with the Advisory Subcommittee on Human Applications. This review usually requires four weeks for completion.

C. TYPES OF CLINICAL RADIOISOTOPE PROGRAMS

The recommendations and requirements established by the Atomic Energy Commission for the clinical use of radioisotopes are designed to provide for two types of medical radioisotope programs. These are defined as follows:

1. Institutional Medical Radioisotope Program

Clinical radioisotope programs established by a medical institution and carried out under the guidance of a medical isotopes committee (See recommendations for membership and duties of a medical isotopes committee in Section IV, A. Page 6) are designated as "Institutional use." Licenses for institutional use require that the physician(s) named on the license form supervise the conduct of

* Allocations Branch, Isotopes Extension, Division of Civilian Application, U.S. Atomic Energy Commission, P. O. Box E, Oak Ridge, Tennessee.

the program with the guidance of the medical isotopes committee. The use of the radioisotope(s) shall be by, or in the presence of or under the supervision of, the physician(s) indicated on the license and confined to the location and the purposes indicated thereon.

NOTE 1. Physicians other than those named on the license form may participate in the medical radioisotopes program with the general supervision of the named physicians and upon approval by the medical isotopes committee. Institutional type programs provide a vehicle whereby physicians other than those named on an AEC license may have an opportunity to gain radioisotope experience commensurate with the recommendations in this announcement. Such experience may assist these physicians in initiating a medical program at other institutions or in their individual practice.

NOTE 2. Individual physicians within an institutional medical program operated under the guidance of a medical isotopes committee are discouraged from initiating separate applications for use of radioisotopes in specific clinical programs where the institution already holds a license (Form AEC-374) for such use. It is recommended that one or more physicians experienced in the use of a radioisotope for a particular clinical situation be designated by the medical isotopes committee as the nominally responsible physician(s) on the application for radioisotopes. Subject to the approval of the medical isotopes committee other staff physicians may administer radioisotopes to patients in consultation with or under the supervision of the physician(s) designated on the license form as mentioned in NOTE 1 above.

2. Individual Practice Medical Program

Medical radioisotope programs which are to be conducted by a physician in his individual practice without the guidance of a medical isotopes committee are designated as "individual practice use." These programs are limited to well-established medical uses of radioisotopes. Licenses for the use of radioisotopes in individual practice require that the physician(s) so licensed personally carry out the program. Such use shall be confined to the location, dosage and purposes indicated on the license form.

D. SUPPORTING INFORMATION TO ACCOMPANY APPLICATION

1. Applications for "institutional use" should provide the supporting information described in Sections III, IV and V of this announcement.

2. Applications for "individual practice use" should provide the supporting information described in Sections III, VI and VII.

III. GENERAL REQUIREMENTS FOR MEDICAL USE OF RADIOISOTOPES

A. PRECEPTOR STATEMENT

A standard preceptor form has been prepared by the Isotopes Extension as a convenient means of furnishing information concerning the physician's basic radioisotope training and clinical experience in the use of radioisotopes. The physician should have his medical preceptor in the clinical radioisotope work proposed forward a completed "Preceptor Statement" to the Isotopes Extension with his initial applications. When a physician wishes to extend his program to include other clinical situations a new preceptor form normally should be submitted if information concerning his experience in these medical uses has not previously been provided.

B. DOSAGE SCHEDULE

Every application shall include the proposed dosage range for each of the diseases or conditions to be followed. When the isotope is proposed for both diagnosis and therapy, the dosage range for each is to be stated separately. The approximate dosage (in millicuries or microcuries) per single administration is to be indicated as well as the number and frequency of such doses.

Applications proposing such experimental or nonroutine uses of radioisotopes in human subjects should be supported by a statement detailing the rationale for the dosage proposed and other data as set forth under Section V.E., Page 10.

C. PREREQUISITES FOR USE

1. The individual to use radioisotopes in human subjects shall be a physician licensed to dispense drugs in the practice of medicine by a state or territory of the United States, the District of Columbia or the Commonwealth of Puerto Rico.

2. Normally the proposal to use radioisotopes in human subjects should be appropriate to the scope of the physician's medical experience, specialty and/or board certification.

3. The physician should have personal experience gained through "basic radioisotope training" and "active participation" as defined in Part (a) and (b) below. The active participation shall be obtained by collaborating in a program using radioisotopes in clinical situations comparable to those proposed in the application. The training and experience should be in accordance with the recommendations cited under Sections V or VII, "Recommendations for MINIMUM Clinical Radioisotope Experience for use of Radioisotopes."

a. Basic radioisotope training* shall provide the physician a working knowledge of
   1. Principles and practices of radiological health safety.
   2. Radioactivity measurement standardization and monitoring techniques and instruments.
   3. Mathematics and calculations basic to the use and measurement of radioactivity.
   4. Biological effects of radiation.
   5. Actual use of radioisotopes in the types and quantities for which application is being made, or equivalent experience.

b. Active participation consists of:
   1. Evaluation of the suitability of the patient for radioisotope diagnosis and/or treatment by taking patient histories and performing medical examinations and/or study of case histories.
   2. Collaboration in diagnosis and/or treatment and dosages prescribed.
   3. Measurement of doses and their administration.
   4. Related measurements and plotting of data.
   5. Active period of training and experience of sufficient duration to permit the following of specific patients through treatment and post-treatment periods, including reevaluation as to effectiveness and complications.
   6. Study of case histories (without seeing patients).
   7. Study of case histories (observed patients).

*Satisfactory completion of the Oak Ridge Institute of Nuclear Studies "Basic Course in Techniques Using Radioisotopes" or its equivalent will serve as evidence of compliance with requirements in basic training.

8. Observation and discussion of diagnostic and/or therapeutic techniques, as well as management of patients during follow-up periods.
NOTE. Details of the physician's active participation should be indicated by his medical preceptor on the standard preceptor form discussed in Section III A, page 4.

IV. SPECIAL REQUIREMENTS FOR INSTITUTIONAL MEDICAL PROGRAM

(See also General Requirements cited under Section III, above)

A. MEDICAL ISOTOPES COMMITTEE

The applicant institution shall appoint a medical isotopes committee to evaluate all proposals for research, diagnostic and therapeutic use of radioisotopes within the institution. The initial application from an institution should include the names, specialties, and pertinent radioisotope experience, if any, of the members of the medical isotopes committee. The functions of the committee, as well as the administrative procedures by which it carries out these functions, should also be defined. In subsequent applications any changes in the membership of the committee should be described.

NOTE. Where the use of radioisotopes in a medical institution is to be limited to sealed radiation sources for well established intracavitary, interstitial or external therapeutic procedures, a medical isotopes committee is not necessary. See Section VIII, Page 15.

1. Formation of a Medical Isotopes Committee

The Medical Isotope Committee shall include at least three members. Membership should include physicians expert in internal medicine (or hematology), pathology, or therapeutic radiology and a person experienced in assay of radioisotopes and protection against ionizing radiations. It is often appropriate that a qualified physicist be available to the Committee, at least in a consulting capacity.

It is recognized that the composition of local isotopes committees may vary from institution to institution depending upon the individual interests of a particular medical facility.

2. Duties of the Medical Isotopes Committee

Generally, the Committee should have the following responsibilities:

a. Review and grant permission for, or disapprove, the use of radioisotopes within the institution from the standpoint of radiological health safety and other factors which the Committee may wish to establish for medical use of these materials.

b. Prescribe special conditions which may be necessary, such as physical examinations, additional training, designation of limited area or location of use, disposal methods, etc.

c. Review records and receive reports from the radiological safety officer or other individual responsible for health-safety practices.

d. Recommend remedial action when a person fails to observe safety recommendations and rules.

e. Keep a record of actions taken by the Committee.

B. RADIOACTIVE PHARMACEUTICALS

Radiomaterials distributed by Atomic Energy Commission-owned laboratories are not necessarily of pharmaceutical quality and are not warranted as to identity, quality or quantity. An applicant desiring to procure radiomaterials for human use, therefore, must either purchase them preassayed and of pharmaceutical quality from commercial concerns or process them himself should he choose to receive these materials from Commission laboratories. Where the latter option is chosen, the applicant should include with his application the following information:

1. His experience in standardization and measurement techniques.

2. The procedures to be employed for identifying and assaying the radiomaterial and carrying out such other testing and processing (sterilization, pyrogen tests, etc.) as may be appropriate.

3. The instruments and equipment available for this purpose.

NOTE. When purchasing radiomaterials from an AEC distributor (e.g. Oak Ridge National Laboratory), all non-federal applicants must use a special "Isotope and Service Irradiation Order Form" (Form AEC-391) and federal agencies must use an "Isotope Order Blank" (Form AEC-375). Copies of these forms are available from the AEC distributors and Isotopes Extension. These forms are not intended for use when ordering materials from other than AEC distributors.

V. RECOMMENDATIONS FOR MINIMUM CLINICAL RADIOISOTOPE EXPERIENCE FOR INSTITUTIONAL USE

(In addition to the requirements discussed in Section III C, Page 5, the physician should have clinical radioisotope experience commensurate with the following recommendation(s) applicable to the use(s) proposed on his application.)

A. IODINE 131

1. Diagnosis of Thyroid Function

The physician should work for at least 30 hours in a medical program where Iodine 131 for diagnosis of thyroid function and treatment of thyroid disease is being used.

During the 30-hour period of time the physician should actively participate in such diagnostic studies in at least 10 patients.

NOTE. The Iodine 131, unless otherwise exempted, shall be procured in precisely calibrated form.

2. Determination of Blood Volume and Plasma Volume

The physician should work for at least 30 hours in a medical program where Iodine 131 for blood determinations is being used.

During the 30-hour period of time the physician should actively participate in 10 such blood determinations.

Physicians already using Iodine 131 in diagnosis of thyroid function can qualify after active participation in 3 such blood determinations.

NOTE. The Iodine 131 unless otherwise exempted shall be procured in a sterilized, precisely calibrated form.

3. Diagnosis of Other Clinical Conditions

The use of Iodine 131 for the localization of brain tumors, hepatic malignancies, etc., represents specialized applications

requiring considerable refinement in techniques and specialized instrumentation. The use of radioiodine for these purposes is normally limited to physicians already having substantial experience in both diagnostic and therapeutic use of radioisotopes as well as specific experience in the modality being proposed.

Applications proposing such use of radioisotopes should be supported with information describing the clinical procedures to be followed and the instrumentation to be used.

4. Treatment of Hyperthyroidism and/or Cardiac Dysfunction

The physician should actively participate in the use of Iodine 131 for the treatment of hyperthyroidism and/or cardiac dysfunction in a minimum of 10 patients.

5. Treatment of Thyroid Cancer

The physician should have (1) experience as set forth in 4 above and (2) active participation in the use of Iodine 131 for the treatment of thyroid cancer in a minimum of 3 patients.

B. PHOSPHORUS 32

1. Diagnosis

The use of Phosphorus 32 for localization of brain tumors, eye tumors, etc., represents specialized applications of radioisotopes requiring considerable refinement in techniques and specialized types of instrumentation. The use of radiophosphorus for these purposes is normally limited to physicians already having substantial experience in both diagnostic and therapeutic use of radioisotopes, as well as specific experience in the modalities being proposed.

Applications proposing such use of radioisotopes should be supported with information describing the clinical procedures to be followed and the instrumentation to be used.

2. Treatment of Leukemia, Polycythemia and Allied Blood Dyscrasias

a. The physician should be expert in therapeutic radiology, internal medicine (or hematology) or pathology. Board certification will serve as evidence of qualifications.

b. Physicians who are not qualified as indicated above should actively participate in the use of Phosphorus 32 for the treatment of leukemia, polycythemia vera and/or other blood dyscrasias in a minimum of 5 patients.

3. Phosphorus 32 — Chromic Phosphate

a. Intracavity Use in the Palliation of Carcinomatous Patients.

(1) The physician should actively participate in the use of Phosphorus 32-labeled chromic phosphate in the treatment of a minimum of 5 carcinomatous patients.

(2) Experience in the intracavity use of colloidal Gold 198 will serve in lieu of the recommendations set forth in (1) above.

NOTE. Applications proposing the intracavity use of Phosphorus 32-labeled chromic phosphate should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

b. Interstitial Use in the Treatment of Prostatic and/or Cervical Cancer.

(1) The interstitial use of Phosphorus 32-labeled chromic phosphate for treatment of prostatic and/or cervical cancer entails a specialized procedure. Such therapy, therefore, should usually be carried out by a team which includes a surgeon of appropriate specialty and a therapeutic radiologist both of whom are experienced in this modality. The surgeon should actively participate in the treatment of 6 to 8 patients and the therapeutic radiologist in the planning for and handling of 1 to 2 patients.

(2) Experience in the interstitial use of colloidal Gold 198 for prostatic and/or cervical cancer will serve in lieu of the recommendation set forth in (1) above.

NOTE 1. The use of Phosphorus 32-labeled chromic phosphate interstitially in the treatment of prostatic cancer and/or cervical cancer is not considered to be routine. Therefore, applications proposing this therapy should be submitted as an investigative program which outlines in detail the study conditions to be evaluated.

NOTE 2. Applications proposing the interstitial use of Phosphorus 32-labeled chromic phosphate should be accompanied by a properly annotated drawing of the injection apparatus or a literature reference to such apparatus.

C. GOLD 198 COLLOID

1. Intracavity Use for Palliation of Carcinomatous Patients

a. Physicians who have personal experience in the actual handling of equivalent amounts of other gamma emitting radioisotopes, e.g., Iodine 131 for the treatment of thyroid carcinoma, should actively participate in the treatment of a minimum of 2 to 3 carcinomatous patients.

b. Physicians without personal experience in the actual handling of equivalent amounts of other gamma emitters should actively participate in the use of Gold 198 colloid in the treatment of a minimum of 5 carcinomatous patients.

NOTE 1. Applications proposing the intracavity use of Gold 198 colloid should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

NOTE 2. Because of the magnitude of the dose of Gold 198 colloid used for palliation of carcinomatous patients and the accompanying gamma ray flux, the application should be accompanied by a detailed discussion of the special instructions to be given hospital personnel concerning the care and handling of such patients and the special radiological health safety procedures to be followed.

NOTE 3. The application should state whether the Gold 198 colloid will be obtained from the supplier in individually prepared doses or whether patient doses will be prepared by the physician from stock solution. If the latter is the case specific details should be presented concerning assay and safe handling procedures.

2. Interstitial Use for Treatment of Prostatic and/or Cervical Cancer

The interstitial use of Gold 198 colloid for treatment of prostatic and/or cervical cancer entails a specialized procedure. Therefore, such therapy should usually be carried out by a team which includes a surgeon of appropriate specialty and a therapeutic radiologist both of whom are experienced in this modality. The surgeon should actively participate in the treatment of 6 to 8

patients and the therapeutic radiologist in the planning for and handling of 1 to 2 patients.

NOTE 1. Applications proposing the interstitial use of Gold 198 colloid should be accompanied by a properly annotated drawing of the injection apparatus to be used or a literature reference to such apparatus.

NOTE 2. Because of the magnitude of the dose of Gold 198 colloid used for interstitial therapy of cancer patients and the accompanying gamma flux the application should be accompanied by a detailed discussion of the special instructions to be given hospital personnel concerning the care and handling of such patients and the special radiological health safety procedures to be followed.

NOTE 3. The application should state whether the Gold 198 colloid will be obtained from the supplier in individually prepared doses or whether patient doses will be prepared by the physician from a stock solution. If the latter is the case specific details should be presented concerning assay and safe handling procedures.

D. CHROMIUM 51

Determination of Blood Volume, Plasma Volume and Erythrocyte Survival

1. The physician should work for at least 30 hours in a medical program where Chromium 51 for blood determinations is being used.

During the 30 hour period of time the physician should actively participate in 10 such blood determinations.

NOTE. The Chromium 51, unless otherwise exempted, shall be procured in a sterilized, precisely calibrated form.

2. Physicians trained in the use of other radioisotopes for diagnostic and therapeutic purposes can qualify after active participation in 3 such blood determinations.

E. EXPERIMENTAL OR NONROUTINE USE OF RADIOISOTOPES IN HUMAN SUBJECTS

The experimental use of radioisotopes in human subjects, whether for research, diagnostic or therapeutic purposes, shall be limited to physicians with broad radioisotope experience and to institutional type programs.

Applications proposing the experimental use of radioisotopes in human subjects should be supported with a detailed proposal outlining the study conditions to be evaluated. Preferably this type of program should be preceded by studies in animals which have established the assimilation, distribution, selective localization and excretion of the radioisotope in question (or its derivatives) sufficiently well to permit extrapolation to man for dosage purposes. These animal data should be included as part of the application.

In the absence of animal data the proposal should include detailed remarks concerning the rationale for the dose to be used.

Ordinarily, radioisotopes with half-lives greater than 30 days will not be available for internal use in human subjects unless prior studies on animals have established the metabolic properties noted above. It is recognized, however, that special circumstances may arise which indicate the desirability or necessity for the use of long-lived radioisotopes in human subjects where prior animal data are not available. Consideration of such proposals shall be limited to patients suffering from diseased conditions of such a

nature (life expectancy of one year or less) that there is no reasonable probability of the radioactivity employed producing manifest injury.

NOTE 1. To assist the Atomic Energy Commission and its Subcommittee on Human Applications in considering like proposals from other groups, it is requested that data obtained in the experimental or nonroutine use of radioisotopes be forwarded to the Isotopes Extension.

NOTE 2. Use of radioisotopes in normal subjects for experimental purposes shall be limited to:

a. Tracer doses which do not exceed the permissible total body burden for the radioisotope in question. In all instances the dose should be kept as low as possible.
b. Volunteers to whom the intent of the study and the effects of radiation have been outlined.
c. Volunteers who are unlikely to be exposed to significant additional amounts of radiation.

NORMALLY EXCLUDES:

(1) Infants and pregnant women.
(2) Use of the same volunteers for a long series of studies.

VI. SPECIAL REQUIREMENTS FOR THE INDIVIDUAL PRACTICE MEDICAL PROGRAM

(In addition to the General Requirements, cited under Section III, Page 4)

NOTE. A distinction is made between (1) individual medical practice programs confined primarily to the use of radioisotopes in the physician's private office and (2) individual medical practice programs confined to the use of radioisotopes within a medical facility.

A. INDIVIDUAL MEDICAL PRACTICE IN THE PHYSICIAN'S OFFICE

1. Clinical Facilities

The application should state that the physician has access to a hospital possessing adequate facilities to hospitalize and monitor the physician's radioactive patients whenever hospitalization is advisable. This does not refer to the physician's staff privileges at an institution, but rather serves to indicate the institution's willingness to have radioactivity on its premises. From the standpoint of radiological safety alone it is advisable that patients with more than 30 millicuries of radioisotopes internally administered be hospitalized. It is strongly recommended that in all cases a patient containing more than 50 millicuries be hospitalized.

a. The application should set forth the following:
   (1) Arrangements which have been made to provide each hospital with the necessary radiation protection instruments and other special equipment as well as instructions given to staff personnel for the care of radioactive patients to provide adequate radiological health safety.
   (2) Arrangements for notification to hospital authorities of admission of a radioactive patient.

b. A statement should be obtained and retained by the physician from EACH hospital in which he has made arrangements to admit patients containing radioisotopes expressing the institution's

willingness to hospitalize his radioisotope patients and acknowledging receipt of adequate radiological health safety instructions.

2. Radiological Health Safety Measures

The application should set forth the following:

a. Outline of a program to observe adequate health safety standards including adequate instrumentation, careful maintenance of case records and activity inventory with respect to isotope use and disposal.

b. A statement should be presented concerning arrangements that have been made with a readily available radiological safety consultant for both periodic and emergency visits if such services are to be used. Although the applicant physician must possess adequate background and experience in radioactivity to assure radiological safety, he may not wish to perform the duties of a radiological safety officer.

c. Provisions for adequate instrumentation for measurement as well as for maintenance of health and safety standards.

B. INDIVIDUAL MEDICAL PRACTICE IN HOSPITALS

In some instances physicians using radioisotopes in their individual medical practice have found it convenient and/or desirable to carry out such use within a medical institution rather than at their private office. The responsibility for this type of use is solely that of the individual physician; the medical institution simply provides physical space for carrying out the program. This type of use of radioisotopes for medical purposes does not require that the program be carried out under the auspices of a medical isotopes committee.

If the applicant physician wishes to use radioisotopes in a hospital as discussed above, he should obtain and retain in his files a statement from the hospital administration expressing the institution's willingness for radioisotopes to be used within their facilities.

Applications for use of radioisotopes by a physician in his individual medical practice, but where such use is physically located in a medical institution should be supported by the following information:

1. Arrangements made to provide the hospital with necessary radiation detection instruments and instructions to be given staff personnel for the care of radioactive patients whenever they are needed to provide adequate radiological health safety.
2. Arrangements for notification to the hospital authorities of admission of a radioactive patient or of a patient admitted for the administration of radioisotopes.
3. Arrangements made to provide for the receipt and safe storage of radioisotope shipments made to the hospital.

C. RADIOACTIVE PHARMACEUTICALS

Radiomaterials distributed by the Atomic Energy Commission owned laboratories are not necessarily of pharmaceutical quality and are not warranted as to identity, quality or quantity. It is usually desirable, therefore, that a physician using radioisotopes in his individual medical practice purchase them preassayed and of pharmaceutical quality.

If the physician in his individual medical practice wishes

to obtain radioisotopes for human use from AEC laboratories he should include with his application the following information:

1. His experience in standardization and measurement techniques.
2. The procedures to be employed for identifying and assaying the radiomaterial and carrying out such other operations (sterilization, pyrogen tests, etc.) as may be appropriate.

NOTE. When purchasing radiomaterials from an AEC distributor (e.g. Oak Ridge National Laboratory), all non-federal applicants must use a special "Isotope and Service Irradiation Order Form" (Form AEC-391) and federal agencies must use an "Isotope Order Blank" (Form AEC-375). Copies of these forms are available from the AEC distributors and Isotopes Extension. These forms are not intended for use when ordering materials from other than AEC distributors.

VII. RECOMMENDATIONS FOR MINIMUM CLINICAL RADIOISOTOPE EXPERIENCE FOR INDIVIDUAL MEDICAL PRACTICE USE

(In addition to the requirements discussed in Section III C., Page 5, the physician should have clinical radioisotope experience commensurate with the following recommendation(s) applicable to the use(s) proposed on his application.)

A. IODINE 131

1. Diagnosis of Thyroid Function

The physician should work for at least 30 hours in a medical program where Iodine 131 for diagnosis of thyroid function and treatment of thyroid disease is being used.

During the 30-hour period of time the physician should actively participate in such diagnostic studies in at least 10 patients.

NOTE. The Iodine 131, unless otherwise exempted, shall be procured in a precisely calibrated form.

2. Determination of Blood Volume and Plasma Volume

a. The physician should work for at least 30 hours in a medical program where Iodine 131 for blood determination is being used.

During the 30-hour period of time the physician should actively participate in 10 such blood determinations.

b. Physicians already using Iodine 131 in diagnosis of thyroid function can qualify after active participation in 3 such blood determinations.

NOTE. The Iodine 131, unless otherwise exempted, shall be procured in a sterilized and precisely calibrated form.

3. Treatment of Hyperthyroidism and/or Cardiac Dysfunction

The physician should associate himself directly with a medical group using Iodine 131 for treatment of hyperthyroidism and/or cardiac dysfunction for a period equivalent to a minimum of two months' full-time work. Participation during the two-month period need not be on a continuous basis but may be arranged on a schedule suited to the needs of the physician and his medical preceptor. During the period of training the physician should actively participate in the use of Iodine 131 for the treatment of hyperthyroidism and/or cardiac dysfunction in a minimum of 25 patients.

4. Treatment of Thyroid Cancer

The physician should have (1) experience as set forth in 3. above and (2) active participation in the use of Iodine 131 for the treatment of thyroid cancer in a minimum of 5 patients.

NOTE. Such therapy should normally be carried out in and the patient confined to a hospital or other medical institution having in-patient facilities and adequate radiation equipment to assure radiological health safety.

B. PHOSPHORUS 32

1. Treatment of Leukemia, Polycythemia and Allied Blood Dyscrasias

a. The applicant physician should be expert in therapeutic radiology, internal medicine (or hematology) or pathology (Board certification will serve as evidence of such qualification), who has actively participated in the use of Phosphorus 32 for the treatment of leukemia, polycythemia vera and/or other blood dyscrasias in a minimum of 5 patients.

b. Physicians who are not qualified as indicated above, should actively participate in the use of Phosphorus 32 for the treatment of leukemia, polycythemia vera and/or other blood dyscrasias in a minimum of 10 patients.

2. Phosphorus 32 — Chromic Phosphate

a. Intracavity Use in the Palliation of Carcinomatous Patients.

The physician should have (1) substantial experience in the use of Phosphorus 32 as well as other radioisotopes for diagnostic and therapeutic purposes and (2) active participation in the use of P 32-labeled chromic phosphate for the treatment of a minimum of 10 carcinomatous patients.

NOTE 1. Since this therapy is not considered routine and the technique is normally a hospital procedure, the use of Phosphorus 32-labeled chromic phosphate shall be carried out in, and the patient confined to a hospital or other medical institution having in-patient facilities and adequate radiation equipment to assure radiological health safety.

NOTE 2. Applications proposing the intracavitary use of Phosphorus 32-labeled chromic phosphate should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

NOTE 3. The application should clearly state whether the Phosphorus 32-labeled chromic phosphate will be obtained in individually prepared doses or whether such doses will be prepared by the physician from stock solution. If the latter is the case, specific details should be presented concerning assay and safe handling procedures.

b. Interstitial Use in the Treatment of Prostatic and/or Cervical Cancer.

The interstitial use of Phosphorus 32-labeled chromic phosphate for treatment of prostatic and/or cervical cancer is normally limited to institutional medical radioisotope programs being conducted under the auspices of a medical isotopes committee. This limitation is made since the use of chromic phosphate interstitially is still considered to be investigative in nature. The use of radioisotopes by a physician in his individual medical practice is normally limited to well-established medical uses of radioisotopes.

C. GOLD 198 COLLOID

1. Intracavity Use for Palliation of Carcinomatous Patients

The physician shall have (1) substantial experience in the use of equivalent amounts of other gamma emitting radioisotopes for therapeutic purposes, e.g., Iodine 131 for the treatment of thyroid cancer, and (2) active participation in the use of Gold 198 colloid for the treatment of a minimum of 10 carcinomatous patients.

NOTE 1. Because the use of Gold 198 colloid for the above purpose is normally a hospital procedure and the magnitude of the dose used results in a high gamma flux during and after instillation into the patient, this clinical application shall be carried out in and the patient confined to a hospital or other medical institution having in-patient facilities and adequate radiation equipment to assure radiological health safety.

NOTE 2. Applications proposing the intracavity use of Gold 198 colloid should be accompanied by a properly annotated drawing of the infusion apparatus to be used or a literature reference to such apparatus.

NOTE 3. The application should be accompanied by a detailed discussion of the special instructions to be given hospital personnel concerning the care and handling of such patients and the special radiological health safety procedures to be followed.

NOTE 4. The application should state whether the Gold 198 colloid will be obtained in individually prepared doses or whether such doses will be prepared by the physician from stock solution. If the latter is the case specific details should be presented concerning assay and handling procedures.

2. Interstitial Use for Treatment of Prostatic and/or Cervical Cancer

The interstitial use of Gold 198 colloid for the treatment of prostatic and/or cervical cancer is normally limited to the institutional medical radioisotope programs being conducted under the auspices of a medical isotopes committee. The limitation is made since the use of gold colloid interstitially is still considered to be investigative in nature. The use of radioisotopes by a physician in his individual medical practice is normally limited to well-established medical uses of radioisotopes.

D. CHROMIUM 51

Determination of Blood Volume, Plasma Volume and Erythrocyte Survival

The physician should work for at least 30 hours in a medical program where Chromium 51 is being used for blood determinations.

During the 30-hour period of time the physician should actively participate in 10 such blood determinations.

VIII. DESIRABLE CLINICAL EXPERIENCE FOR MEDICAL USE OF SEALED RADIATION SOURCES

The recommendations for training and experience, as set forth below, for use of radioisotopes as sealed radiation sources for external, interstitial or intracavitary therapy are applicable to both institutional programs and individual medical practice.

Where the use of radioisotopes in medical institutions is to be limited to sealed radiation sources for well established intracavitary, interstitial or external therapeutic procedures, a medical isotopes committee is not necessary.

A. TELETHERAPY UNIT

A separate announcement entitled, "Present Procedures of the Atomic Energy Commission for the Allocation of High Intensity Gamma Radioisotope Sources for Teletherapy Devices," is available from the Isotopes Extension upon request.

B. SEALED AND PARTICULATE RADIATION SOURCES FOR INTERSTITIAL, SURFACE OR INTRACAVITARY USE

The physician should be (1) a qualified specialist in therapeutic radiology (diploma of the American Board of Radiology will serve as evidence of such qualification) in addition to having at least three years' experience in therapeutic radiology or (2) a qualified specialist in another field (diploma of the respective specialty board will serve as evidence of such qualification) appropriate to the use being proposed, with training and experience in radiation dosimetry in addition to having at least three years' experience in interstitial, surface or intracavitary use of radiation sources.

NOTE. If the radioisotope requested is to be used as an adjunct to or replacement for radium, information should be presented concerning the means by which radium dosages are to be converted to dosages in terms of the radioisotope requested and the procedure to be employed to account for the decay of the latter.

C. BETA-RAY APPLICATORS

1. Superficial Lesions of the Eye

The physician should be a qualified specialist in therapeutic radiology, or ophthalmology (diploma of the appropriate specialty board will serve as evidence of such qualification), in addition to having at least three years' experience in such specialty. The three years' experience should include the use of beta-rays or soft x-rays in the treatment of superficial lesions of the eye. The applicant should furnish evidence of knowledge and experience concerning the problem associated with beta-ray depth dosage.

2. Superficial Lesions of the Skin

The physician should be a qualified specialist in dermatology or therapeutic radiology (diploma of the appropriate specialty board will serve as evidence of such qualification) in addition to having at least three years' experience in such specialty. The three years' experience should include the use of beta-rays or soft x-rays in the treatment of superficial lesions of the skin. The applicant should furnish evidence of knowledge and experience concerning the problems associated with beta-ray depth dosage.

NOTE. The present procedures of the Atomic Energy Commission for sealed radioisotope sources such as are contained in beta-ray applicators require that they be tested for leakage of radioactivity at intervals of 6 months. A separate announcement concerning leak testing requirements is available from the Isotopes Extension.

IX. RADIOACTIVE MATERIALS AND SERVICES

The radioactive materials and special irradiation services available from the Atomic Energy Commission are described in the catalogs and bulletins issued by the operating contractors of the Commission: the Oak Ridge National Laboratory, Brookhaven National Laboratory, Argonne National Laboratory and National Reactor Testing Station. A number of commercial concerns also offer materials and services in areas of radioisotope distribution.

NOTE. When purchasing radiomaterials or related services from an AEC distributor (e.g. Oak Ridge National Laboratory), all non-federal applicants must use a special "Radioisotope and Service Irradiation Order Form" (Form AEC-391) and federal agencies must use an "Isotope Order Blank" (Form AEC-375). The isotope order blank and isotope order form incorporate certain terms and conditions; copies are available from AEC distributors and the Isotopes Extension. These forms are not intended for use when ordering materials from other than AEC distributors.

On pages 18-21 are the two application forms for "Byproduct Material License." They have been filled out as an example of a representative application. Accompanying these two forms, we have reproduced the U.S. Atomic Energy Commission's Instructions.

U. S. ATOMIC ENERGY COMMISSION

INSTRUCTIONS FOR PREPARATION OF "APPLICATION FOR BYPRODUCT MATERIAL LICENSE," FORM AEC-313 AND SUPPLEMENTS "A" AND "B"

GENERAL INFORMATION

An applicant for a "Byproduct Material License" should complete Form AEC-313 in sufficient detail to permit a realistic evaluation by the AEC of the radiological safety aspects of the proposed use of byproduct material.

A "Byproduct Material License" can be issued for more than one byproduct material and for multiple uses, but use will ordinarily be limited to one location. It may be more convenient and desirable to present supporting information using a separate form AEC-313 for each byproduct material.

Two copies of completed form AEC-313 should be forwarded to the Isotopes Extension, Division of Civilian Application, U. S. Atomic Energy Commission, P. O. Box E, Oak Ridge, Tennessee. An extra copy of the form is furnished for those applicants who may wish to prepare a duplicate file copy for their retention.

Provided Form AEC-313 is completed in the detail requested thereon, AEC review will ordinarily require from one week to one month, depending upon the nature of the proposed application. New and unique proposals will, in general, require more time for review than will routine applications where experimental techniques and radiological safety precautions are well established. Submission of an incomplete Form AEC-313 will result in unnecessary delay and correspondence.

If space is inadequate on the form, the applicant should include information on an additional sheet or letter and attach to the application.

Form AEC-313

(Items not discussed here are self-explanatory on the form)

Specific Instructions

1. (a) The "applicant" is the organization or person which

ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE

INSTRUCTIONS: Complete Items 1 through 19 if this is a new application. If renewal is requested, complete only Items 1 through 11 provided that with respect to the other items there has been no change in the information previously submitted. Mail two copies to: U. S. Atomic Energy Commission, P. O. Box E, Oak Ridge, Tennessee, Attention: Isotopes Extension, Division of Civilian Application. Upon approval of this application, the applicant will receive an AEC Byproduct Material License. General requirements for issuance of an AEC Byproduct Material License are contained in Title 10, Code of Federal Regulations, Part 30.

John A. Doe, M. D.
202 South Cedar, Ann Arbor, Michigan

202 South Cedar, Ann Arbor, Michigan

Personal use in my individual medical practice.

John A. Doe, M. D.

None

None

BYPRODUCT MATERIAL OR IRRADIATION SERVICE DESIRED

Iodine 131
Cr 51
Co 60

Sodium radio-iodide (I 131)
Abbott List # 6700-----25 millicuries
(Cyanocobalamine) Radiocaps, Abbott list #6766

Not desired

STATEMENT OF USE

See supplement "A"

CERTIFICATE

State of Michigan
County of Washtenaw
Subscribed and sworn to before me this 23rd day of February, 1956
Mabel Smith

John A. Doe, M.D.

WARNING

18 U. S. C., Section 1001; Act of June 25, 1948; 62 Stat. 749; makes it a criminal offense to make a willfully false statement or representation to any department or agency of the United States as to any matter within its jurisdiction.

ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE Page Two

INSTRUCTIONS: Complete Items 12 through 19 if this is a new application. This information may be omitted from subsequent applications provided there is no change in the information previously submitted, and reference is made in Item 5 to the application on which this information appears.

TRAINING AND EXPERIENCE WITH RADIOACTIVITY OF INDIVIDUAL USER NAMED IN ITEM 3

1.	University Hospital Ann Arbor, Michigan	eight weeks	(Yes) No	(Yes) No
2.	"	" "	(Yes) No	(Yes) No
3.	"	" "	(Yes) No	(Yes) No
4.	"	" "	(Yes) No	(Yes) No
5.	"	" "	(Yes) No	(Yes) No

I 131	250 millicuries	Radioisotope Unit	8 weeks	Medical
RISA	50 millicuries	University Hospital	8 weeks	
Cr-51	20 millicuries	Ann Arbor, Michigan	8 weeks	
P-32	50 millicuries		8 weeks	

PHYSICAL FACILITIES, EQUIPMENT, AND RADIATION INSTRUMENTATION

Portable Survey Meter (Tracerlab #SU-14)--one — beta, gamma — 0-25mr/hr — 30mg/cm.² — monitoring & surveying.
Tracerlab Scaler, Model #SC-33A
Medical Scintillation Detector # P-20M ---------------- for tracer studies

None

Portable survey meter: mr/hr. ranges calibrated on gamma rays from cobalt checking source.
Scintillation detector: will be used for comparative counting of patient against standardized doses from Abbott Labs.

One 1" lead pig for storage of Radiocaps (Abbott).

Yes (No)

Recommendations outlined in Bureau of Standards Handbook to be followed.

ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE

SUPPLEMENT A—HUMAN USE—PAGE 1

John A. Doe, M.D.
202 South Cedar
Ann Arbor, Michigan

PROPOSED DIAGNOSTIC OR TREATMENT

Diagnosis: Thyroid function, pernicious anemia, plasma volume and blood volume determinations.
Treatment: Thyroid hyperfunction, thyroid carcinoma, intractable heart disease, polycythemia vera, chronic granulocytic leukemia.

Sodium iodide (NaI) Sodium phosphate (Na_2PO_4)

Remote handling equipment - 8 inch forcep - ½ inch lead containers for I131 & P32. Treatment doses to be ordered precalibrated for use on the day of arrival from the Abbott Laboratories. Heavy rubber gloves worn when administering treatment doses. Separate rubbish disposal containers to allow sufficient time for decay before discarding.

PROPOSED DOSAGE SCHEDULE

Thyrotoxicosis -------------- Maximum 10 to 12 millicuries I131

Intractible heart disease ---- " 15 to 20 " "
Polycythemia vera and chronic
granulocytic leukemia ----- " 3 to 5 " P32

Material for testing and treatment will always be obtained in individual pre-calibrated and pharmaceutically correct form from the Abbott Laboratories.

HOSPITAL FACILITIES FOR INDIVIDUAL PRACTICE USE ONLY

ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE

SUPPLEMENT A—HUMAN USE—PAGE 2

John A. Doe, M.D.
202 South Cedar
Ann Arbor, Michigan

A ISOTOPE	B CONDITIONS DIAGNOSED OR TREATED	C NUMBER OF CASES	D TYPE OF PARTICIPATION FOR ALL CASES IN COLUMN C
I 131	[illegible]	264	50 / 254
	[illegible]	17	
	[illegible]	8	
	[illegible]	9	
	[illegible]		1 2 3 4
	[illegible]	40	8 / 32
	Others: PBI I131 Conversion	15	5 / 12
	Intestinal Absorption Test	8	4 / 6
P 32	[illegible]	14	
	[illegible]		1 2 3 4
	[illegible]		1 2 3 4
	Others		1 2 3 4
			1 2 3 4
P 32 $CrPO_4$	[illegible]		1 2 3 4
	[illegible]		1 2 3 4
	[illegible]		1 2 3 4
	Others		1 2 3 4
			1 2 3 4
Au 198 Colloid	[illegible]		1 2 3 4
	Treatment of cervical cancer		1 2 3 4
	[illegible]		1 2 3 4
	Others		1 2 3 4
			1 2 3 4
Cr 51	[illegible]	11	4 / 7
	Others		1 2 3 4
			1 2 3 4
Other Isotopes			1 2 3 4
			1 2 3 4
			1 2 3 4

Total number of hours of experience in clinical training: 160 hours

W. H. Beierwaltes, M.D., University Hospital

will be responsible for possession and use of the byproduct material specified in the application.

(b) Indicate address at which byproduct material will be located and used.

2. The "department" is the department or similar subdivision (of the applicant) which will use the byproduct material.

3. The "individual user" is the qualified person, or persons, who will use or directly supervise the use of the radioisotope or radioactive material. If the application is for "human use," the user named in item 3 must be a physician licensed by a State or Territory of the United States to dispense drugs in the practice of medicine. It is not necessary to furnish information regarding persons supervised by the individual user.

5. If renewal is requested, give previous AEC license or authorization number, (e.g., AEC 23542) and a reference to your previous application (e.g., No. 123, X Company, Dept. B, Richard Roe). If this is a new application insert "Not Applicable."

6. Specify the byproduct material desired such as "Carbon 14."

7. State the chemical or physical form such as "solid $BaCO_3$". If the catalog number is known, this may be stated such as "ORNL-C-14-P-1."

8. State the MAXIMUM amount in millicuries of all byproduct materials requested in Item 6 that will be possessed at any one time. This amount should be consistent with physical facilities and handling equipment and procedures stated in Items 10(b), 18, and 19.

10. The purpose for which the byproduct material will be used should be stated briefly in 10(a) but in sufficient detail to permit a realistic evaluation of radiological safety procedures described in 10(b). If "human use" is involved insert "See Supplement A."

11. The Certificate should be signed by the applicant or an appropriate official on behalf of the applicant. The signature, under oath (or affirmation) should be notarized.

NOTE. All items (1 through 19) should be completed on a first application. If information under Items 12 through 19 has been furnished previously and there have been no changes in information furnished, these items need not be completed on later applications, but a reference should be made in Item 5 to the previous application on which the information appears.

12. Complete information regarding radioisotope training and isotope handling experience should be given to demonstrate that the user has a working knowledge appropriate to the proposed use. Use additional sheet if necessary. A full and complete answer will facilitate handling of future applications as well as the current one.

FORM AEC 313a

If byproduct material is desired for "human use," Supplement A —Human Use—Page 1 and, if appropriate, Supplement A—Human Use—page 3, should be completed in addition to the basic application Form AEC-313.

Specific Instructions

Item No. — Supplement A—Human Use—Page 1

3. Federal Regulations provide that the using physician have "extensive experience in the proposed use, the handling and administration of radioisotopes and, where applicable, the clinical management of radioactive patients. (The physician shall furnish suitable evidence of such experience with his application.)" Supplement A—Human Use—Page 3 is provided for conveniently presenting these details.

4. Describe purpose or use of each byproduct material, chemical form administered, and radiological safety procedures to be followed in sufficient detail to permit a realistic evaluation of the potential radiological safety hazards.

5. (a) Dosage for routine treatment of patients will depend upon the clinical judgment of the responsible physician and the AEC is only interested in the proposed dosage range. Routine medical uses are considered to be:
   (1) diagnosis and therapy of thyroid disease and cardiac conditions;
   (2) brain tumor localization;
   (3) liver function tests;
   (4) therapy of polycythemia vera and leukemia;
   (5) therapy of carcinoma metastatic to bone;
   (6) tracer blood studies (e.g., blood volume, red cell mass, etc.);
   (7) peripheral vascular disease studies (e.g., circulation time determination);
   (8) intracavitary administration in cases of effusion and ascites; and
   (9) interstitial use in cases of cervical and prostatic carcinoma.

   (b) For experimental programs or new and unusual uses, the maximum single dose of radiomaterial to be administered should be included and the approximate number and frequency of such doses. Rationale for unusually high dosages should be presented. The proposed use should be outlined in detail demonstrating that radiological health safety will not be jeopardized. If the use duplicates or is based on a use reported in the technical literature, an abstract of such a report or article and a brief statement as to how such use will be followed or modified will suffice.

6. Radioisotopes furnished by AEC facilities are pharmaceutically UNREFINED. An applicant should include information regarding processing or standardization procedure if byproduct material will not be obtained in precalibrated form for oral administration or precalibrated and sterilized form for parenteral administration.

Specific Instructions

Item No. — Supplement A—Human Use—Page 3

9 (a), (b), 10, 11, 12 To be completed by using physician.

It is recommended that these items be completed by the using physician's preceptor in the medical use of radioisotopes who may be the chairman of the medical isotopes committee of the institution where experience was acquired or the licensed physician under whom the using physician's radioisotope training and experience was acquired. Care should be exercised not to omit information called for. If possible, the using physi-

cian's entire clinical radioisotope experience should be included. Additional comments may be presented in the space provided on page 4.

Form AEC-313b

If byproduct material is to be used in or manufactured as a sealed source, Supplement B should be completed in addition to the basic application Form AEC-313.

Information on file with the Isotopes Extension need not be repeated, but appropriate reference to such information will suffice.

Item No.	Specific Instructions
1-3	are to be completed by an applicant who will use the sealed source—e.g., a firm using a beta ray thickness gage, a physician using a beta ray eye applicator.
4-20	are to be completed by applicants who will fabricate or manufacture a sealed source. If the source is designed to transmit only gamma rays and contains in elemental form (but not powder) Cobalt 60, Iridium 192, Gold 198, Tantalum 182, or Thulium 170, Item 4 should be completed by the manufacturer and other items may be disregarded.
13-18	are applicable only if a sealed source is to be mounted in a device such as a thickness gage, gamma ray camera, static elimination device, etc.

If the user processes the isotope himself, he must fill out and send in Form 465, an example of which follows:

Form AEC-465
(Revised 4-53)

Budget Bureau No. 38-R032.2
Approval Expires April 30, 195

UNITED STATES
ATOMIC ENERGY COMMISSION
CERTIFICATE OF COMPLIANCE WITH FEDERAL FOOD, DRUG, AND COSMETIC ACT

(For use only when purchasing from AEC distributors)

Regulations in effect under section 505(i) of the Federal Food, Drug, and Cosmetic Act provide that the shipper have the following statement on file prior to distribution of radioelements in interstate commerce if the material is intended for drug use or investigation, whether for experimental animals or human beings.

One copy of this statement must be signed and forwarded with your purchase order for radioisotopes.

This is to certify that any portion of a shipment or delivery of a radioisotope received under AEC Authorization No. , which is used as a drug will be employed solely for investigational use by, or under the direction of, an expert qualified by scientific training and experience to evaluate the safety of the drug, unless and until an application becomes effective with respect to such drug, in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act.

Date: August 2, 1955
Signature: James D. Smith, M. D.
Title: Chief, Medical Service
Institution or Firm: Community Hospital

A MINIMUM KNOWLEDGE OF RADIOACTIVITY

The physician must have a certain minimum knowledge of radioactivity to understand the use of radioisotopes in clinical practice. We wish to present this information in as simple a manner as possible and yet make it as accurate as the needs of a physician require. Since radioactivity is an atomic phenomena, we will start with a simplified description of an atom.

The Atom

An atom consists of an inner section or "nucleus" around which rotate small particles called "electrons." This combination is in effect a miniature solar system, the nucleus representing the sun and the electrons representing the encircling planets (Fig. 1).

The diameter of the nucleus is approximately 10^{-13} cm.* while the diameter of the atom as a whole, i.e., the electron orbit, is about 10^{-8} cm. Thus the ratio of the size of an atom to the size of its nucleus is $\frac{10^{-13}}{10^{-8}} = 10^5$. If we were to draw an atom to scale using a circle one inch in diameter for the nucleus, the diameter of the electron orbit would be about 1.6 miles! It is readily apparent from these considerations that what we ordinarily think of as solid matter is in reality mostly empty space.

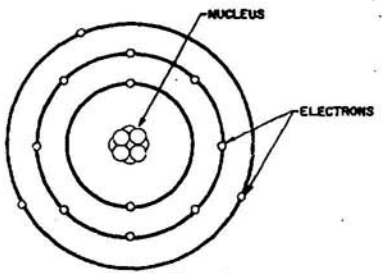

Figure 1. Diagram of an atom.

Since almost all of the weight of an atom is in the nucleus, we can compute the density of the nucleus by first determining the weight of a single atom (the gram atomic weight† divided by Avogadro's number‡). This weight is then divided by the volume of the nucleus.

* $10^{-13} = \frac{1}{10^{13}} = \frac{1}{10{,}000{,}000{,}000{,}000}$ cm.

† Gram atomic weight = the atomic weight expressed in grams.

‡ Avogadro's number = (6.02×10^{23}) = the number of atoms (molecules) in a gram atomic (gram molecular) weight.

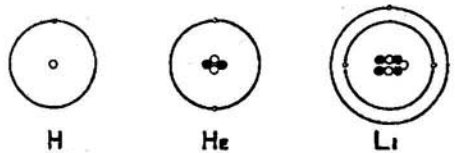

Figure 2. Atomic structure of hydrogen (H), helium (He) and lithium (Li).

When this simple calculation is performed, the density of the nucleus is found to be about 40 million tons per cubic centimeter!

All material is constructed from three simple building blocks. The *electrons* rotate about the nucleus. The two other building blocks, the *proton* and the *neutron*, are within the nucleus. The proton weighs about 1.7×10^{-24} grams and has a positive electrical charge. The neutron has approximately the same weight but no electrical charge. The electron weighs only $\frac{1}{1840}$ times as much as the proton or neutron but it has a negative electrical charge equal in magnitude to that of a proton, but of opposite sign.

To show how matter is constructed, let us examine the first three elements of the chemical periodic table. The first element is hydrogen (Fig. 2). Its atoms consist of a single proton in the nucleus and one electron in an orbital ring. The next element is helium (He). A helium atom is made up of two neutrons and two protons in the nucleus and two electrons in orbital rings. The third element is lithium whose atoms each have three protons and four neutrons in the nucleus and three electrons in three orbital rings (Fig. 2). Note that (unless we ionize an atom by removing or adding electrons) the number of electrons equals the number of protons. The atom is therefore electrically neutral.

An *atomic number* (Z) is given to each atom according to the number of protons the atom contains in its nucleus. This is the same as the atomic number assigned to the element in the chemical *periodic table*.

Isotopes

When the physicist began to determine *atomic weights* of elements, he did it by shooting beams of ionized atoms into a magnetic field and observing how they were deflected. The principle is as follows: If an electrically charged atom moves through a magnetic field, the field exerts a force on the moving atom perpendicular to the direction of motion. In a uniform magnetic field perpendicular to the direction of motion

CHAPTER 3
RADIOISOTOPE PROGRAM

CONTENTS

CHAPTER 3. RADIOISOTOPE PROGRAM

CHAPTER 3. RADIOISOTOPE PROGRAM

3.01 STATEMENT OF POLICY

The VA will provide suitable facilities for, and a staff properly qualified in, the use of radioisotopes in clinical diagnosis, treatment, and medical research within selected VA hospitals.

3.02 AUTHORIZATION FOR USE OF RADIOISOTOPES

Radioisotopes will be used for clinical diagnosis, medical treatment, or research only in those VA hospitals or centers specifically approved by the Assistant Chief Medical Director for Research and Education upon the recommendation of the Central Advisory Committee on Radioisotopes.

a. Approval will generally be given only to a hospital having an approved Radioisotope Service.

b. Requests may be submitted for the use of radioisotopes in diagnosis or treatment of patients in hospitals not having a Radioisotope Service, provided there is available locally a hospital or clinic which has been approved by the U. S. Atomic Energy Commission for the receipt of radioisotopes and where the desired procedure may be carried out if it is not deemed feasible to transfer the patient to a VA hospital having a Radioisotope Service.

3.03 ESTABLISHMENT OF RADIOISOTOPE SERVICES

Radioisotope Services will be established in selected VA hospitals as authorized and approved by the Chief Medical Director.

3.04 ORGANIZATION OF RADIOISOTOPE SERVICE

a. A physician, qualified in the use of radioisotopes, will be designated Chief, Radioisotope Service. He may be appointed on a full-time, regular part-time, or additional-duty basis. The Radioisotope Committee representing the Deans Committee will recommend a qualified physician to the Deans Committee which, in turn, will make the appropriate recommendation to the Manager. The Manager will forward the recommendation with supporting documents for the approval of the Assistant Chief Medical Director for Research and Education.

b. A Radioisotope Committee representing the Deans Committee will be appointed to advise and assist in formulating a proposed plan for the Radioisotope Service. Actions of the committee will at all times be subject to review by, and the approval of, the Deans Committee. The Deans Committee will nominate committee members. The chairman of the Radioisotope Committee will be a physician, and the committee will include representation of the professional and scientific specialties recommended by the U. S. Atomic Energy Commission. The Manager will forward the nominations for the approval of the Assistant Chief Medical Director for Research and Education. Full-time VA employees may not be appointed to this committee. For purposes of the U. S. Atomic Energy Commission, this Radioisotope Committee serves as the "Local Isotope Committee." It advises the Manager and Chief, Radioisotope Service, on all matters of a professional, scientific, or technical nature in the administration and operation of the Radioisotope Service, including matters of radiological safety.

c. Personnel for key positions with the Radioisotope Service will be appointed on nomination of the Radioisotope Committee through the Deans Committee.

d. A Hospital Radioisotope Committee will be appointed by the Manager before radioisotopes are used for clinical purposes. The Director, Professional Services, will be designated as chairman and the Chief, Radioisotope Service, as secretary, with such other chiefs of services as members, as desired. The committee advises the Manager regarding administrative policies involving representatives of the Radioisotope Service and those of the clinical services, as well as between these services, in matters relating to the use of radioisotopes in patients within the hospital.

e. Within the Radioisotope Service, there are three sets of functions which must be clearly recognized and provided for in the staffing pattern of the service. These are:

(1) Administrative matters, including radiological safety;

(2) Scientific activities within the radioisotope laboratories; and

(3) Clinical activities involving the human application of radioisotopes.

The organizational pattern within the service must show assignment of responsibility for these sets of functions.

f. The Radioisotope Service is not a part of the general medical research program and is not under the jurisdiction of the hospital Research Committee.

g. The Chief, Radioisotope Service, is, for administrative purposes, responsible to the Director, Professional Services.

3.05 PERSONNEL COSTS

a. The costs of full-time or part-time physicians and nurses and housekeeping and janitorial employees will not be charged to radioisotope research funds but will be furnished from general hospital funds (program 8400).

b. Scientific, technical, and clerical personnel serving in the Radioisotope Service may be employed with funds specifically provided under program 8210.

3.06 RESPONSIBILITIES IN USE OF RADIOISOTOPES

a. The use of radioisotopes will be in accordance with policies and regulations established by the U. S. Atomic Energy Commission and with policies recommended by the Central Advisory Committee on Radioisotopes and approved by the Chief Medical Director.

b. The Chief, Radioisotope Service, is responsible for approving and carrying out such clinical uses of radioisotopes, including those for clinical investigation, as may be requested or approved by chiefs of services in accordance with the general policies approved by the Radioisotope Committee representing the Deans Committee.

c. The chief of the service to which a patient is assigned is responsible for the medical care of the patient, and a patient on his service will not receive a radioisotope without prior approval of the chief of the service or the person acting for him.

d. Studies involving the effects of external radiation are not considered appropriate activities of the radioisotope program.

e. Clinical use of Sr-90 applicators, Co-60 needles, teletherapy devices, or other external radiation sources are properly the responsibility of the Radiology Service, though the Radioisotope Service within a VA hospital may assist in technical matters of procurement or calibration when desired.

3.07 RADIOLOGICAL SAFETY PLAN

a. Before applications for radioisotope procurement are submitted, a complete radiological safety plan must be prepared by the Chief, Radioisotope Service, with the assistance and approval of the Radioisotope Committee representing the Deans Committee, and a Radiological Safety Officer must be specifically assigned responsibility for effecting the plan. In the discharge of these duties, he will be responsible to the Chief Radioisotope Service, who will, in turn, be directly responsible to the Manager for matters of radiological safety.

b. Complete records will be maintained for radiological safety purposes. These records will include:

(1) Records of all radioactive materials received, in storage, and expended;

(2) Film badge and pocket chamber readings for all personnel working with radioisotopes or exposed to their radiations;

(3) Results of health examinations and blood counts for personnel working with radioisotopes. Complete blood counts of unit employees must be made when employed, when separated, and at such other intervals as may be recommended by the Radioisotope Committee representing the Deans Committee.

3.08 RADIOISOTOPE PROCUREMENT

a. Applications for licenses for possession and use of byproduct material (radioisotopes) will be prepared on AEC Form 313 in accordance with U. S. Atomic Energy Commission requirements and submitted in triplicate to Department of Medicine and Surgery (153A), Veterans Administration Central Office, Washington 25, D. C. For uses in humans or for sealed sources, the application will include AEC Form 313a or AEC Form 313b, as appropriate. Requests for the necessary AEC forms will be addressed directly to Isotopes Extension, Division of Civilian Application, U. S. Atomic Energy Commission, P. O. Box E, Oak Ridge, Tennessee. A single application may include all required radioisotopes, attaching separate pages if space requires. The certificate, item 11 of AEC Form 313, will be signed by the Chief, Radioisotope Service. This signature does not require notarizing. Each application will be approved by the Radioisotope Committee representing the Deans Committee. A statement of committee approval will be attached to the third copy. Requests for amendments to existing licenses, or supplemental applications, will be routed in the same manner as the AEC Form 313.

b. The cost of radioisotopes procured for use in clinical diagnosis and therapy will be charged to the inpatient-care program and not to research funds.

3.09 USE OF RADIOISOTOPES IN VA PATIENTS IN NON-VA INSTITUTIONS

VA hospitals without authorized Radioisotope Services desiring to utilize non-VA hospitals or clinics for diagnostic or therapeutic procedures involving radioisotopes will submit requests to the Department of Medicine and Surgery (153A), Veterans Administration Central Office, Washington 25, D. C. These request will include the name of the AEF-approved hospital or clinic to provide the procedures. The physician administering the radioisotopes is responsible for determining when the patient may be returned to the VA hospital without radiological hazard.

3.10 UNIFORMS

Uniforms prescribed in VA Circular 11, 1955, will be worn by Radioisotope Service personnel. Coats worn by scientific and technical personnel working within the radioisotope laboratories will not be worn in other areas of the hospital. Uniforms and rubber shoes or boots worn by laboratory animal caretakers will be kept in the animal area and not worn in other parts of the hospital. Shoes and clothing will be monitored for radioactive contamination daily, as arranged by the Radiological Safety Officer.

3.11 GRANTS, GIFTS, AND DONATIONS

Acceptance of grants, gifts, and donations will be in accordance with part XIII, DM&S Manual M-2.

3.12 PAPERS AND NEWS RELEASES

Professional, scientific, and technical papers, as well as scientific exhibits, and news releases relating to the use of radioisotopes will be cleared in accordance with paragraphs 405.20b and 405.22, part I, VA Manual MP-1, and, in addition, will be given prior approval by the Radioisotope Committee representing the Deans Committee.

3.13 EMPLOYEE TRAVEL FOR RESEARCH PURPOSES

Requests for employee travel for research purposes will be submitted to the Department of Medicine and Surgery (153A), Veterans Administration Central Office, Washington 25, D. C., at least 30 days prior to desired date of travel, giving name of traveler, date, places and purpose of travel, method of travel, and estimated cost of travel and per diem.

3.14 REPORTS

a. A narrative annual progress report will be submitted by each Radioisotope Service, covering the fiscal year. This report will be prepared in accordance with an outline supplied annually by the Assistant Chief Medical Director for Research and Education and must reach the Radioisotope Division not later than July 31. Reports Control Symbol 10-108 has been assigned to this report.

b. A Bio-Sciences Information Exchange "Notice of Research Project" will be prepared for each active research study initiated in the Radioisotope Service. The blank forms may be obtained from, and the completed forms will be submitted to, the Department of Medicine and Surgery (15), Veterans Administration Central Office, Washington 25, D. C. The form requires a summary, not to exceed 200 words, of the proposed study. This summary will be carefully worded to explain properly the purpose and methods of the study, and sufficiently explicit to permit indexing under all categories with which the study is concerned. Submission of these forms is a continuing responsibility, to cover each new study and such annual revision as may be requested by the director of the exchange. Reports Control Symbol 10-120 is assigned this report.

VETERANS ADMINISTRATION
NUCLEAR MEDICINE PROGRAM

In 1947 Dr. George M. Lyon was released from active duty as a captain in the Navy Medical Corps, and joined the Veterans Administration with the title Special Assistant to the Chief Medical Director for Atomic Medicine. This position was set up to prepare for the proper evaluation of future claims, from veterans who might claim injuries from exposure to atomic radiation. Dr. Lyon had been a pediatrician in Huntington, W.Va., but held a commission inthe U.S. Naval Reserve and had been called to active duty about 1941. He had been involved with the Manhattan Project, had experience with safety aspects of the thermal diffusion plant tried as a means of concenttrating fissionable uranium, was present for the first atomic bomb test in Alamagordo in 1945, and had served as personnel safety advisor to Admiral Blandy for the bomb tests at Bikini in 1946. Since this area was not being publicized and was in the area of research, Dr. Lyon's office was made a part of the Research and Education organization, with Dr. E.H. Cushing as the Assistant Chief Medical Director. At this time Dr. Paul B. Magnuson was the Chief Medical Director.

The only other person who was considered a part of this Atomic Medicine effort at first was Dr. Charles Spruitt, a retired Brig. Gen. in the Army Medical Corps, who was employed as a consultant, doing library research to compile statistics on radiation injuries.

Also in 1947 radioisotopes became available to medical investigators under strict licensing requirements of the Atomic Energy Commission. Recognizing the need for coordination of any use of radioisotopes in VA hospitals, a Radioisotope Section was set up in the Research Service, and Dr. Lyon wore a second hat as Chief, Radisotope Section. In early 1948, I believe, Dr. Lyon recruited Dr. Herbert C. Allen, Jr. as his Assistant Chief, Radioisotope Section. Dr. Allen was newly released from active duty in the Air Corps, as a flight surgeon, and agreed to help in the starting of this new program if he could later be assigned to a VA hospital to actually practice atomic medicine. In keeping with this commitment, Dr. Allen was transferred to the VA Hospital, Van Nuys, Calif. in late 1948. He later moved to the VA Center, Los Angeles and subsequently to the VA Hospital, Houston, Texas.

In July 1948, I , A. Graham Moseley Jr., agreed to join Dr. Lyon, to succeed Dr. Allen. I had been a college chemistry teacher for about 20 years , the past 18 at Marshall College in Huntingon, W.Va., where I

I had known Dr. Lyon. I was commissioned a Lt.(jg) in t he Naval Reserve and placed on active duty in July 1942. Upon release in December 1945 I returned to my teaching, but went back on active duty to serve as a radiological safety monitor in Operation Crossroads, the Bikini bomb tests in 1946.

At the time I joined the program there were eight VA hospitals using radioisotopes to some extent. These were: 1946

VAH Framingham, Mass.	VAH Bronx, N.Y.
VAH Cleveland, Ohio	VAH Hines, Ill.
VAH Minneapolis, Minn.	VAH Dallas, Texas
VAH Van Nuys, Calif.	VAC Los Angeles, Calif.

Dr. Lyon had set up a Central Advisory Committee on Radioisotopes, which held frequent meetings to review policy and activities of the program. The committee also advised Dr. Lyon, I am sure, on matters relating to his Special Assis tant for Atomic Medicine duties. The Members of this committee were:

Dr. Shields Warren, Boston	Dr. Perrin H . Long , Baltimore
Dr. Stafford L. Warren, Rochester (later, Los Angeles)	Dr. Hymer Friedell, Cleveland
	Dr. Hugh Morgan, Nashville

These experts also served as consultants to the VA hospitals in their areas, as needed.

Late in 1948 Dr. Lyon recruited Harold F. Weiler to join the Radioisotope Section Staff. Mr Weiler had been a public school teacher and administrator in Fairfax County, Va., and was teaching in a private school in Alexandria at that time.

Early in 1950, I believe, Dr. Cushing resigned as ACMD for Research and Education, with about 3 years remaining of his current four year term. Dr. Lyon was appointed to fill this unexpired term. Dr. Lyon reorganed the office, retaining the three divisions, (research, edumation, and atomic medicine). Under research General Medical Research was under Harold F. Weiler as Chief, and I was made Chief of Radioisotope Research. During this approximate time also, Dr. Magnuson resigned as Chief Medical Director and Dr. William S. Middleton became his successor.

Also, about this time (1950) Dr. W. Edward Chamberlain was brought in, to assume Dr. Lyon's duties as Special Assistant for Atomic Medicine but titled as Chief Atomic Medicine Service, and the Radioisotope Division was designated under that service.

In 1953, I believe, Dr. Lyon's appointment as ACMD for R.& E. expired and he left Central Office to become Director of the VA Hospital in Huntington, W.Va.. After a period when Dr. John C. Munemaker served as Acting ACMD for R. & E. , Dr.John B. Barnwell was appointed ACMD for R. & E..

During the terms of Drs. Cushing and Lyon , Mr. Ralph T. Casteel had served as Special Assistant to the ACMD for R.& E, handling most administrative matters for all of R. & E. . Soon after Dr. Barnwell's appointment Mr. Casteel was promoted to a position as Special Assistant to the Chief Medical Director, and I was asked to take over the position as Special Assistant to the ACMD (Dr. Barnwell). I did not want to relinquish the radioisotope program, but agreed to try to handle both for a trial period. This trial period turned out to be for a period of about nine years during which I wore both "hats", under Dr. Barnwell and his successors, Dr. James Musser and Dr. E.E. Wells, until about a year before my retirement, when I was relieved of the Special Assistant duties and gave full time to the Radioisotope Program.

During this period the use of radioisotopes had expanded greatly, and at the time of my retirement in 1966 , there were radioisotopes in use in sixty six VA hospitals.

During all these years the use of radioisotopes had been carried as a research activity, and funded entirely (except for physicians' salaries) from funds appropriated for research. The rapidly expanding use of radioisotpes for diagnostic purposes, and to a lesser degree for therapy, indicated that we were getting to the stage Dr. Lyon had foreseen. In 1964, I believe, I was successful in getting funds from the patient care category to those hospitals doing clinical radioisotope work, and recovered some research funds for other uses. The amount here was not nearly the total budget needed for the clinical program, but was a start in this direction. This was the first step toward what Dr.Lyon had foreseen as a part of patient care, after the early days of research support.

In 1965 the Atomic Energy Commission licensing division began to relax the stringent requirements for individual licensing of each radioisotope and each use, and we selected the VACenter in Los Angeles as the first to apply for a broad medical license, the uses and isotopes.within a stated group, to be approved by a local Isotope Committee.This was approved by the AEC and several other VA hospitals were approved within the next six months or so.

In early 1966, I arranged a meeting of several VA physicians using radioisotopes, at the VA hospital in Minneapolis, where we discussed the growing clinical applications of radioisotopes and drew up a proposal for the establishment of a Nuclear Medicine Service in the Department of Medicine and Surgery. This proposal was submitted, through the Deputy Chief Medical Director, who referred it to the Assistant Chief Medical Director for Professional Services for review and comment. The proposal disappeared for several months, but in the fall it was exhumed by Dr. Musser, then Deputy Chief Medical Director, submitted to the Chief Medical Director, who as I recall, was Dr. Engle at that time. (He served between the terms of Dr. Middleton and Dr. Musser). It was approved and Dr. Richard E. Ogborn of the VA Hospital, Omaha, Nebraska, was appointed as the first Director of the newly approved Service.

I retired on December 30, 1966, with the feeling I had left an established Service that would continue without interruption. Unfortunately, no one knew that Dr. Ogborn was suffering from metastatic carcinoma of the pancreas, which within a few months had invaded both lungs and caused his death.

After my retirment I had no contact with VA activities, so my summary of my recollections of the program ends at this point. I would like to mention a few items that seem of great importance.

1. The early days were times of great problems with instrumentation, recruiting, methodology, licensing, and information exchange between users. One development has been controversial. I know that Dr. Allen was trying to do "scans" by laboriously taking individual Geiger measurements over a grid arranged over the patient. Who first suggested or conceived the automatic scanner for thyroid use is controversial, but there is no doubt that the first clinical trials of this machine, built by scientists of the UCLA Medical Center, was at the VA Center, Los Angeles. This began an era of rapid development of scanners.

2. The VA Hospital, Omaha, was, I believe, the first to have a nuclear reactor installed in the hospital itself. The story of how this was done perhaps should not be told. There were no construction funds available. These were requested and controlled outside the Department of Medicine and Surgery. Somehow we stumbled on the technique of buying the reactor as a piece of equipment on an installed basis. That is, the vendor did the installation as a part of the total bid price. It was a bit difficult to explain photos that showed up in Central Office

showing heavy equipment [illegible]

showing heavy equipment working at a VA Hospital that had no construction project. We used this technique successfully to install a radiation free room below ground at VAHospital, Iowa City, Iowa. This was two concentric metal tanks separated by 5 feet of distilled water on sides and top and entered through a serpentine passage from the sub-basement. We also furnished a third floor laboratory at VAHospital Minneapolis, by buying benches and hoods installed onutilities roughed in during another project.

3. In 1947 when Dr. Bernard Roswit started using radioisotopes in the VA Hospital Bronx, N.Y., he found a physicist who was teaching at Hunter College, as a consultant on his instrumentation problems. Later, this physicist, Dr. Rosalyn S. Yalow, joined the VA staff full time. Her work in collaboration with Dr. Soloman Berson covered a wide field of investigation, but the development of the technique of radioimmunological assay brought them great recognition and to Dr. Yalow the Nobel Prize in Medicine, after Dr. Berson's untimely death.

4. No report of the Radioisotpe program, now Nuclear Medicine would be complete without mention ofa person who was associated through most of my service. When I reported in 1946 I was assigned a secretary, o a temporary basis, since she was a grade above that approved for me. This was Ms. Clo Nolen. She helped me through the very abrasive period of adjustment to the bureaucracy (I never really accepted it), then was transferred. A bit later she was married, left tha VA, had two children, got them to school age and returned to the VA in another office. Some years later she rejoined my program and stayed on until after my retirment. She knew the program and was of great help to me throughout. It is rare that a person in a government position could enter employment with the same secretary he had upon retirment over eighteen years later. Mrs. Clo N. Gooding is now retired from VA.

NOTE: This material has been written strictly from memory and so the dates may not be precise. I believe the events described are correct, however.

A.Graham Moseley Jr.
April 1985

5.

RADIOISOTOPE UNITS IN OPERATION 1954

	Director (or Acting Director)
Atlanta, Ga.	Dr. Walter H. Cargill
Birmingham, Ala.	Dr. Wm. L. Hawley
Boston, Mass.	Dr. J. F. Ross
Bronx, N.Y.	Dr. Bernard Roswit
Cleveland, Ohio	Dr. Reginald A. Shipley
Coral Gables, Fla.	James E. Miller
Dallas, Texas	Dr. Donald A. Sutherland
Denver, Colo.	Dr. Harold Elrick
Durham, N.C.	Dr. Wallace N. Jensen
Fort Howard, Maryland	Dr. Arthur F. Abt
Hines, Ill.	Dr. John A. D. Cooper
Houston, Texas	Dr. Herbert C. Allen, Jr.
Iowa City, Ia.	Dr. R. E. Peterson
Kansas City, Mo.	-------
Long Beach, Calif.	Dr. M. E. Morton
Los Angeles, Calif.	Dr. Franz K. Bauer
Louisville, Ky.	Dr. Maurice Nataro
Martinsburg, W. Va.	--------
Memphis, Tenn.	Dr. B. R. Gendel
Minneapolis, Minn.	Dr. Leslie Zieve
Nashville, Tenn.	Dr. G. R. Meneely
New Orleans, La.	Dr. Julian D. Boyd
Omaha, Neb.	------
Philadelphia, Pa.	Dr. Robt. M. Dowben
San Francisco, Calif.	Dr. Wm. A. Reilly
Seattle, Wash.	Dr. Rex L. Huff
West Haven, Conn.	Dr. Donald L. Buchanan

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Distinguished Professor

5/10/94

LORI FERTEL
HOUSE VETERANS AFFAIRS COMMITTEE
CANNON HOUSE OFFICE BUILDING
WASHINGTON, D.C.

Lori -

Here are the two references I hope can be added to my references at the end of my written testimony. They add a lot to the understanding of concerns about radiation protection. Since one is not too long, I'll send you that one by regular mail, in case you or somebody else around there is interested (the one by Samuel Walker: "The Atomic Energy Commission and Politics of Radiation Protection, 1967-1971." **Isis** **85**:57-78, 1994). The other's a book, so I won't send that!

Best regards,

James A. Pittman, Jr., M.D.

Enclosure

The University of Alabama at Birmingham
Center for Advanced Medical Studies • 1924 Seventh Avenue South
Birmingham, Alabama 35294-0007 • (205) 934-3414 • FAX (205) 975-4976

ADDITIONAL REFERENCES FOR TESTIMONY OF JAMES A. PITTMAN, Jr., M.D. 2/8/94

Walker, J. Samuel: The Atomic Energy Commission and the Politics of Radiation Protection, 1967-1971. **Isis** **85**:57-78, 1994.

Brucer, Marshall: **A Chronology of Nuclear Medicine 1600-1989**. St. Louis, Heritage Publications, Inc., 1990 (especially the sections titled "Radiation Hysteria").

TESTIMONY OF DAVID J. ROTHMAN

BEFORE THE U.S. HOUSE COMMITEE

ON VETERANS' AFFAIRS

DAVID J. ROTHMAN PH.D IS

BERNARD SCHOENBERG PROFESSOR OF SOCIAL MEDEICINE

AND DIRECTOR OF THE CENTER FOR THE STUDY OF

SOCIETY AND MEDICINE

COLUMBIA COLLEGE OF PHYSICIANS AND SURGEONS

NEW YORK CITY

FEBRUARY 8, 1994

The recent expose of the research done on prisoners and patients without their informed consent by the Department of Energy during the 1950s joins a long roster of similar experiments carried out by the U.S. Army and the National Institutes of Health. During World War Two, psychotic back ward patients were subjects in experiments to find a cure for malaria and mentally retarded inmates were used in an effort to devise vaccines for dysentery. After the war, U.S. army funds supported research on retarded infants at New York's Willowbrook State School to understand the causes of hepatitis. The University of Cincinnati General Hospital, with funding from the Department of Defense and without patient consent, applied whole and part body radiation to terminal cancer patients. The CIA provided funds for physician research that, without patient consent, explored whether LSD might make prisoners more cooperative and whether psychiatric interventions might facilitate brain-washing.

The very large number of incidents might appear to buttress the argument offered by the institutions and investigators involved that they were merely following the standard practices of the time. Ostensibly, informed consent was not yet an established principle and researchers should not be faulted for ignoring it. Apparently, to condemn their practices is to invoke the standards of the 1990s in judgment on the 1950s.

Despite the surface plausibility of the argument, it is mistaken on several fronts. The standards of informed consent were already present in the 1940s and were still more clearly formulated by the 1950s. That researchers ignored them had much more to do with a definition of national interest and scientific privilege.

Already in 1865, the noted French physician, Claude Bernard had written: "The principle of medical and surgical morality consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others." Still more immediately, the principles had been set forth at Nuremberg, the first of which declared: "The voluntary consent of the human subject is essential," and the subject must have

"sufficient knowledge and comprehension of the elements of the subject matter involved as to make an enlightened decision." And when investigators thought public opinion might deem the research controversial, as was the case with wartime experiments using prisoners to find a cure for gonorrhoea, they wrote full and accurate consent forms.

So why did American investigators so frequently transgress the standard? For one, the war effort, first in 1940-1945, and then in the Cold War era after 1948, fostered utilitarian judgments. When the social values attached to consent gave way to miliary conscription and obedience to orders, there seemed little reason for medical researchers to worry about the rights of incompetent human subjects or terminally ill patients. For the sake of national security, investigators had to know more about the effects of radiation, and so it seemed acceptable to expose fetuses to radioactive iron, prisoners' genitals to x-rays, and terminal cancer patients to high concentrations of plutonium.

Moreover, American investigators ignored the principles set forth at Nuremberg, on the belief, mistaken, that madmen had been at work in Nazi Germany, not scientists. Medicine had nothing to learn from the trials of Hitler's henchmen. For still another, researchers' avoided obtaining consent so as to satisfy their scientific ambitions. If only they could perform their experiments, diseases would be cured and other lives saved.

Why dwell on these past incidents and dispute the defense of ignorance? After all, in the aftermath of the exposes in the 1960s and 1970s, the U.S. government did create regulatory bodies, Institutional Review Boards as they are called, to make certain that consent is now obtained from subjects and the boards have done their job well. Still, the lessons to be drawn from these earlier incidents remain highly relevant.

First, the record reminds us how vital it is to continue to regulate human research closely. Some patient groups are bridling at the bureaucratic oversight, desperate to pursue a cure for HIV disease or to test out the efficacy of purported therapies like

Lorenzo's Oil. To them, research seems so full of potential to cure and so benign that they forget just how dangerous an activity it is. The unknowns involved in testing new agents are great-- unanticipated side-effects can be lethal-- and human subjects, now as then, had better understand what they are confronting.

Second, the record of the 1940's and '50s demonstrates what happens when medicine becomes too closely identified with the state, when medical ethics become subservient to national interests. There is a tension between a code of "do no harm" and a commitment to promote the interests of the larger society. Medicine is at its core a liberal profession, bound to promote and protect the well-being of the individual patient. Violate this ethic, even in the name of wartime needs, and the consequences turn out to be disastrous. Ultimately, it is to all our benefit that medicine retain something of a subversive character.

Third, it is vital that the full record of government research be opened for independent review, including not only the activities of the Department of Energy but of Defense, Intelligence, etc.. All of the record must be fully known, not only to compensate victims but to help us understand the dynamics that brought the research about. This is one important way in which we can prevent recurrence of abuses. At the same time, and as we have already seen, analyzing the record becomes an important exercise in public education. The better informed the public, the better the protections against abuse in human experimentation.

Finally, it is vital that current regulations governing the IRB undergo scrutiny. There must be greater national oversight of local IRB decision-making. It is important to have a national commission address larger issues in human experimentation, but that should not be at the expense of having greater administrative oversight of day to day IRB decision-making. There is always the risk that the enthusiastic investigator or the complacent IRB will minimize risks and exaggerate benefits from the research, and we need a way to make more certain that this does not happen.

Testimony Before
THE U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON VETERANS' AFFAIRS

HEARING ON GOVERNMENT SPONSORED RESEARCH INVOLVING RADIOACTIVE MATERIALS CONDUCTED IN V.A. MEDICAL CENTERS

Prepared by
Charles R. McCarthy, Ph.D.
Senior Research Fellow
Kennedy Institute of Ethics
Georgetown University
Washington, DC 20057

February 8, 1994

Charles R. McCarthy, Ph.D.
Testimony before the House Committee
on Veterans' Affairs 2/8/94

Mr. Chairman and distinguished members of the Committee:

I am Dr. Charles R. McCarthy. I served for fourteen years as the Director of the Office for Protection from Research Risks (OPRR) in the Department of Health and Human Services. I retired from government service in 1992 and since that time I have been affiliated with the Kennedy Institute of Ethics at Georgetown University. In my capacity as Director, OPRR, I had responsibility for promulgating and implementing regulations for the protection of human research subjects involved in research conducted or supported by the Department of Health and Human Services. My remarks are based on that experience.

Recently, through actions of the President, the Secretary of the Department of Energy and heads of other federal departments and agencies, including the Department of Veterans Affairs, the executive branch of the government has initiated a massive program to identify and evaluate records pertaining to government sponsorship of research involving exposure of human research subjects to ionizing radiation. I know that this Committee understands that collection and evaluation of all of those records is a massive undertaking that may require years of effort.

That effort must be carefully conducted so that it will: (1) produce an accurate historical record ; (2) identify and compensate persons who been injured as a result of their participation in government sponsored research; and (3) avoid needless frightening of people who may have participated in such research.

Charles R. McCarthy, Ph.D.
Testimony before the House Committee on Veterans' Affairs 2/8/94

My testimony today will include three parts:

A summary history of the development of federal regulations for protection of the rights and welfare human research subjects; a commentary on current federal efforts to protect human research subjects; and recommendations for strengthening the federal system for the protection of human research subjects.

I. A SUMMARY HISTORY OF THE DEVELOPMENT OF FEDERAL POLICIES AND REGULATIONS FOR PROTECTION OF THE RIGHTS AND WELFARE OF HUMAN RESEARCH SUBJECTS.

A. The Impact of the Nuremberg Code

The modern era of medical research ethics began in 1946 with the Nuremberg war crimes trial of 23 Nazi doctors and scientists for crimes against humanity. In the case of the U.S. v. Brandt et al. (Brandt was Hitler's personal physician) dreadful experiments in which death was often the endpoint were carried out under the authority of and with the approval of the Third Reich. The trial of the Nazi Doctors and the resultant Code of Research Ethics known as the Nuremberg Code issued by the court, have been well documented in a book edited by George J. Annas and Michael A. Grodin .[1]

The significance of the Nuremberg Code for research in the United States ; the contributions made to development of the Code by Drs. Andrew C. Ivey and Leo Alexander; and the role of the House of Delegates of the American Medical Association have been summarized for the Congress by my colleague Dr. LeRoy Walters, Ph.D. of the Kennedy Institute of Ethics. I should like to submit for the record Dr. Walters' testimony before the House of Representatives Subcommittee on Energy and Power on January 18, 1994. Dr. Walters reached ten conclusions:

Conclusion 1: In the United States, basic ethical standards for research involving human subjects were outlined in an editorial published in the Journal of the American Medical Association in November of 1946. These standards were summarized in three principles and formally adopted by the American Medical Association in 1946, The topics covered by the three principles were voluntary consent to participation by subjects, the establishment of probable risk levels for human subjects through prior animal experimentation, and the need for medical protection and management in the performance of experiments.

Conclusion 2: In August 1947 a detailed code of research ethics was presented as part of the judgment of the Nuremberg medical trial. The ten principles of the Nuremberg Code covered the topics of voluntary consent, research design, prior animal experimentation, limits on anticipated harm to research subjects, the qualifications of investigators, and the freedom of subjects to withdraw from a study at any time.

Conclusion 3: By the end of 1947, at the latest, general information about the Nazi medical crimes and the outcome of the Nuremberg medical trial was available to all informed citizens.

Conclusion 4: By early 1948, research involving prisoners was judged by two commentators and a governor's advisory committee to be ethically acceptable, if the prisoners freely volunteered to participate and if their rewards for participating were not excessive.

Conclusion 5: By mid 1948, research involving the mentally ill and the mentally incompetent was judged by two commentators (Drs. Leo Alexander and Andrew Ivey) to be ethically acceptable. Both commentators required the prior

consent of the prospective subject's legal guardian. In addition, Alexander stipulated that research on the mentally ill should be related to their condition and that consent should also be obtained from the prospective subjects if possible.

Conclusion 6: In a summary of German medical war crimes published in 1948, the United Nations War Crimes Commission reprinted the ten principles of the Nuremberg Code and seemed to regard the Code as an important statement on research ethics.

Conclusion 7: Representatives to the United Nations Commission on Human Rights were deeply concerned about the Nazi medical experiments and asserted a general human right not to be a subject of medical or scientific experimentation "against one's will" (1948) or "without one's free consent" (1952 and 1958).

Conclusion 8: In October 1948, the World Medical Association condemned the Nazi medical experiments and urged physicians to act with the utmost respect for human life and never to use their medical knowledge contrary to the laws of humanity.

Conclusion 9: By early 1949, the book, Doctors of Infamy made the Nazi medical war crimes and the ten principles of the Nuremberg Code readily accessible to any person who had not previously been aware of the crimes, the trial, and the code.

Conclusion 10: In 1949, the framers of the Geneva Conventions also wished to avoid a repetition of the Nazi war crimes and therefore incorporated explicit protections against unwanted biological or medical experimentation into all four of the new conventions.

B. The complacency of the '50s

The Nuremberg Code represents the highest ethical standards for biomedical research of the period. It would be a mistake, however, to assume that these standards were understood and practiced by most scientists of the day. Despite the conclusion reached by Dr. Walters that information about the Nazi crimes and the outcome of the Nuremberg trial were readily available to informed citizens at that time, the evidence suggests that those standards were not incorporated in the design and conduct of much of the biomedical research of the 1950s.

In 1950-1951 I was, for a period of about fifteen months, involved as a research subject in a trial conducted by a sensitive and enlightened physician. Nevertheless I never consented to participate in the research. I learned that I had been a research subject after the fact. It never occurred to my physician that he was in violation of the standards to which the United States held World War II Nazi scientists. I believe the lack of ethical sensitivity that I observed first hand, was typical of biomedical research in that period of history. It may help to explain, but not excuse, the ethical flaws in the ionizing radiation experiments conducted during that decade.

When the Warren Grant Magnuson Clinical Center at the National Institutes of Health (NIH) was opened in 1953, it issued the first federal policy for the protection of human research subjects. The Clinical Center Policy applied only to "normal" or "healthy" research volunteers. Persons who participated in research designed to study a disease or condition from which they were suffering, were not covered by the policy. As a result, the first policy provided protections for only a fraction of the subjects participating in research within the NIH Clinical Center.

Charles R. McCarthy, Ph.D.
Testimony before the House Committee
on Veterans' Affairs 2/8/94

Following World War II, the federal government dramatically expanded its support of biomedical research. The NIH budget shot from $180,000 in 1945 to $8 million in 1947.[2] The bulk of new research money was channeled to academic research centers throughout the United States. NIH research budgets continued to rise precipitously throughout the '50s and somewhat more gradually in the '60s until they began to level or decline in 1971. The National Science Foundation, the Atomic Energy Commission, the Veterans' Administration (now Veterans' Affairs) and the Departments of Defense and Energy also received (less dramatic) increases in their budgets for biomedical research. [In FY 1993 the NIH health R&D budget was $9.8 billion and the total federal health R & D budget was just under $12 billion.[3]]

Although I have not made an exhaustive search, I asked a student to check all of the issues of the Journal of the American Medical Association (JAMA) and the New England Journal of Medicine (NEJM) between 1950-1960 for articles pertaining to the protection of human research subjects. The student reported only a handful of passing references to the rights and welfare of human subjects.

Despite increased federal support of biomedical research, no federal laws and no regulations were enacted or promulgated for the protection of human research subjects in the decade of the '50s. The decade of the '50s appears to have been a decade of complacency in regard to the rights and welfare of research subjects.

In 1958 Senator Estes Kefauver (D. Tenn) brought the period of complacency to an abrupt end when he initiated a series of hearings pertaining to the practices of the pharmaceutical industry. The hearings culminated in the Kefauver-Harris amendments to the Food Drug and Cosmetic Act of 1962. Senator Kefauver directed sharp criticism at drug manufacturers and physicians for their widespread collaboration in testing drugs without the patients' knowledge or consent. Many patients paid for drugs whose

effectiveness had never been established. The resultant legislation mandated the issuance of regulations requiring informed consent from research subjects. Although the regulations were issued by the Food and Drug Administration, a number of years passed before FDA found a way to enforce them.

C. The Phrenetic Decade of the '60s

Many will recall the turbulence of the 1960s: baby boomers came of age; the Cold war flourished; the threat of thermo-nuclear war hung heavy over the world; the civil rights movement, and civil disobedience changed the mores of the nation; the conflict in Vietnam divided the country, communities and families; President Kennedy, Martin Luther King and Bobby Kennedy were all assassinated; crime and the use of illicit narcotics increased; and the abortion debate further divided the country.

In the midst of the tumult of the '60s, dramatic changes within the research community were scarcely noticed. Nevertheless disturbing reports of unethical research shook the complacency of the research community. These included "bugging" of jury deliberations and spying on homosexuals by social scientists, injection of live cancer cells into elderly, indigent patients and whole body radiation by cancer researchers, "inoculation" of severely retarded children with hepatitis before admitting them to a state institution. Although some of these events had occurred in the '50s, they received public attention in the '60s.

In 1964 the World Medical Association published the Declaration of Helsinki reiterating the standards of Nuremberg and focussing special attention on "therapeutic" research.

In 1966, Professor Henry Beecher of Harvard, one of the most respected researchers in the country, published an article in the New England Journal of Medicine identifying 22

different research projects in the published literature which were, in his judgment, conducted in an unethical manner. Because of Beecher's impeccable reputation, his article sent a shockwave through the American research community.

In February 1966, Surgeon General Stewart, urged by Dr. James Shannon then Director of the NIH, issued the first Public Health Service Policy for the Protection of Human Subjects. The Policy applied to all institutions that received support from any of the Public Health Service agencies for research involving human subjects. Although vague in its formulation, the Policy required each institution that received research money to assure the Public Health Service that an independent committee would prospectively review research project for ethical acceptability. Informed consent procedures and assessment of risks and expected benefits to subjects were included in the Policy.

The Public Health Service Policy subsequently revised and clarified later in 1966 and again in 1967 and 1969.

D. The Decade of the '70s: A Decade of Both Progress and Stalemate for Human Subjects Protections

In 1971 the PHS Policy for the Protection of Human Subjects underwent major revision and was extended to all research supported by the Department of Health, Education and Welfare.[4] The federal government, largely through the leadership of the NIH, began a slow process of refining and extending protections for human research subjects -- a process that would continue for twenty years.

In 1971 then Senator Mondale called for a national advisory body to evaluate the impact of and to recommend policies concerning the ethics of federal support for biomedical and behavioral research.[5] Although the Senate as a whole took no action, Senator

Kennedy, Chairman of the Senate Health Subcommittee, began a series of hearings that continued for four years.

During the same year, the infamous Tuskegee syphilis study came to public attention. That study, ostensibly designed to study the natural course of syphilis, had been initiated by the Public Health Service more than thirty years prior to the publication of the PHS Policy. Because the study substituted deceit for informed consent, and because the four hundred black male subjects of the study were systematically denied treatment for their syphilis over decades of time, it has rightly been condemned as immoral. A panel chaired by Professor Jay Katz of Yale University condemned the study and called for its immediate cessation. Senator Kennedy proposed legislation for the protection of human subjects. The NIH increased its efforts to make its policy effective.

Robert Q. Marston, Director NIH, in a commencement address delivered to the Medical College of Virginia in 1972 called for a revision of the PHS Policy with special emphasis on vulnerable populations. He created a PHS committee to draft recommendations for upgrading and strengthening enforcement of Protections for Human Research Subjects. He also created the Office for Protection from Research Risks (OPRR) and gave it prominence within the Office of the Director, NIH. That Office, with authority delegated to it by the Secretary, HEW, (later HHS), assumed primary responsibility for making the entire HHS system work.

In 1974 Congressman Angelo Roncallo (D. NY) charged the NIH with irresponsible research involving the perfusion of decapitated heads from aborted fetuses. His charges, later proved to be false (since the research was conducted in Finland), caused an uproar in the Congress. Civil rights activists, outraged by the Tuskegee study and anti-abortion groups outraged by the Roncallo allegations, joined forces in calling for

action. Senator Kennedy and Congresman Paul Rogers both held hearings and introduced legislation for the protection of human subjects. HEW, again led by NIH, upgraded its Policy for the Protection of Human Subjects to regulations, issued May 30, 1974.

Senator Jake Javits (R. N.Y.) played a key role in harmonizing the Mondale Resolution, the Kennedy bill and the Rogers bill. On July 12, 1974, Congress enacted the National Research Act (PL 93-348) that: (1) required HEW to issue regulations for the protection of human subjects; (2) required HEW to establish a National Commission for the Protection of Human Subjects Involved in Biomedical and Behavioral Research; and (3) imposed a moratorium on all federal support of research involving the human fetus until such time as the National Commission could make recommendations concerning the conduct of such research.

For four years, 1974-1978 the National Commission, under the leadership of Chairman Kenneth Ryan, M.D. held hearings and issued reports and recommendations concerning the protection of human subjects in general, and additional protections for vulnerable populations such as human fetuses, pregnant women, the mentally infirm, prisoners and children. The Commission completed its work, forwarded its reports and recommendations to the HEW, and closed its doors in 1978.

In 1975 Casper Weinberger, then Secretary, HEW, created a task force to examine the question of compensation for injured research subjects. The Task Force strongly endorsed the creation of a system for providing compensation for injured research subjects -- a system analogous to the provision of benefits for service related injuries of military personnel. No action was ever taken on the recommendations of the Task Force.

Charles R. McCarthy, Ph.D.
Testimony before the House Committee
on Veterans' Affairs 2/8/94

HEW Secretary Califano created an Ethics Advisory Board (EAB) in 1978 to provide advice on ethically controverted research. The EAB submitted four reports and recommendations to the Secretary. Its best known work was its report on *Human In Vitro Fertilization* (1979). Although he agreed to accept the recommendations of the Board, Califano was replaced by Secretary Patricia Harris who failed to endorse the EAB report. In fact, although it has had a profound influence on the practice of *in vitro* fertilization in the U.S. and abroad, the EAB report has never been acted on by the federal government. Contrary to its own regulations, HEW (later HHS) failed to re charter the EAB after 1980. (The regulatory provisions calling for an EAB were finally withdrawn by act of Congress in 1992.)

E. The '80s A Time of Gradual Consolidation

In January, 1981, HEW regulations for the protection of human subjects were revised to reflect the recommendations of the National Commission. The regulations capped several years of national debate within the research community on how best to regulate research. The OPRR recognized that the most effective way to implement the regulations is to involve the research community. In public hearings and meetings extending over two years, the OPRR had discussed a variety of ways provide protections for research subjects through regulation. OPRR became aware that the members of the research community, with very few exceptions, are prepared to carry out research in an ethical manner. The key to compliance is education of the regulated community. The regulations provide a stick that gains the attention of the research community, accompanying education programs provide the carrot that persuades the research community that the regulations are reasonable and worthy of careful respect and attention.

For several years, following promulgation of the regulations, OPRR entered into intense negotiations with HHS awardee institutions. The purpose of the negotiations was to require each institution to complete a document called an Assurance of Compliance that commits the institution to follow the regulations in every detail. These documents, signed by the CEO of the institution state that the awardee institution is dedicated to the protection of human subjects. Each awardee institution was required to: (1) commit its personnel to follow ethical procedures for informed consent, risk assessment and equitable distribution of risks; (2) identify chairpersons and members of Institutional Review Boards, to document their qualifications for service on the IRB, and to set forth procedures to be followed by both research investigators and the IRBs; (3) provide a plan whereby the institution would commit staff, resources to the protection of human subjects; and (4) educate both research investigators and staff regarding their responsibilities for protecting the rights and welfare of human subjects.

Assurance negotiation is the never-ending process by which the OPRR both reminds institutions of their responsibilities to human subjects and exercises quality control over institutional efforts to protect subjects. When new regulations were promulgated in 1981, an intense process of Assurance negotiation occupied OPRR staff for the next four years. Once the first wave of Assurances was in place the process has continued at a steady pace because Assurance Documents are renewed at intervals of no more than five years. OPRR has ongoing Assurance agreements with 406 major research institutions (measured in terms of numbers of awards and dollar amounts awarded to institutions) and with approximately 3000 institutions with smaller research portfolios. It is estimated that more than 80% of HHS funded is carried out in the 406major research centers. Although research conducted or supported by the Administration for Veteran's Affairs was not directly covered by HHS regulations, most VA hospitals come under HHS regulations. This is the case because most of the research conducted in VA hospitals is supported through awards made to academic institutions by the HHS. For

example, when a principal research investigator from Emory University conducts clinical research at the nearby VA hospital, an HHS Assurance is negotiated with the VA hospital, and HHS regulations apply.

In 1980 the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research was established by act of Congress (P.L. 95-622). Although most of the deliberations of that Commission are not relevant to this hearing, the Commission made one recommendation that is of critical importance.

> The President should, through appropriate action, require that all federal departments and agencies adopt as a common core the regulations governing research with human subjects issued by the Department of Health and Human Services (codified at 45 CFR 46) as periodically amended or revised, while permitting additions needed by any department or agency that are not inconsistent with these core provisions.

An Interagency Coordinating Committee was established under the auspices of the Office of Science and Technology in the White House, and after many years of internal negotiations, a Common Federal Rule for the Protection of Human Research Subjects was promulgated on June 18, 1991. The rule now is shared by sixteen federal Departments and Agencies, including the Department of Veterans Affairs . Since 1991 a research subject involved in any research project conducted or supported by the federal government is protected by the provisions of the Common Federal Rule. The rule is administered by the Interagency Coordinating Committee chaired by the Director, OPRR. If the rules are followed, then violations of the rights and welfare of human subjects will be a thing of the past.

II. FEDERAL EFFORTS TO PROTECT THE RIGHTS AND WELFARE OF HUMAN SUBJECTS

Charles R. McCarthy, Ph.D.
Testimony before the House Committee
on Veterans' Affairs 2/8/94

The federal process for protecting human subjects has been developing since 1966, a period of nearly thirty years. Although there were many abuses of human subjects in our history, the federal government has slowly built, not only the most comprehensive system in the world for the funding of biomedical research, but the best system in the world for protecting the rights and the welfare of human subjects involved in research. The system is far from perfect, but it compares favorably with other regulatory systems in the country and the world. We can be justly proud of what has been accomplished.

The process of achieving a common federal rule required ten years of intense effort, education and dedication. During that time responsible individuals had to be identified and trained within each agency of each department. Rules were proposed, modified, reproposed and finally promulgated. All of this has occurred without additional support, budgets or personnel. The OPRR, which exercises "lead agency" responsibility across the entire government is operating on essentially the same budget and with less personnel than it had in 1985 when its responsibilities were much narrower.

Although each agency, including Veterans' Affairs, has designated a person or an office to take responsibility for the protection of human research subjects, the assigned responsibility is in virtually every case an "add on" to responsibilities already imposed on those individuals and offices. No additional personnel or budgets have been dedicated to the protection of human subjects.

III. RECOMMENDATIONS FOR MAKING THE SYSTEM WORK

A. Provide Adequate staff and budget for Protection of Human Subjects

Mr. Chairman, the situation is critical. The summary history of the development of policies and regulations shows that the United States took seriously a number of research

scandals that occurred more than twenty years ago. To prevent repetition it has erected an enlightened and comprehensive system for protecting the rights and welfare of human research subjects. The decline in research scandals, including unethical radiation experiments of the past, provides strong evidence for the soundness of the system. That system could become a mere shell and sham because of the failure of our government to provide necessary support for the system it has created. If this committee wishes to prevent abuses such as those that have occurred in the past, it needs only to insist that this effort be adequately staffed and funded.

The federal government has been downsizing its human subjects staff while increasing staff responsibilities -- throughout the past decade and across three administrations. No new personnel have been added. Staff who have retired from this work have not been replaced. To give you an example, Dr. Katherine Duncan is the only M.D. still on the OPRR staff. She recently celebrated her 80th birthday. She volunteers four days of work each week, without pay, to the protection of human subjects. Dr. Duncan came out of retirement approximately five years ago because she recognized that the protection of human research subjects is of critical importance to this country. She also realized that present staff is too small to meet its responsibilities. Budgets are so slender that OPRR personnel have been, in many cases, prevented from educational and investigative travel. Most of the agencies, outside of the HHS, including Veterans' Affairs have one part time professional and one part time secretary and no budget for implementing the regulations.

The government, over the past ten years, has been penny wise and pound foolish. A single investigation often costs the government as much as a year's preventive effort. I am informed that there are currently 56 cases of alleged noncompliance backed up in OPRR's files. OPRR has two investigators to handle 56 complex cases! Most agencies, including Veterans Affairs have no trained personnel dedicated to investigating alleged

breaches of the regulations. Regulations that remain unenforced are an open invitation to abuse. I salute the staff who continue to work days, nights, and weekends to make the system effective. Nevertheless, if this Committee wishes to assure itself that protection for human research subjects is in place, it should cooperate with the Administration in providing personnel and budgets for the task.

B. Create an Ethics Advisory Board or Commission

If human subjects are to be protected, then public policies concerning what will, and what will not be tolerated in research should be established. The history presented above indicates that each time a national commission or board has been established, significant progress has been made in protecting the rights human subjects. When such boards have been absent, researchers become confused concerning what is, or is not permissible.

Such issues as the cloning of human embryos, mandatory freezing of unused embryos, regulation of sperm banks, privacy protection of HIV infected persons, surrogate pregnancies, genetic manipulation of germ lines, family research, and research into causes of violent behavior are only a few of the areas for which the technology is at hand, but the policy guidance is lacking. IRBs need principled guidance if they are to be effective.

Senator Mark O. Hatfield has introduced legislation to create such a board. This Committee could do a great service to the country by supporting that legislation.

C. Develop a System for Compensating Injured Research Subjects

As was noted in the historical summary above, plans for compensating human subjects injured in the course of research have been in existence since 1975. Nevertheless, they have never received more than token support from the Congress. This is not the place to discuss details of a compensation program. But this Committee with its outstanding record of support for veterans, who have suffered injury in the service of their country, can take a bold and ethically imperative step of creating a system of compensation for subjects who, while allowing their bodies to be used for the good of society, have suffered injury.

Mr. Chairman, that concludes my remarks. I will be pleased to answer any questions that the Committee may wish to raise.

1. The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation, George J. Annas and Michael A. Grodin, Oxford university Press, 1992.

2. Encyclopedia of Bioethics, Warren T. Reich, ed. THE FREE PRESS, a Division of Macmillan, New York, 1978, Vol. 4, p. 1492, Research Policy C. McCarthy

3. NIH Data Book, 1993

4. The Institutional Guide to DHEW Policy on Protection of Human Subjects; U.S. Department of Health Education and Welfare, DHEW Publication No. (NIH) 72-102, Dec. 1, 1971; U.S. Government Printing Office Stock Number 1740-0326.

5. S.J. Res. 65, 1971. This resolution was reintroduced repeatedly in subsequent years.

The Hazards to Humans of Internal Radioisotopes and of External Ionizing Radiation

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We live in a world full of hazards. Some are the results of our lifestyles, some the results of chemical reactions that take place in our bodies at 37°C, and some arise from ionizing radiations and radioisotopes. The radiation hazards arise from background radiations, therapeutic irradiation, diagnostic radiations and radioisotopes, and experimental procedures. Although ionizing radiations are far from being the principal cause of death in the United States, they are viewed as very dangerous by the public because it is well documented that large doses may induce cancer and, moreover, it is easy to measure radiation doses compared to measurements of other hazards, such as chemical exposures for example.

It is important to understand the background radiation in the United States, over which we have little control. Table 1 illustrates the annual effective dose equivalent to individuals in the United States. The principal natural sources of radiation are: 1) cosmic ray background (a function of latitude and altitude: the average is 28 mrem/yr but Denver has 50 mrem/yr); 2) terrestrial background from radioactivity in rocks; 3) internal radioactivity from radioisotopes that are a natural part of our foods such as radioactive potassium and radioactive carbon (we cannot eliminate them) that contribute 39 mrem/yr and correspond to approximately 1 μcurie of radioactivity, that is, approximately 200,000 disintegrations per minute; and 4) the biggest contributor, radon leaking out of the soil (this number varies greatly from house to house and place to place in the United States.

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*I am a Senior Biophysicist and the Associate Director for Life Sciences. I do not do experiments on people but I am knowledgeable about the physical and biological effects of radiations. My own research has dealt with the effects of radiation on molecules, viruses, bacterial cells, and human cells in culture. I received my A.B. in Physics from Swarthmore College in 1941 and my Ph.D. in Physics from Yale University in 1947. I was on the staff of the Physics and the Biophysics Departments of Yale University from 1943 to 1961. I was the Scientific Director of Physics and Cell Physiology at the Oak Ridge National Laboratory and was also the Director of the University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences. I have been at Brookhaven since 1974. I am a member of the National Academy of Sciences and have served on numerous committees dealing with the effects of radiation. From 1985 to 1986 I was Chairman of the Board on Radiation Effects Research and was a member of the Commission on Life Sciences from 1986 to 1992. In January 1989 I received the Enrico Fermi Award from the Department of Energy for "pioneering and far-reaching contributions to the fields of radiation biophysics and molecular biology, beginning with the discovery and conceptualization of the processes of DNA repair that have had an impact on research in genetics, recombination, mutation, and carcinogenesis."

Medical procedures contribute, on the average, about 55 mrem/yr but obviously very greatly among individuals. These procedures are looked upon as essential for good health but they are far less than the average from natural sources. The overall background from such sources amounts to 360 mrem/yr (note that the average exposure from the radioactivity in smoking tobacco almost equals this number, although nonsmokers are not exposed whereas smokers are exposed to much higher doses). Smokers not only run the risk of carcinogenic chemicals in smoke but also radioactive elements in smoke. The total lifetime exposure to background radiation for a 70 year old individual amounts to 360 mrem/yr x 70 yrs which equals approximately 20,000 mrem (20 rem) per lifetime. This radiation is delivered slowly. We call it chronic and it produces less of an effect than such radiation given in a short interval of time, an acute dose, because there is sufficient time for DNA repair to take place during the long exposure. As a matter of fact, if there were no DNA repair, there would be no human life as we now know it because the internal chemical reactions make several thousand DNA (genetic) damages per hour per cell. In 70 years, 10% of our genetic material in each cell would be altered.

Table 1

Annual effective dose equivalents (H_e)
(The collective dose equivalent of the U.S. population divided by the population)
from background and diagnostic medical radiation

Sources		Average Annual H_e (mrem)
Natural Sources:	Radon[1]	200
	Cosmic	28
	Terrestrial	28
	Internal	39
Medical:	Diagnostic	40[2]
	Nuclear Medicine	14[2]
Consumer Products:	Water Supplies[1]	3
	Other	5
Total, including lung		~ 360
Total, excluding lung		~ 150
	Smoking Tobacco	~ 280[3] !!

Source: NCRP Reports 93, 94, 95, 100.
1. These sources deliver radioactivity almost exclusively to the lung.
2. Not adjusted for skewed age distribution.
3. An uncertain number. For the smoking population, the value would be ~ 1,300 mrem/yr.

Background radiation represents the noise to which we are all exposed. The biological effects of radiations of this magnitude are not detectable because the variations among individuals in their genetic makeup and their lifestyles are large and result in "epidemiological noise" far greater than that from background radiation.

Dose Response Curves: Quantitative Estimates of the Effects of Radiation on Humans

Almost all the data on the effects of different doses on humans come from an analysis of the results of the acute exposures to radiations of the atomic bombs dropped in Japan. At a cellular level a dose of 100 rem produces damage in all cells of the body. Most of the damage is either repaired or ignored and only less than one cell may go on to become a cancer. Hence, cancer is a relatively rare event and the effects of radiation difficult to observe precisely. Some cancers increase proportionately to the radiation dose and, in such cases, an extrapolation from high acute exposures to low exposures is reasonable although the extrapolation from acute exposures to chronic exposures may overestimate the hazard by a factor of 2 or more. Other cancers, such as leukemia, increase disproportionately as the dose increases. Hence, the extrapolation from high to low exposures must be made on the basis of mathematical models more complicated than a straight line. The Report of the National Research Council Committee on the Biological Effects of Ionizing Radiation V (BEIR V, 1989) estimates (Table 2) excess cancer mortality as a result of a single exposure of 10 rem to 100,000 people. Such an exposure would increase the normal cancer incidence by 3.7% in males and 5% in females. These numbers have large uncertainties, 2.6 to 6.0% for males and 3.9-7.2% for females. Females have a higher excess risk because their normal cancer risk is significantly less than for males.

Table 2
Excess cancer mortality from an acute dose of 10 rem
(Lifetime risks per 100,000 exposed persons)

	Male	Female
Normal unexposed expectation	20,510	16,150
Excess mortality	770	810
99% confidence limits	540 - 1,240	630 - 1,160
% of normal	3.8 (2.6-6.0)	5.0 (3.9-7.2)

Source: BEIR V, NAS Press (1989).

Estimation of Risk

In 1989 the total number of deaths in the United States were 2,150,000 of which 496,000 (23% of the total) were cancers. Note that approxiately 30% of the cancer deaths were the result of lung cancer. To estimate the risk of ionizing radiation in producing cancers, we must have estimates of the doses to which people are exposed. Given these estimates and the dose-response data, mostly as a result of the Japanese experience, permits one to estimate the probability that a given cancer came from a given exposure. Obviously for low acute doses, the probabilities are low. For high acute doses, the probabilities become large and associating cancer with a given exposure is comparably easy. The irradiation doses from diagnostic or therapeutic procedures are comparably easy to measure, or to calculate, and the uncertainties in these doses are appreciably less than the uncertainties in our knowledge of the biological effects of such radiations. It should be clear that at low levels of exposures the risk is low and very uncertain. It becomes an ethical, or political matter to determine the risk level at which individuals should be compensated for exposures that were given in the absence of informed consent.

Nuclear Medicine

Nuclear medicine arose from the initiatives in the Atomic Energy Commission and its research contractors to make and to use new radioactive isotopes--low dose tracers--to diagnose diseases. Such tracers are now used to diagnose cardiovascular diseases, thyroid abnormalities, cancers and brain dysfunctions. At Brookhaven such studies are also aimed at understanding the biochemical nature of substance abuse and how various drugs may minimize the drug craving. Table 3 indicates the uses of radioisotopes in nuclear medicine and also gives the number of procedures used per year in the United States. These numbers are impressive.

Table 3
Radioisotopes in Nuclear Medicine

Uses

- Diagnostic Imaging
- Measurement of Physiological Parameters
  - Function
  - Biochemistry
  - Pharmacokinetics
- Monitoring of Disease
- Treatment (therapy) of Disease

Numbers of Procedures Per Year in the U.S.

Diagnosis	13.2 million
Therapy	> 75,000
Laboratory Tests	> 100 million

Over 80% of the diagnostic procedures used ^{99m}Tc. This isotope has a half-life of about 6 hours so that its radioactive concentration falls over 100-fold in 2 days. Hence, even large initial concentrations, useful for imaging the heart and other organs, fall to negligible levels quickly and, therefore, result in negligible risk to a patient. The reason that ^{99m}Tc is so useful is not only that it emits gamma rays for imaging, and its short half-life, but that it is a decay product of ^{99}Mo which has a half-life of 66 hours. In actual nuclear medicine procedures the ^{99}Mo is distributed to hospitals before the Mo decays. After a decay the Tc is separated chemically and so is available for a large number of days for diagnostic procedures. The utility of using this group of isotopes originated in the National Laboratories supported, at present, by the Department of Energy. Such isotopes are important for health purposes and, as used at present, have negligible risks to the recipient. Even so the present recipients give informed consent for the use of such procedures.

Statement of
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before the
Committee on Veterans' Affairs
U.S. House of Representatives
G.V. (Sonny) Montgomery, Chairman
February 8, 1994

Thank you, Mr. Chairman, for this opportunity to appear before the House Committee on Veterans' Affairs. I am William R. Hendee from the Medical College of Wisconsin, a large private medical school affiliated with several hospitals including the Zablocki Veterans Administration Hospital in Milwaukee. I am here today at your invitation to discuss the issue of government-sponsored research involving ionizing radiation conducted in the past in Veterans' Administration Medical Centers.

My position at the Medical College of Wisconsin is Senior Associate Dean for Research and Vice President for Technology. I am a Professor in the Departments of Radiology and Radiation Oncology, the Biophysics Research Institute and the Center for the Study of Bioethics. In addition, I am Adjunct Professor of Bioengineering at Marquette University. I am a past president of the American Association of Physicists in Medicine and the Society of Nuclear Medicine, and have authored or coauthored over 350 scientific articles and authored or edited over 20 books, including one entitled Health Effects of Low-Level Radiation published in 1983 and another entitled Health Effects of Low-Level Exposure to Ionizing Radiation which is currently in preparation. I have served as a consultant to many federal agencies, including the Nuclear Regulatory Commission, Veterans Administration, Department of Energy, Department of Defense, Department of Labor, Environmental Protection Agency, National Institutes of Health, National Science Foundation, and Food and Drug Administration. My complete curriculum vitae is appended to one copy of my written testimony for the *printed* hearing record.

Today I wish to discuss four relatively simple concepts that help provide a scientific and historical perspective on experiments involving exposures of human subjects to ionizing radiation that may have been conducted in the 1940s and 1950s. These concepts are presented in sequence in separate sections of this testimony.

1. Knowledge of Long-Term Effects of Ionizing Radiation: The scientific understanding of the effects of exposure to radiation is much more sophisticated today than it was a few decades ago. For example, although it had been known since shortly after the turn of the century that radiation can cause cancer, it was thought for many years that large amounts of radiation were required to cause the disease, and that the onset occurred relatively soon after exposure. There was little evidence to suggest that persons receiving small amounts (i.e. low doses) of radiation were placed at increased risk for cancer that might show up several years after exposure. It was not until survivors of the atomic bomb blasts at Hiroshima and Nagasaki had been studied for several years by the Atomic Bomb Casualty Commission (now the Radiation Effects Research Foundation) that data began to reveal increased cases of leukemia in some individuals, and, later, increased numbers of cases of other forms of cancer in some other survivors. The appearance of increased numbers of cancers in a population of individuals several years after exposure is known as a long-term effect of radiation exposure. This effect was not appreciated until well into the 1950s. Before that time, individuals exposed to radiation were not thought to be at increased risk, provided that the doses were kept low enough to prevent short-term effects. This concept is familiar to all of us: none of us believes that an aspirin now and then increases our risk of injury, even though aspirin in large doses can be lethal. The concept was even embodied in expressions for radiation protection standards such as "tolerance dose" and, later, "maximum permissible dose" that implied that doses of radiation are innocuous if they are small enough that they do not produce short-term effects. These expressions for radiation protection standards are no longer used now that we understand long-term effects of radiation exposure.

2. Estimation of Radiation Effects at Low Doses of Ionizing Radiation: Survivors of Hiroshima and Nagasaki that have been followed for almost 50 years were all exposed to relatively large amounts of radiation, expressed in radiation terminology as average whole-body doses of 50 rems (0.5 sieverts) and above. Once the greater numbers of cancers were discovered in the survivors, the question arose of how to estimate the magnitude of risk of radiation-induced cancer at much lower exposures in the range of those that might be received by a radiation worker (eg a nuclear weapons or power plant employee or a doctor or nurse using radiation to diagnose and treat patients). This question was very important

to setting protection standards for radiation workers at levels low enough to ensure safe working conditions. The preferred model for making these estimates was to assume that there is no amount of radiation below which the risk was zero, and that the level of risk increases in a straight-line fashion with the amount of radiation received. This model is known as the no-threshold, linear model of radiation damage, and was developed initially solely for the purpose of setting protection standards for radiation workers. It is important to point out that we have very little direct data on the health effects of exposure of humans (or animals) to small amounts of radiation similar to those received occupationally, and that the data we do have is inconsistent. For example, some data even suggest that there is a beneficial effect of small exposures, a phenomenon known as radiation hormesis, analogous to the scientific finding that an aspirin or two each day decreases the risk of a heart attack. The important point for this discussion is that risk estimates of radiation exposure at small doses are just that - estimates - obtained from a hypothetical model of radiation injury that extrapolates from measured effects in humans at much larger amounts of radiation. Experimental confirmation of these estimates at low doses in humans is essentially impossible to achieve at low doses because 1). the cancers caused by radiation are no different than cancers that occur normally in a population; 2). cancers of various organs and tissues are common diseases that make it difficult to detect small increases in numbers that may be caused by radiation; 3). very large populations of exposed individuals would be required to quantify radiation risk at low doses, and even then the results might not be conclusive. Most scientists believe that the no-threshold linear model is a very conservative approach to estimating radiation risk, and that the actual risk is probably overstated, perhaps by a rather large ratio, by using the model.

3. Purposes of Early Experiments Employing Ionizing Radiation: There has been considerable discussion in the press about "radiation experiments on human subjects" in the 1940s and 1950s. It is apparently true that a few experiments were performed to determine effects such as plutonium retention and excretion in humans, and the ability of radiation to induce sterility in men. However, most of the experiments employed radiation not as a causal agent, but as a means to collect data about human health and disease. For example, in the highly-publicized study at the Fernald State School, adolescent boys received a very small (less than 1 microcurie) amount of radioactive calcium in milk in order to study the metabolism of calcium. The radioactivity was used as a tracer so that the study of calcium metabolism could be performed, and not for the purpose of studying the effects of radiation on the body. At the time, the amount of radioactive calcium used was thought to be innocuous. That conclusion is still true today, because the amount of radioactivity used in the study is so small as to constitute an insignificant (although theoretically not zero according to the no-threshold, linear model) risk to the 19 boys studied. Many studies were performed on individuals in the years after World War II in an effort to develop procedures employing radiation that would benefit patients suffering from a variety of illnesses and injuries. Such studies continue today and constitute the research aspect of disciplines such as diagnostic radiology, nuclear medicine and radiation oncology. The payoff of these studies has been spectacular: for example, 500,000 cancer patients in the United States underwent radiation treatments last year, and over 10 million nuclear medicine procedures were performed.

4. Ethical Considerations of Human Experimentation with Radiation: Just as our knowledge of the health effects of radiation exposure has evolved over the years, so has our appreciation of the rights of individuals involved in human experiments. For example, today a physician is required to provide enough information about a medical procedure to permit "a reasonable person" to make a decision, and to ensure that the patient fully understands the risks of the procedure and the option to decline from participating. Such openness has not always been the case. In the 1940s and 1950s, the process for deciding whether "informed consent" was required for a particular procedure was whether it was customary among physicians to seek consent from patients participating in similar procedures. Since for many of the radiation experiments the risk was thought to be nonexistent or negligible, and since informed consent was not a customary practice for the experiments, it is relatively easy to appreciate how individuals may have unknowingly participated in experiments that involved exposure to radiation. Understanding how this may have happened is not equivalent to condoning the practice from the perspective of today's ethical standards. It is simply a recognition that those standards are different today from those in place in years past.

I wish to end my remarks with a few specific suggestions for the House Committee on Veterans Affairs. First, I fully endorse full disclosure to the public of information about experiments involving radiation that may have been conducted in past decades in Veterans Administration hospitals. Second, this disclosure should be accompanied by best estimates of the amount and type of radiation employed, the resultant risks to exposed individuals, the reasons why the experiments were conducted, and the contributions of the experiments to increased knowledge and improved diagnosis and treatment of disease and disability. Third, the experiments should be judged according to the ethical standards in effect when the experiments were performed and not those in place today. And finally, a followup program should be instituted as appropriate for individuals identified as participants in the experiments.

Thank you for the opportunity to appear before you today.

HONORABLE G.V. (SONNY) MONTGOMERY
QUESTIONS SUBMITTED FOR THE RECORD
HONORABLE JESSE BROWN
DEPARTMENT OF VETERANS AFFAIRS
FULL COMMITTEE
HEARING ON
RESEARCH INVOLVING RADIOACTIVE MATERIALS CONDUCTED IN VA MEDICAL CENTERS

FEBRUARY 8, 1994

Mr. Secretary, a concern has been raised about the current levels of budget and staffing to oversee protection of human subjects in research conducted at VA medical centers.

Question 1: If a VA medical center is failing to follow proper procedures for protecting human subjects, what assurance can you personally provide the committee that such a failure would be detected?

Answer: VA medical centers are required to follow the Federal Policy for the Protection of Human Subjects (codified for VA at 38 CFR 16), as are 15 other Federal departments and agencies. Compliance with regulations is monitored locally by the Subcommittee on Human Studies (of the Research and Development Committee). Additional monitoring is provided by Central Office through review of informed consent documents by both scientific reviewers and research administrative staff.

Question 2: How many persons are employed to oversee the protection of human subjects who participate in the research under VA auspices?

Answer: All VA research utilizing human subjects, both funded and unfunded, undergoes rigorous review at the local facility level. Protocols are reviewed for their scientific merit by the Research and Development Committee. In addition a review to assure informed consent and a risk/benefit analysis by the Human Studies Subcommittee is required. The members of this Subcommittee include VA researchers, clinicians, ethicists or clergymen, non-VA patient advocates and legal consultants; a minimum committee membership of five persons is required. When these studies are submitted for Central Office review for funding, the Merit Review (peer review) process includes an additional review of the impact of the study on human subjects. Due to the variety in expertise required for appropriate evaluation and analysis, FTE cannot be devoted solely to assurance and compliance. Nonetheless, a close estimate of the number of VA and non-VA people involved yields a figure in excess of 700.

Question 3: How many veterans participated in research conducted under VA auspices in the last three years?

Answer: Records on each human research subject are kept at each medical center. However, we do not at this time keep such records centrally. We are currently exploring the feasibility of collecting this information on a national basis.

(Page 2)

HONORABLE G.V. (SONNY) MONTGOMERY

Question 4A: How many facilities were visited by persons charged with overseeing the protection of human subjects in the last three years?

Answer: Site visits are regularly carried out on all human subject research within the Cooperative Studies Program. In FY 1993 12 such visits were made. In all instances, the facilities were found to be in full compliance with regulations.

Question 4B: How many research projects involving human subjects did such persons review?

Answer: As indicated in the response to question 4, 12 multi-site (cooperative) studies were reviewed.

Question 5: Could current VA efforts to oversee the protection of human subjects be augmented?

Answer: Yes. Such efforts could be augmented by the addition of sufficient Central Office staff and travel funds to permit medical center site visits; however, current review and oversight procedures are adequate for this protection of human subjects in research.

Question 6: How does VA staffing of this function compare with that of other research sponsors, such as NIH?

Answer: Our impression is that VA, by virtue of the intramural nature of its research program, exercises tighter control of (or monitors more closely) the behavior of its investigators than do many other Federal agencies that provide grants. However, we would acknowledge that, at the Central Office level, NIH, in its Office for Protection from Research Risks, is much better staffed than VA. Comparisons are difficult, however, because department/agency responsibilities vary significantly.

Question 7: What would be the cost and benefits of increasing staffing donated to such oversight in the VA?

Answer: Any increase in staffing at the Central Office level would have to be funded by increased appropriations or by taking staff away from other critical health programs. Since current procedures are adequate to protect human subjects involved in research, additional staff and cost would have little added value.

HONORABLE BOB STUMP
QUESTIONS SUBMITTED FOR THE RECORD
HONORABLE JESSE BROWN
DEPARTMENT OF VETERANS AFFAIRS
FULL COMMITTEE
FEBRUARY 8, 1994

Question: Is it correct that only research on human subjects with ionizing radiation before 1972 is being investigated, because after 1972 the basic standards which are observed today were in effect and because after 1972 there was so much research conducted that it would be nearly impossible to evaluate all of it?

Answer: The Advisory Committee on Human Radiation Experiments will focus its attentions on experiments conducted between 1944 and 1974. Federal guidelines requiring Institutional Review Boards (IRBs) to scrutinize human subjects research, to which many agencies voluntarily adhered, were introduced in 1974, thus Committee and agency investigatory efforts were directed toward the earlier period. The Department of Veterans' Affairs has expanded the scope of its initial investigation to cover 1975-1979 to account for the fact that IRBs in VA facilities were phased in throughout the 1970's. We are working closely with the Committee to determine the appropriate and manageable scope of the VA investigation.

Question: What is the VA's estimate for the manhours and cost of conducting its department-wide internal investigation of VA research on human subjects with ionizing radiation?

Answer: It is not really possible at this point in time to estimate either the manhours or cost of the internal investigation which is ongoing. All 169 facilities have conducted an initial search to identify existing information on nuclear medicine (radioisotope) research. This phase was conducted in January 1994 and revealed that 46 have located some protocols used during that period, 20 have some patient names, and 52 have located some publications related to the research. Inventorying and retrieving the information for review by the Advisory Committee on Human Radiation Experimentation will be accomplished utilizing guidelines promulgated by the interagency steering committee.

Question: Will the resources needed for the VA's department-wide internal investigation of VA research on human subjects with ionizing radiation have any effect on VHA's ability to provide timely and quality health care services to veterans?

Answer: The Veterans Health Administration (VHA) is trying to conduct the investigation in such a way as to minimize the impact on the timeliness and quality of health care services to veterans because the delivery of high quality services in a timely manner is VHA's highest priority.

HONORABLE G.V. (SONNY) MONTGOMERY
QUESTIONS SUBMITTED FOR THE RECORD
DEPARTMENT OF VETERANS AFFAIRS
HOUSE COMMITTEES ON VETERANS AFFAIRS
HEARINGS

FEBRUARY 8, 1994

Question 1: Would you consider research conducted decades ago to have been "inappropriate" if the protections afforded those research subjects conformed with then-accepted practice but were substantially below those currently in place, or below those that might be developed by the President's advisory committee?

Answer: Research conducted in the past should not be considered "inappropriate" if it conformed to the accepted ethical standards of the day unless there is evidence that basic principles of ethics were violated e.g., deceptive practices, duress on the individual, disregard for well-being of subjects. Such violations would depend upon case-by-case analysis. Standards of today are very detailed, having evolved over many years and they are, in many respects, based on past experience. It should not be assumed that previous standards were faulty even though they were not as detailed as today's or future standards.

Question 2: To the extent that you have uncovered records documenting VA-conducted research prior to 1961, what kind of information is contained in such records?

Answer: VA's initial survey of all VAMCs who may have done nuclear medicine research between 1947 and 1980 shows that of the 168 VA facilities, 135 have Nuclear Medicine Services at this time. The numbers which had radioisotope units (as they were called in the early days) or Nuclear Medicine Services according to the years established are listed below:

Decade Service was Established	Number of VAMCs
1940-50	6
1951-60	47
1961-70	29
1971-80	38
1981-90	11
1991-	3

Of those facilities having nuclear medicine capability:

- 46 have located some protocols used during that period for radioisotope research,
- 20 have names of patients who participated in at least some research projects,
- 52 have some publications available on specific research projects done during that period.

There was no evidence found of any research involving Plutonium and no VAMC had contracted out research.

The next step in the process will be retrieval and inventory of these records prior to in-house review. However, the process for actual inventory and retrieval is being developed by the Interagency Committee on radiation. A rigorous "chain-of-custody" in accordance with the interagency committee direction will be established. In the meantime, an additional search for any other

HONORABLE G.V. (SONNY) MONTGOMERY

human research related to ionizing radiation is being done and affiliated institutions are being queried about the availability of records relating to research involving VA patients but not done at VA facilities. Copies of all records eventually will be made available to the Advisory Committee on Human Radiation Experiments for their review.

Question 3: Does there exist any current VA policy that requires follow-up studies or periodic examinations (after the research has been completed) on the health status of research subjects, or is the conduct of such studies left to medical judgment of the investigators? (If so, what does that policy provide?)

Answer: There is no specific policy which requires periodic follow-up or examination after completion of a research study, unless there is a relevant aspect of the study which involves appropriate periodic re-examination e.g., long-term therapy, implantable devices, etc., and this would be part of the study protocol. Institutional review boards are intensely concerned with long-term health consequences of research studies and would not approve studies which were inadequate in following the human subjects.

HONORABLE LANE EVANS
QUESTIONS SUBMITTED FOR THE RECORD
DEPARTMENT OF VETERANS AFFAIRS
HOUSE COMMITTEES ON VETERANS AFFAIRS
HEARINGS

FEBRUARY 8, 1994

Question 1: How many VA employees are currently engaged in research which exposes human subjects to radioactive material and how many human subjects in total are participating in this research? How many such projects are there and please identify the locations of these projects.

Please summarize this research for us.

Answer: The Research and Development Information System (RDIS) does not have the capability of identifying numbers of employees involved in a given subject area of research nor can it identify numbers of human subjects.

There are about 450 active research projects which expose human subjects to radioactive materials in the course of diagnosis or treatment of numerous medical conditions. These projects are distributed among 78 VAMCs.

Question 2: Some human subjects who were reported to have been exposed to ionizing radiation during scientific or medical research or experiments were not able to give informed consent. Describe current safeguards to prevent this from happening today.

Answer: In 1976, Congress enacted a law, currently codified at 38 U.S.C. § 7331, that requires the Secretary to prescribe regulations establishing procedures to ensure that all medical and prosthetic research, as well as all medical care, be carried out only with the full and informed consent of the subject or patient. To meet the requirements of the law, VA promulgated regulations establishing procedures for obtaining informed consent from patients and research subjects. The regulations are published at 38 C.F.R. § 17.34. VA has also promulgated VA Policy Manual M-2, Part I, Chapter 23, which provides even more detailed procedures for obtaining informed consent.

Answers by Dr. Belton Burrows

DEPARTMENT OF VETERANS AFFAIRS
VA Medical Center/Outpatient Clinics
Boston, Massachusetts 02130

QUESTION 1: In conducting radiation related research in the VA, what were the highest dosage levels to which your subjects were exposed? What was your understanding at the time as to what risks were entailed in such dosage levels? Can you recall whether you described those risks to the research subjects and, if so, how would you have described them?

ANSWER: The highest dose levels to which subjects were exposed were below the limits of Atomic Energy Commission regulations; 350 microcuries for potassium-42; 150 microcuries for sodium-24; 15 microcuries for sodium-22; and 300 microcuries for tritium. Those dosage levels were insignificant compared to environmental and body burden exposures from naturally occurring radionuclides. The risks to the subjects were described to the subjects in those terms.

QUESTION 2: If by the term "informed consent" we mean freely given consent following a full and careful explanation of the research project, whether or not the subject is given a form and asked to sign it, did you conduct research in the VA which did not seek your subjects' informed consent?

ANSWER: No.

QUESTION 3: Who was responsible for informing patients of the possible risks of participating in a particular study and who was responsible for determining this risk? How was the risk determined?

ANSWER: Physicians were responsible for informing patients about possible risks from or posed by participating in a particular study and for determining the risks. In patient studies, the risk-to-benefit relationship was determined by the physician's knowledge of the patient's medical problem. Consideration was given to other radiation, such as x rays, to which the patient might be exposed to as part of routine medical or dental care. For diagnostic studies and particularly for therapeutic procedures, such as iodine-131 administration for hyperthyroidism and thyroid cancer, patients were also informed about precautions to be taken and possible side effects such as hypothyroidism.

QUESTION 4: Do you agree with current restrictions and regulation of research involving human subjects? Has this trend of increasing protection gone too far?

ANSWER: Dr. Burrows agrees with current restrictions and regulations. The trend of increasing protection has been enabled by improved technology and increased sensitivity of radiation measurement procedures.

QUESTION 5: Would you have had the cooperation of so many patients if the current restrictions had been in place back in the 1940s and 1950s?

ANSWER: Dr. Burrows is of the opinion that, had current restrictions for research been in place in the 1940s and 1950s, it is unlikely the restrictions would have discouraged or prevented patients from participating in VA's research activities.

QUESTION 6: Dr. Rothman cites the principle set forth at Nurenburg that calls from voluntary consent of research subjects and for the subjects to have "sufficient knowledge and comprehension of the elements of the subject matter involved as to make an enlightened decision." Would you comment on how one insures that patients have achieved that level of understanding?

Any level of patients' understanding will be dependent on patients' general knowledge and physicians' communication skills. For clinical research using tracer doses (which are not considered to be of physiological significance). Patients can readily understand physicians' explanations.

Chairman Montgomery to Ervin Kaplan, M.D.

1. Question:

In conducting radiation related research in the VA, what were the highest dosage levels to which your subjects were exposed? What was your understanding at the time as to what risks were entailed in such dosage levels? Can you recall whether you described those risks to the research subjects, and if so, how would you have described them?

Answer: In conducting research with radioactive materials during my VA career, the highest dosage employed was one millicurie per day, five doses per week, of P-32 labeled polymetaphosphate, for a total of 20 millicuries for the therapy of carcinoma of the prostate metastatic to bone. This dosage was determined by our own pilot studies and those by other workers employing P-32 labeled orthophosphate. This dosage was subsequently changed to two millicuries, three time per week for a total dosage of 16 millicuries. The effectiveness of the therapy did not appear altered; however, it was more convenient for the patient and therapist.

The risk entailed in these studies may be evaluated by indicating the type of patient selected. All patients were in the terminal phase of carcinoma of the prostate metastatic to bone; their survival was estimated at under one month, all were suffering from intractable bone pain and several were suffering from paraplegia due to spinal cord compression secondary to malignant involvement of the vertebrae. The goal of our research was the control of pain secondary to the bone lesions. We treated a total of eight patients and were successful in reducing or eliminating bone pain in seven of the eight patients.

The patients involved were dying and suffering severe pain. Their risk of death without our experimental therapy was absolute. With the P32 polymetaphosphate we might diminish their pain. This was communicated to the patient by William Walsh, M.D., the chief of our hospital tumor section and by me. They were told that the treatment would probably have some depressing effect upon their blood forming tissue. We did not indicate that this treatment would cure their cancer. The consent of the patients to participate in this study was readily obtained. No patient who was approached refused to participate.

Reprint enclosed:

Ervin Kaplan, M.D., et al. Therapy of Carcinoma of the Prostate Metastatic to Bone with P32 Labeled Condensed Phosphate, J. Nucl. Med. 1:1-13, 1959.

2. Question:

If by the term "informed consent" we mean freely given consent following a full and careful explanation of the research project, whether or not the subject is given a <u>form</u> and asked to sign it, did you conduct research in the VA which did <u>not</u> seek your subjects' informed consent?

Answer: Using the definition of informed consent as stated in the above question, when a new or untried radioactive material was administered to a patient for research purposes, informed consent was obtained. When radioactive substances were employed upon the body fluids of a patient obtained for other purpose, but not administered to a patient and this was done for research purposes, this was designated an in vitro procedure and informed consent was not obtained. Statistical research was performed upon information obtained while performing accepted clinical procedures; informed consent was not obtained. Research on devices and procedures which were modified to measure radioactivity by improved methodology was not considered a reason for informed consent. The instances in which informed consent was not obtained were without risk to the patient.

3. Question:

Who was responsible for informing patients of the possible risks of participating in a particular study and who was responsible for determining this risk? How was the risk determined?

Answer: The person or persons responsible for informing patients of risk in a research project were a collaborative group. Specifically, the physicians in charge of the patients' clinical care and those physicians involved in the study. Those included the ward physician, the section chief and those physicians involved in the medical aspects of the technical area of the research, the chief of nuclear medicine and nuclear medicine physicians when radioactivity was employed. In addition, various basic scientists were among the collaborators. These individuals ordinarily produced a protocol defining the research. Risk was determined when radionuclides were used by the review of previous relevant works, the intensity of the radiation dose, the type of emission, the physical and biologic half life of the radionuclide and the site of localization as related to the chemical properties. Radiation risk is determined by the health physicist and the nuclear medicine physician using standard reference information. The protocol is subject to further review by the institutional Radiation Safety Committee and the institutional research committee. The Committee of Affiliated University Medical Schools may be involved. Oversight of the VA Director of Nuclear Medicine and the then Atomic Energy Commission was obtained. Additional review and oversight was often obtained by peer review by the National Institutes of Health or other review groups. It must be assumed that the responsibility for any risk to a patient is that of any physician performing a procedure. It may be stated that the consideration of patient risk is more carefully taken in a research study than in ordinary clinical practice. The use of radioactivity might be the least component of risk.

4. Question:

Do you agree with current restrictions and regulation of research involving human subjects? Has this trend of increasing protection gone too far?

Answer: The restrictions and regulations of research should be proportional to the risks involved, the importance of the information that may be obtained, the direct benefit of the study to the patient, and finally, should not ever be in violation of the patient's personal rights. The various risks involved in human research using physical agents, pharmaceuticals or invasive procedures must be thoroughly considered. When comparing radiation from radioisotopes to other agents or procedures, the radioactivity is often of lesser risk than the pharmacologic, allergic and chemical side effects of food and drugs or the trauma of invasive procedures. Despite this comparison, these other agents or effects seldom evoke the hysteria occasioned by radiation and particularly radiation from radioactivity. The need exists to level the playing field when studying the effects of any chemical or physical agent to be investigated for use in medicine. The regulative function in relation to experimental risk should be defined by competent scientific review rather than by legislation.

5. Question:

Would you have had the cooperation of so many patients if the current restrictions had been in place back in the 1940s and 1950s?

Answer: I do not feel that informed consent is a limiting factor in conducting research on patients in a VA hospital or that it ever was. The limiting factor is the patient/doctor relationship. The patient very quickly knows when the physician perceives a patient as an object rather than a person!

6. Question:

Dr. Rothman cites the principle set forth at Nuremburg that calls for voluntary consent of research subjects and for the subjects to have "sufficient knowledge and comprehension of the elements of the subject matter involved as to make an enlightened decision." Would you comment on how one insures that patients have achieved that level of understanding?

Answer: The essence of Dr. Rothman's statement is morally correct, but should include two additional words, "when possible." Following Dr. Rothman's instructions verbatim would place a significant and unnecessary stricture upon medical research. To assume that patients could always be objective about their own illness is nonsense; they are always subjective. Further, the statement would preclude research on diseases of infants, most children, psychotics, the mentally unstable and infirm, terminal patients and would certainly inhibit a scientist seeking better methods to diagnose brain death. Problems are seldom solved by oversimplification or aphorisms. Comparing research in VA hospitals to Nazi Germany is, to say the least, inappropriate. One cannot insure that patients always achieve that level of understanding. We cannot conclude that we should not learn from patients who lack that level of understanding. The best that we can do in the real world is to insure that physicians engaged in research in the VA are of such moral stature as to have "sufficient knowledge and comprehension of the elements of the subject matter involved as to make an enlightened decision." We thank Dr. Rothman for making a very flexible statement.

Therapy of Carcinoma of the Prostate Metastatic to Bone with P^{32} Labeled Condensed Phosphate

Ervin Kaplan, M.D., I. Gordon Fels, Ph.D., Bruno R. Kotlowski, Joseph Greco, B.S., and William S. Walsh, MD.

Chicago

PHOSPHATE LABELED with P^{32} has been used in palliative therapy of malignant tumors metastatic to bone (1,2). As previously reported, therapeutic benefit is probably related to incorporation of P^{32} phosphate in regenerating bone adjacent to the intraosseous lesions (3). It would appear advantageous to increase the concentration of P^{32} in the areas of osteoblastic activity, thereby enhancing the radiation dosage to the tumor while simultaneously sparing the non-tumorous soft tissue. Using P^{32} labeled polymetaphosphate, a high molecular weight condensate of phosphate (Fig. 1), the authors have demonstrated significant preferential localization of radioactivity in growing areas of bone as compared to deposition from P^{32} labeled NaH_2PO_4 (4). The polymetaphosphate is hydrolyzed to phosphate by mammalian phosphatases, and may be presumed to be poorly available to the soft tissue phosphate pool, until so released by tissue phosphatases, particularly the alkaline phosphatase of growing bone.

METHOD

Selected cases of carcinoma of the prostate with widespread metastasis to bone were treated with intravenous injection of sterile polymetaphosphate solu-

From the Radioisotope and Surgical Services of the Veterans Administration Hospital, Hines, Illinois.

Presented at the Sixth Annual Meeting of The Society of Nuclear Medicine, Chicago, June 18, 1959.

Reprinted from the January, 1960 issue of the Journal of Nuclear Medicine

tion.[1] The preparation was synthesized from NaH_2PO_4 by the method of Jones(5). No free phosphate remained as determined by the absence of precipitate with $AgNO_3$. The pH of the non-radioactive control solution in 1 percent concentration was 5.5; phosphorus content was 28 percent.

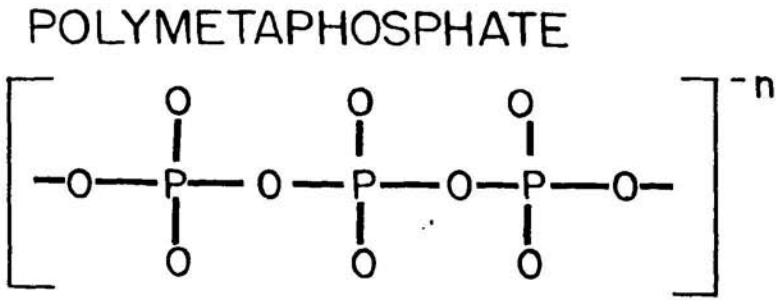


Fig. 1. Polymetaphosphate, a high molecular weight condensate of phosphate.

The therapeutic regimen consisted of the intravenous injection of one millicurie of P^{32} metaphosphate five days per week until a total dosage of 20 millicuries was administered. This dosage has been modified and is not currently recommended. The modified dosage is given in the result section of this report. Evaluation was based upon clinical response, radiographs of the involved areas, bone biopsy in selected instances, serial determination of hemoglobin, erythrocyte, leucocyte and platelet counts, serum phosphate determination and serum acid and alkaline phosphatase determinations. A modified Bodansky technique was employed in the latter. Evaluation of post-mortem specimens was based upon autoradiographs, tissue assay of P^{32} activity, and histological sections.

RESULTS

Of the eight patients given a full course of therapy, seven showed palliation of pain and clinical improvement (Table 1). The palliative effects became apparent during the administration of metaphosphate—they were marked in four patients. One patient (WF) with metastatic involvement of the tibia had experienced severe pain for several weeks. The pain subsided dramatically after the first week of therapy. Several bedfast patients became ambulatory for the first time in many months.

Several weeks following completion of therapy, a transient leucopenia was noted in the patients who experienced clinical benefit. During this period some patients experienced nausea, developed low-grade fever and petechiae. One developed multiple small abscesses of the scalp which responded to antibiotic therapy.

The patients who died showed a progressive deterioration with weight loss and progressive cachexia which followed the period of palliation. The white

[1]Prepared by the Volk Radiochemical Company, Chicago, Illinois according to the authors' directions.

TABLE 1. PALLIATION AND SURVIVAL POST POLYMETAPHOSPHATE THERAPY

Patient	Palliation	Days of Palliation	Days of Survival	Status
A. J.	+	40	111	Dead
P. S.	+	30	100	Dead
E. L.	+	60	230	Dead
S. S.	0	0	110	Dead
B. H.	+++	465	490	Living
W. D.	++	100	270	Dead
E. W.	+++	100	475	Living
W. F.	+++	70	230	Dead

blood count did not remain depressed in any instance, even in the presence of progressive anemia. Terminal pneumonia was the apparent immediate cause of death in each case.

Roentgenograms of the metastatic bone lesions showed an increased radiodensity of the sclerotic areas following metaphosphate therapy. In two patients (B.H., E.W.), still surviving weeks after a full course of metaphosphate therapy, areas which initially were sclerotic and then showed intensification of sclerosis now showed some clearing. A biopsy of the intensified bone sclerosis from one patient showed large patches of non-viable bone and necrotic tumor tissue.

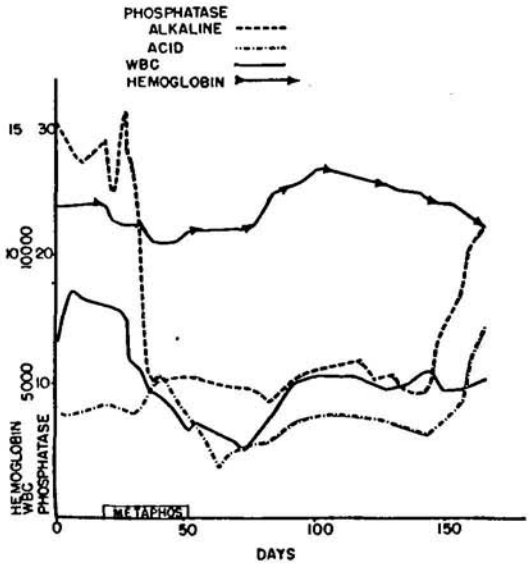


Fig. 2. Clinical laboratory values patient W.D. (See text)

TABLE 2. POST THERAPY CHANGES IN LEUCOCYTE COUNTS AND VALUES OF PHOSPHATASES

Patient	Leucocyte Counts		Alkaline Phosphatase[a]			Acid Phosphatase[b]		
	Lowest	Time of lowest days post treatment	Pre-treatment	Lowest	Time of lowest days post treatment	Pre-treatment	Lowest	Time of lowest days post treatment
A. J.	1600	20	17	2.6	53	1.8	0.8	40
P. S.	2200	14	21	3.0	56	5.0	0.8	34
E. L.	2200	20	16.6	6.0	35	1.6	0.8	55
S. S.	No drop	—	Norm.	No change	—	3.4	No change	—
B. H.	2450	27	8.4	3.2	6	1.8	0.4	12
W. D.	2300	21	29	8.4	32	8.0	3.4	11
E. W.	2400	24	5	3.0	41	3.0	1.0	142
W. F.	2600	13	40	13.2	33	30.0	15.2	83

a. Expressed in Bodansky units. (Normal = 2.0–4.0)
b. Expressed in Bodansky units. (Normal = < 1.0)

TABLE 3. ORGAN OR TISSUE P^{32} RADIOACTIVITY AT NECROPSY FOLLOWING POLYMETAPHOSPHATE THERAPY

Organ or tissue	Patient (dose-days post treatment)		
	B.H. (5 mc-1 day)	P.S. (20 mc-63 days)	A.J. (20 mc-111 days)
Adrenal	14,512	242	388
Aorta	2,464	156	58
Bladder	———	———	138
Bladder Stone	———	2515	———
Brain	1,380	210	310
Bone			
Metastatic, marked	41,743 rib	5013 left clavicle 5205 iliac crest 2201 vertebra	2723 vert.
Metastatic, moderate	———	1728 right clavicle 1094 rib	1173 rib
Normal cancellous	8,589 skull	401 skull	———
Cartilage	1,363	527	289
Diaphragm	5,800	151	120
Adipose	3,233	124	0
Heart	7,416	377	163
Intestine	4,551	192	117
Kidney	11,575	218	65
Liver	20,013	281	452
Lymph Node (normal)	5,155	———	188
Lymph Node (metastatic)	———	195	———
Lung	0?	118	157
Muscle (pectoralis)	3,936	141	339
Pancreas	5,930	243	234
Periosteum	6,053	———	———
Prostate	4,150	302	67
Thyroid	4,669	———	132
Skin	2,022	70	0
Spleen	21,669	351	301
Tumor, metastatic soft tissue	12,867	243	———

The decreases in white blood cells and alkaline and acid phosphatase levels in the blood are indicated in Table 2. The leucopenia was transient. The drop in the alkaline phosphatase level was marked and prolonged. The drop in acid phosphatase level though less dramatic was significant in every case in which the leucocyte count and alkaline phosphattase level decreased, and it paralleled the alkaline phosphatase.

Assay of P^{32} shows a marked preponderance and persistence of P^{32} in metastatic tumors of bone, when compared with normal cancellous bone, and prostate carcinoma in soft tissue. A comparison was made of organ and tissue P^{32} activity in necropsy specimens following metaphosphate therapy (Table 3).

Radioautography demonstrates that the greatest activity in metastatic bone is in the bone spicules and not in the tumor nodules.

The correlation between therapy, laboratory findings and clinical course is best demonstrated by several case reports and the accompanying graphs.

The first example (W.D.) was a 68 year old Negro male with widespread metastatic involvement of the pelvis and spine (Fig. 2). Therapy with metaphosphate was given as indicated, orchiectomy was not done nor was any other specific therapy employed. A marked drop in alkaline phosphatase is seen. Acid phosphatase decrease is less marked but parallels the alkaline phosphatase. WBC showed a transient drop and recovery. Hemoglobin values fell moderately with therapy and rebounded to values above pretherapy level; after reaching a peak coinciding with clinical improvement, a gradual decrease is noted. A sharp rise in acid and alkaline phosphatase values about three and one-half months after therapy coincided with marked increase in bone pain.

The second case (E.W.) a 69 year old Negro male had widespread metastatic involvement of the pelvis and spine (Fig. 3). He had been previously treated by orchiectomy and estrogen therapy. Before metaphosphate therapy he had ceased responding to estrogen therapy and was bedfast for many weeks with severe pain radiating from the lumbar region into the legs. The phosphatase elevations were not remarkable. However, on therapy, both acid and alkaline phosphatase values returned to normal. He became asymtomatic and ambulatory and spent several months at home. His leucocyte count and hemoglobin after a temporary fall returned to and remained at normal levels. After four symptom-free months his phosphatase values increased and pain returned to his back

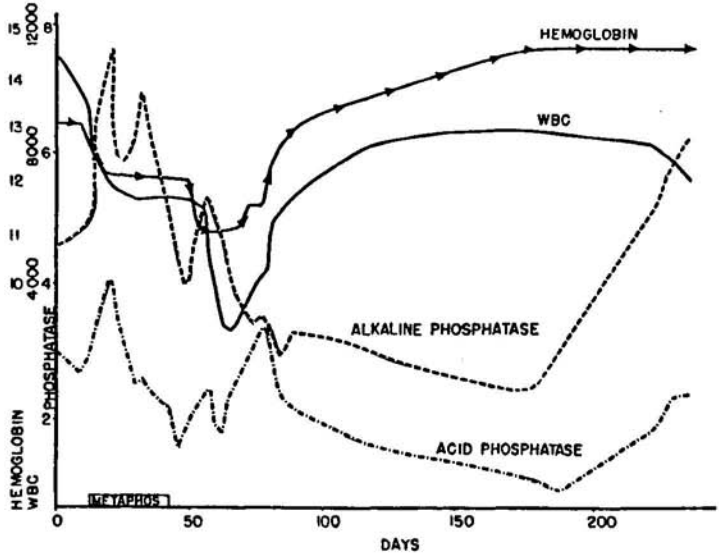
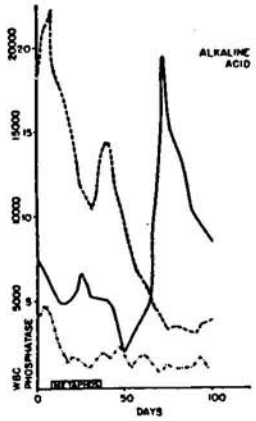


Fig. 3. Clinical laboratory values patient E.W. (See text)



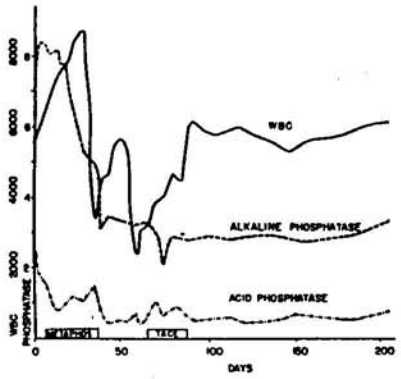


Fig. 4. Clinical laboratory values patient P.S. (See text) *(left)*
Fig. 5. Clinical laboratory values patient B.H. (See text) *(right)*

and legs. He received a second course of therapy subsequent to the time period on the graph (Fig. 3). He is again asymptomatic and has been discharged from the hospital.

The third case (P.S.) a 66 year old white male had widespread involvement of the bony skeleton with pain in the back, pelvis and legs. His alkaline and acid phosphatase values showed a dramatic drop to normal with a transient period relatively free of symptoms (Fig. 4.). X-ray examination of his bony skeleton showed a widespread increase in bone sclerosis. The patient became cachectic, anemic and died. At autopsy, areas of normal bone and bone marrow were viable. The P^{32} activity in the normal bone was significantly lower than that in bone infiltrated with tumor. Assays for radioactivity revealed that the soft tissue tumor nodules contained only one-tenth the activity of metastatic bone. The tissue areas which had been heavily irradiated contained a relatively large amount of necrotic bone, bone marrow and tumor tissue. These necrotic areas were reinvaded by bone from the periosteum and by tumor. These changes are illustrated in the photomicrographs (Figs. 6 a-g).

The next patient (B.H.) was a 68 year old white male with paraplegia. Radiographs revealed widespread metastatic involvement of the spine and pelvis. A biopsy of the vertebrae at laminectomy was diagnosed as metastatic carcinoma from the prostate. He was given metaphosphate therapy a number of weeks post-orchiectomy. Alkaline and acid phosphatase values dropped to normal. (Fig. 5) At that time he was placed on TACE (chlorotrianisene), an oral estrogen-like substance, in doses of 12 mg twice daily for about one month. Since that time he has received no other therapy directed toward his carcinoma. The phosphatase values have remained normal for more than 400 days post-metaphosphate therapy. During this time he has gained fifty pounds in weight and has symptoms only of his paraplegia. In recent weeks, back pain has returned without alteration of phosphatase values.

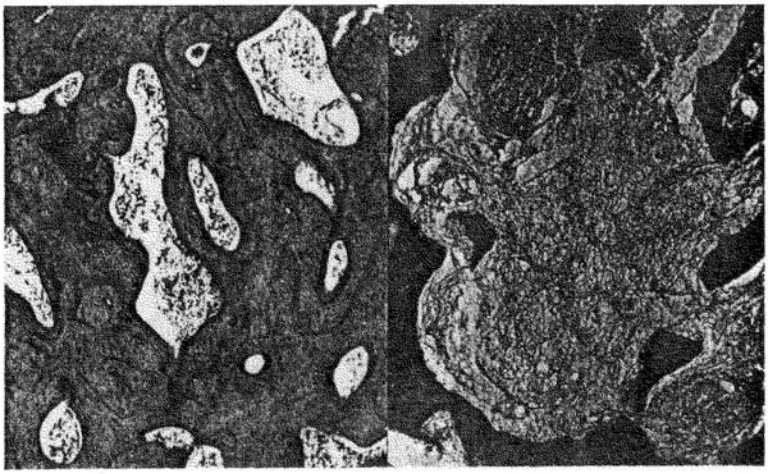


Fig. 6a. Normal Bone—The bone obtained from a normal area of the right clavicle showed normal architecture, viable osteocytes in the lacuni and bone marrow cells in the intratrabecular spaces. *(left)*

(Legend applicable to all of figure 6, a-g: Specimens of bone were obtained at necropsy from patient P.S. 63 days following completion of a course of 20 millicuries of P^{32} labeled polymetaphosphate.)

Fig. 6b. Metastasis to Bone—The trabeculae were not viable, the lacuni were empty, and large areas of necrotic tumor are visible. Islands of tumor with pyknotic nuclei survive in several areas. These areas coincided with high levels of P^{32} activity in bone. *(right)*

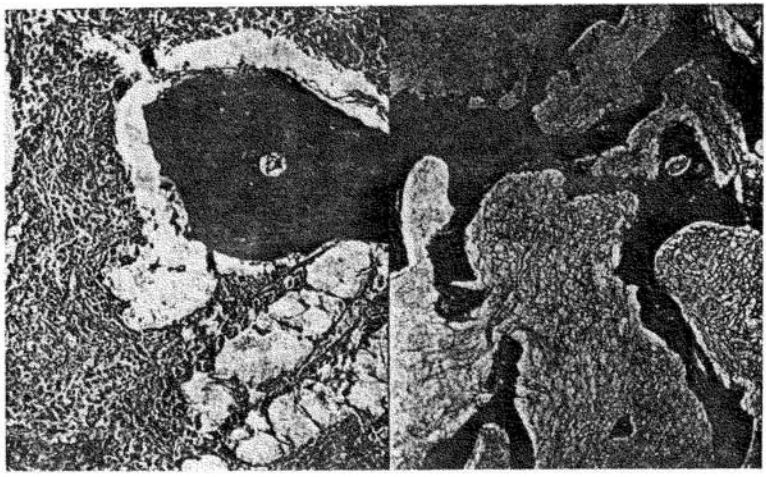


Fig. 6c. Necrotic Tumor—A high-powered view showing necrotic tumor in sheets occupying the marrow space. *(left)*

Fig. 6d. Necrotic Bone—An area of radionecrosis which is completely acellular; architecture of the previous cellular content of marrow space cannot be determined. *(right)*

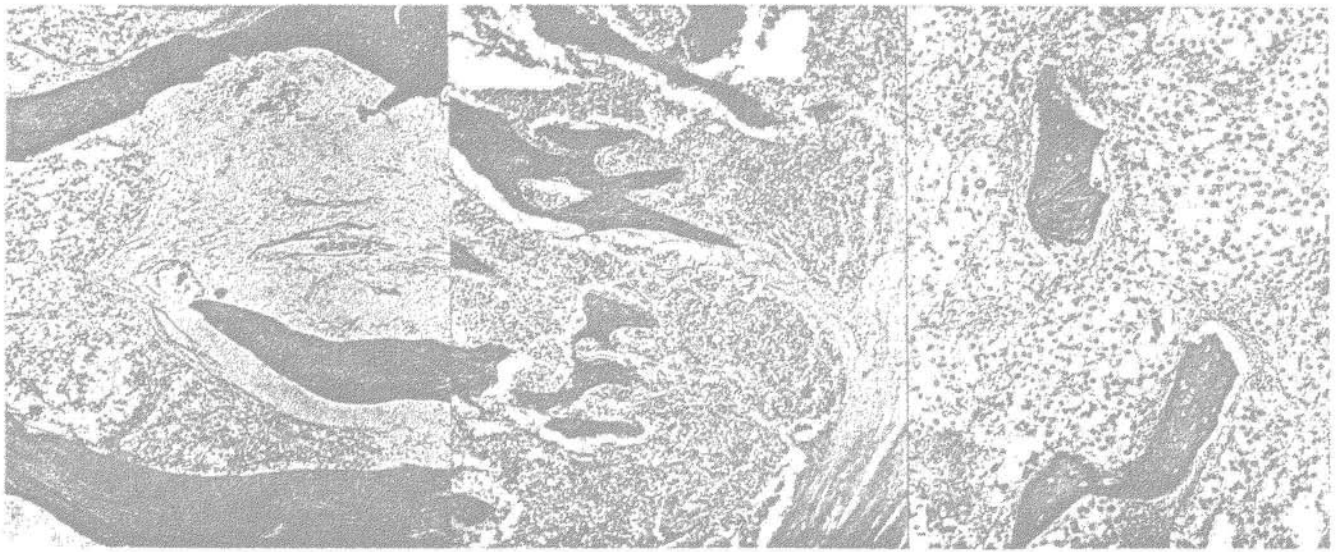


Fig. 6e. Tumor Invasion—The area contains acellular bone spicules. NOTE the empty lacuni. The marrow space is fibrotic and is being invaded by sheets of malignant cells. *(left)*

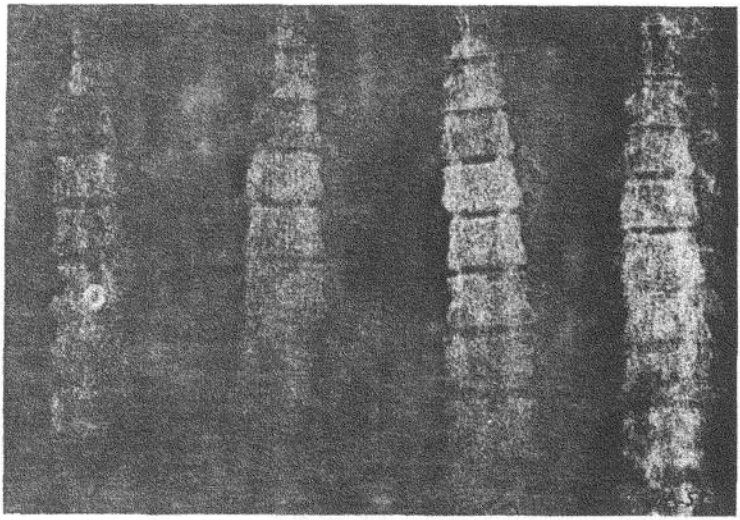
Fig. 6f. Regrowth of Bone—Viable periosteous bone was preserved around the necrotic areas and may be seen growing into the destroyed areas. *(center)*

Fig. 6g. Reestablished Tumor—Many areas containing dead bone spicules had been completely overgrown by sheets of very viable new tumor growth. The balance between tumor and new bone regeneration appears crucial. *(right)*

Serial x-ray examinations (Fig. 7) of his spine show the pretherapy status, the immediate post-therapy sclerosis and in the final film, the decreased sclerosis seen at about six months post-therapy.

A lesion in the pelvis studied during the same period shows progressive change from sclerosis toward radiologically normal bone (Fig. 8).

Another group of patients with metastatic carcinoma to bone from the prostate have been treated since the above observations were made. These patients were under therapy with 12 mg of TACE twice daily at the time metaphosphate therapy was initiated. The metaphosphate was administered intravenously in 2 millicurie doses three times per week until a total dose of 16 millicuries was injected. This is the dosage currently suggested. Of the five patients so treated, all have shown rapid complete disappearance of bone pain, weight gain, and minimal radiation side effects. Two of the patients had paraplegia of recent onset. Following therapy one has a complete remission of his paraplegia; the other is markedly improved. In another patient the acid phosphatase level had remained at a level of approximately 120 Bodansky units for four months (Fig. 9). The patient had refused orchiectomy but had been on TACE therapy for about one month with little improvement. Within 18 days of the onset of metaphosphate therapy, the acid phosphatase value dropped from 120 Bodansky



(a) (b) (c) (d)

Fig. 7. Radiographic evaluation of lumbodorsal spine (B.H.) in metastatic carcinoma of prostate.
a) Pre-Therapy with polymetaphosphate.
b) Immediately post 20 millicuries of P^{32} polymetaphosphate therapy.
c) 6 weeks post polymetaphosphate therapy.
d) 5 months post polymetaphosphate therapy.

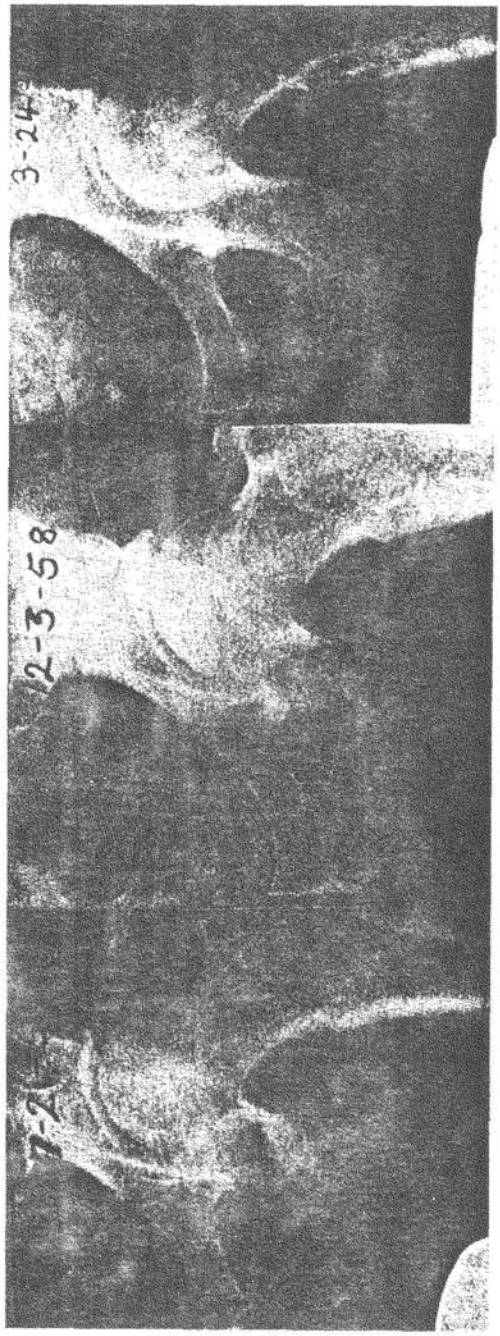


Fig. 8. Radiographic evaluation of pelvis (B.H.) in metastatic carcinoma of prostate showing a sclerotic lesion in the ischium prepolymetaphosphate therapy (a) and progressive clearing of the lesion six weeks (b) and five months (c) post therapy.

units to 7; he gained weight; and there was complete disappearance of bone pain which had been present for many months. The rise in alkaline phosphatase levels in this patient is a pattern not previously observed. Further followup of the combination of estrogen-metaphosphate therapy will be made as well as more detailed comparison with the patients treated only with polymetaphosphate.

DISCUSSION

Localization of P^{32} activity from polymetaphosphate in growing sclerotic metastatic carcinoma of bone from the prostate has a palliative effect upon the pain associated with this lesion. Its preferential deposition in growing bone as compared to orthophosphate may be related to hydrolysis at the site of the bone lesion by the local high concentration of alkaline phosphatase, thus bypassing the soft tissue phosphate pool, and sparing this tissue from excessive beta irradiation.

Lack of concentration in the tumor nodule suggests a palliative use only; however, depression of the carcinoma by estrogenic substances in conjunction with metaphosphate therapy has produced a superior palliative effect in a small group of patients. The mechanism of this apparent synergism is not known.

P^{32} labeled metaphosphate has been used in several cases of metastatic carcinoma from the breast to bone with palliation of bone pain. It is also strongly suggested that metaphosphate be given a therapeutic trial in osteogenic sarcoma with active growth of malignant bone and high alkaline phosphatase activity.

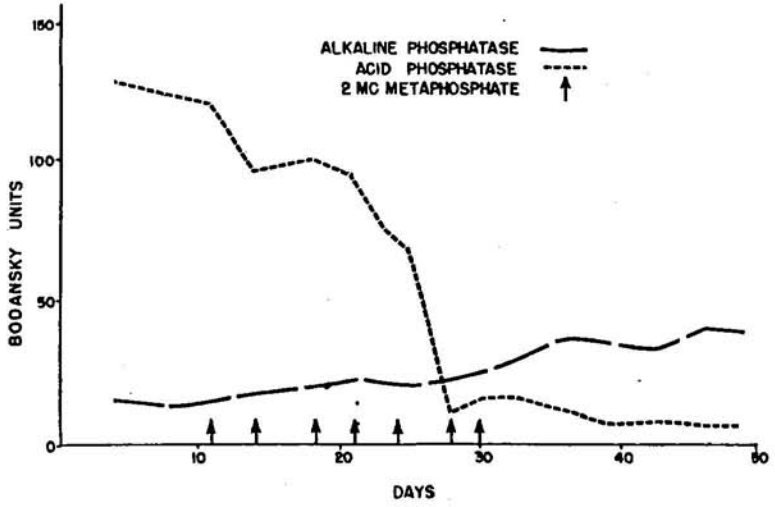


Fig. 9. Alkaline and acid phosphatase values in patient treated with polymetaphosphate while on estrogen therapy. A rapid and marked drop in acid phosphatase level coincides with the polymetaphosphate administration.

SUMMARY

The use of a new palliative agent, P^{32} labeled polymetaphosphate, for the therapy of metastatic carcinoma from the prostate to bone has been discussed. Its localization in regenerating bone surrounding intraosseous, osteoblastic tumor is a function of phosphatase activity. Effective palliation of bone pain, a decrease in alkaline and acid phosphatase and radiographic regression of lesions were observed. A combination of estrogen and polymetaphosphate therapy produces a synergistric palliative effect apparently superior to either agent alone.

ACKNOWLEDGEMENT

Acknowledgment is gratefully made to the resident physicians of the Orthopedic, Tumor and Urologic Sections of the Surgical Service, Veterans Administration Hospital, Hines, Illinois for their invaluable clinical aid.

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Chairman Montgomery to James A. Pittman, Jr., M.D., The University of Alabama at Birmingham

QUESTIONS FROM CHAIRMAN MONTGOMERY'S LETTER OF 2/14/94
for Hearing of 2/8/94

1. The highest dosage levels to which subjects in my experiments were exposed were about 100 μCi (=3.7 MBq) from radioactive iodine (^{131}I, an emitter of both β and γ radiation), usually in the form of iodide or in an organic molecule such as thyroxine, to study the metabolism of the atom or molecule in the human body under the influence of various diseases, drugs (e.g., reserpine), or physiological states (e.g., after TSH, thyroid stimulating hormone, **J. Clin. Endocrin. & Metab. 25**:266-277, 1965). When labeled organic molecules were studied, the uptake of iodide by the thyroid was generally blocked by the simultaneous administration of stable ^{127}I. Since the body's pool size, metabolic clearance rate, half-life of the molecule in question, etc., varied from patient to patient and in the same patient according to the physiological or disease state, whole body dose and maximum dose to any target organ (e.g., thyroid gland or urinary bladder) would have to be calculated for each patient taking these into consideration, assuming anticipated values if such calculations were done in advance of the studies. Such calculations in advance were required by the Radioisotope Committee for approval of the proposed research protocol prior to committee approval and conduct of the study.

In one study (**Endocrinologia Experimentalis 3**:117-125, 1966; and **American J. Med. 40**:49-57, 1966) we studied two cretins (non-veterans, but some of the measurements were done in the Birmingham VA Hospital with VA research equipment) 100 μCi doses of ^{131}I were given with no blockade of thyroidal iodide uptake in order to study the ability of perchlorate to "flush" accumulated radioiodine from the gland, in an attempt (successful) to demonstrate the defect in organification of trapped iodide (due to defective thyroidal peroxidase) as the cause of the disease. In this case the thyroid would be the target organ and would receive the maximum dose. However, it should be noted that only a few years prior to these studies doses of 100 μCi were used in routine clinical determinations of thyroidal radioiodine uptake with no apparent ill effects. In order to calculate the dose received by the thyroid in each of these patients the actual thyroid retention time and thyroid size would have to be known or estimated. In some studies we did not go into this degree of precision for presentation to the Radioisotope Committee but gave only general dose estimates based on overall body burden of the radioisotope and expected target organs.

In the study of the effects of changing iodine content of bread in the United States and its effect on thyroidal radioiodine uptake measurements in patients (**New England J. Med. 280**:1431-1434, 1969) 20 μCi of ^{131}I was given in order to determine thyroidal and renal iodide clearances and plasma inorganic iodide concentrations.

My understanding of the risks involved for the subjects or patients at that time was that they were quite small, since doses 1,000 to 5,000 or more times this large were routinely used for treating thyroid carcinoma; and the doses of ^{131}I used in other studies were smaller than 100 μCi.

Yes, we did describe the risks of the proposed studies to the patients prior to obtaining their permission to proceed. We did this by sitting down with the patient and reviewing the proposed study, explaining that this was primarily to learn about the drug being tested or disease being studied rather than for the benefit to the patient himself, and discussing any hazards or inconveniences we foresaw or he wished to ask about. The inconvenience of remaining in the hospital or coming to the laboratory, plus in some cases the risks from the drugs given for study, seemed greater and more important to the patients or subjects than the radiation involved. Since we believed the actual risk of harm to the patient to be very small, the determining factor for the patient was usually the inconvenience of staying in the hospital or GCRC (General Clinical Research Center in the University Hospital, where some VA patients were studied) or coming to the lab for tests not necessary for the care of the patient.

2. No, we did not conduct research on patients or human subjects without first obtaining informed consent. We began using written consent forms sometime around 1961 or '62 in accordance with VA regulations. We have searched for records of such consents since the advent of the House Committee's interest in this, but we have been unable to find any, since they were filed with the patients' hospital charts, and these are no longer available and probably no longer exist.

3. The clinician-scientist doing the study (i.e., the "PI," or "Principal Investigator" in current parlance) was the one responsible for informing patients or volunteer controls regarding possible risks of participating in a particular study, but the consent was required as a condition of approval by the Radioisotope Committee, composed of a number of physicians. The risks were determined by reference to animal studies and/or the proposed doses of radioactive isotopes involved.

4. I agree with current regulations concerning research on human subjects. However, sometimes the regulations are implemented in an unthinking or unreasonably heavy-handed and obstructive manner, and some informed consent forms have been very poorly worded. I also believe that the ultimate guarantor of patient safety and well being is not a written form, but the ethical character and attitude of the physicians involved.

No, I don't think the trend has gone too far; but obstructions and costly problems can be caused by poor implementation, as just mentioned.

5. With regard to cooperation of patients in the 1950s (I did no human experiments in the 1940s), if current regulations had been in place, yes, probably I would have obtained the cooperation of the patients anyhow, though the wording of some of the later VA forms was frightening, onerous, and more legalistic ("hold harmless," etc.) than informative, and these might have dissuaded some from participation.

6. With regard to the research subjects' having "sufficient knowledge and comprehension of elements of the subject matter," this is discussed in my written testimony. I also have a number of anecdotes of my experiences during attempts to explain physiological studies or

medical procedures to patients with very limited educations. I suppose asking a patient read and sign a piece of paper helps improve his/her understanding, but, as mentioned above, the only guarantor of the patient's welfare is the attitude and empathy for the patient on the part of the physician.

Honorable G. V. (Sonny) Montgomery
Questions and Answers Submitted for the Record
House Veterans Affairs Committee
February 8, 1994

Richard Setlow
Brookhaven National Laboratory

Question 1

During the hearing, there was mention of the National Research Council's Committee on the Biological Effects of Ionizing Radiation V. Is it your understanding, of the exposure that patients received in the research discussed during the hearing, there was little risk of health damage as a result of such exposure?

Answer 1

Yes. The risk of health damage was the equivalent of, or less than, only several years of exposure to the average background radiation in the USA.

Question 2

The statement was made that, "American investigators frequently transgressed the standard of informed consent," which seemed at odds with the recollection of research that was presented during the hearing. What questions would you have liked to ask the witnesses?

Answer 2

Did you explain carefully to your patients, or subjects, why you were performing the procedure, how it would benefit the patient and what were the hazards, if any? If not, why not? If yes, did the patient (subject) give consent? Was such consent informed consent and given without duress?

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February 21, 1994

Honorable G.V. (Sonny) Montgomery
Chairman, Committee on Veterans' Affairs
U.S. House of Representatives
335 Cannon House Office Building
Washington, DC 20515

Dear Mr. Chairman:

Attached find responses to the questions attached to your letter of February 14, 1994. I have answered them to the best of my ability. I should like to reiterate two points that I made in answer to the attached questions or in previous correspondence:

1) It is more important to establish a "no fault" system of compensation for injured research subjects than it is to try to fix blame on researchers in the past. Research involving human subjects, by its very nature, includes risks. No matter how careful investigators are, it is inevitable that some percentage of research subjects will be injured. My experience of exercising oversight for many years at the NIH indicates that the numbers of injured subjects will be small, and the numbers of serious or life threatening injuries will be smaller still. Nevertheless, those numbers will never be zero (over time). Consequently research subjects should be compensated for research-connected injuries in a fashion that parallels compensation provided for service-connected injuries.

2) Although federal support for biomedical research has grown steadily since World War II, federal oversight of the rights and welfare of human subjects grew until about 1985 and has declined since that time. As a consequence, our government is supporting more invasive research with less oversight and regulation than we have had in the past. The situation is ripe for transgression of the rights and welfare of human subjects. Since about 10% of the research community is new each year, we have had about a 90% turnover in research investigators since we began to reduce oversight. That means that the numbers of investigators trained to comply with the regulations are falling. It also means that serious breaches of the regulations are predictable in the near future.

Charles R. McCarthy, Ph.D.
Hearing before House Committee on
Veterans' Affairs 2/8/94

I cited in my testimony one case of research conducted in 1951, in which I was subjected to considerable radiation without my consent. In that case the investigator was unaware of his obligation to obtain consent.

Senator Estes Kefauver held hearings in 1958 that demonstrated that it was common practice to test drugs on patients without their knowledge or consent. What was true for drug research was probably true of other kinds of research as well.

I have reviewed the consent document used in a leukemia study involving whole body radiation conducted by the Atomic Energy Commission in 1965. In that case the expected benefits were clearly overstated, and the risks were understated. The research was intended *both* to provide therapy for the subjects *and* to gather data concerning "radiation sickness". I have not been able to determine whether the consent document used in that study was typical of the time. It stated only the therapeutic intent of the study. It did not mention the second purpose of the study: to gather data regarding radiation sickness. The second purpose of the study required exposing subjects to higher doses of radiation than would otherwise have been necessary.

It is my opinion that in the U.S. the obligation to obtain informed consent from research subjects gradually came to be understood and implemented by researchers over a period of 20 years, 1946-1966. It is also my opinion that the quality, accuracy, and completeness of the information conveyed gradually improved over that same period. I should caution the Committee, however, that these opinions are based on many conversations with investigators over many years, not on scientific evidence.

For these reasons, I find it hard to know what the "standard of informed consent" was at the time. If one uses the Nuremberg Code or the statements of the AMA as the standard, then I believe most investigators at the time fell short of meeting those standards. If one uses the standard of practice widely employed by the U.S. medical/research community at that time, then, in all probability, most investigators met the standard.

In fairness to the research community, the standard of practice in the medical/research community at the time should be used in making retrospective judgments concerning the ethics of their research. If they are to be blamed, then we must also extend the blame to the medical schools where they took their training.

Q.3. *Dr. McCarthy, in your opinion, who should be compensated for participating in research sponsored or supported by the government, and what standard or test should be used to identify those who should receive compensation.*

A.3. I should like to see the federal government establish a "no fault" care and compensation system for persons injured as a result of their participation in government sponsored research. I take this position because I believe that research volunteers provide a service to their fellow countrymen analogous to the service provided by military personnel. Just as we regard it as an ethical obligation to provide care and compensation to persons who suffer service-connected injuries, so I believe we should regard ourselves as ethically bound to provide a system of care and compensation for persons who suffer research-connected injuries. Eligibility for care and compensation should be determined by committees or juries that decide whether there is probable cause to believe that an injury is research-connected. If the jury finds probable cause to believe that an injury is research-connected, care and compensation should be provided.

Charles R. McCarthy, Ph.D.
Hearing before House Committee on
Veterans' Affairs 2/8/94

In exchange for the prompt provision of care and compensation, injured subjects should be asked to relinquish their right to bring tort actions or charges of malresearch against the investigator, the institution, or the government.

One of the reasons why the system should be a "no fault" system is already addressed in relation to question 2 above. Although research should always be conducted in accord with the principle of respect for persons, the common understanding and application of that principle as requiring subjects' informed consent has changed over time. We should not hold investigators of the decades of the '50s and '60s to standards developed and refined in the '70s, '80s and '90s. Just as the government has only gradually come to realize its obligation to regulate research, so the research community has only gradually come to understand fully its ethical obligations to research subjects. Because research injuries may manifest themselves long after the research has been completed, we should compensate for them on a "no fault" basis so that we do not have to reconstruct the standards used at the time the research was conducted and try to determine if those standards were met.

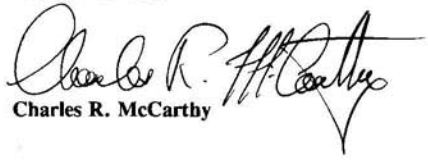
Care for injured subjects could be provided at VA hospitals and clinics that already treat service-connected injuries. Compensation should be limited to the level of pay provided to a civil servant at the level of GS-9, and continued until such time as the injury is corrected. If the injury involves death, then compensation should be provided in the form of a tax-free lump-sum (for example, $100,000) paid to the immediate family of the deceased subject.

Monies for care and compensation of research connected injuries should be derived from a government-wide assessment placed on monies budgeted for research conducted or supported by the federal government. Since research-connected injuries are relatively rare, the entire compensation program could probably be funded out of a pool created by a one-time 1/2% levy imposed on the research budgets of federal agencies for one year. That pool, properly invested, would be self-sustaining.

I believe that the Veterans' Affairs Committee is an ideal locus for the drafting of such legislation because the Committee already has demonstrated expertise and broad experience with the management and compensation of service-connected injuries.

I applaud you and your Committee for attempting to determine whether subjects were injured in the past, and providing compensation for those who were injured. I urge you to exercise the same zeal in protecting subjects from injury in the future.

Yours sincerely,



Charles R. McCarthy

MEMORANDUM

Date: February 21, 1994

From: Charles R. McCarthy, Ph.D.

To: Hon. G.V. (Sonny) Montgomery, Chairman
House Veterans' Affairs Committee

Subject: Additional questions in reference to hearing conducted Feb. 8, 1994 regarding research involving radioactive materials conducted in V.A. Medical Centers

Q. 1. *During the hearing, there was mention of the National Research Council's Committee on the Biological Effects of Ionizing Radiation V. Is it your understanding, of the exposure that patients received in the research discussed during the hearing, there was little risk of health damage as a result of such exposure?*

A.1. I should preface my answer by stating that I am trained in philosophy, ethics, and political science. I have no professional training in medicine, radiation or biological science. I have reviewed the testimony presented by Drs. Yallow, Burrows, Kaplan, Pittman, Settlow and Hendee. They are consistent in their statements that -- to the best of their knowledge -- research patient/subjects were not exposed to levels of radiation known to cause health damage.

While the experts cited above are able to describe a portion of the research conducted at the time, they could not know all of the research in which radiation was used that transpired in VA hospitals. To obtain a comprehensive answer to your question it may be necessary to await the results of the ongoing research review described by VA's Secretary Brown. Even when the report is as complete as possible, we may never know whether harmful experiments were carried out because: a) many records may never be recovered, and b) no effort was made to follow up patient/subjects to determine whether they manifested long-term harmful effects of the radiation.

Q.2. *The statement was made that "American investigators frequently transgressed the standard of informed consent," which seemed at odds with the recollection of research that was presented during the hearing. What questions would you have liked to ask the witnesses?*

A.2. I should like to have asked the witnesses what they considered to be the standard of informed consent that prevailed at the time. In 1946-7 the U.S. war crimes tribunal found, among other matters, that Nazi scientists had failed to meet the standards of the Nuremberg Code. In the testimony I presented to the Committee, I cited evidence that by early 1949 the Nazi war crimes and the ten principles of the Nuremberg Code were readily available to anyone. That does not mean , however, that the Nuremberg standards were actually used by U.S. researchers at the time.

We know that *written and signed* informed consent by research subjects was not routinely documented in research conducted prior to 1966. No federal laws or regulations governing protection of human research subjects, including requirements for obtaining subjects' informed consent, had been promulgated. Consequently, research investigators appear to have been guided primarily by procedures regarded as the "standard of practice" in their communities at that time. We believe that research communities varied widely in their practice. Anecdotally, we know that some investigators failed to obtain any consent from subjects, and we know anecdotally that many others did convey information, and did seek consent from subjects. In cases where consent was obtained, there appears to have been wide variation in the kind and amount of information conveyed to prospective subjects.

1. During the hearing, there was mention of the National Research Council's Committee on the Biological Effects of Ionizing Radiation V. Is it your understanding, of the exposure that patients received in the research discussed during the hearing, there was little risk of health damage as a result of such exposure?

   Research presented by VA clinical investigators at the hearing on February 8 described efforts to develop and apply radioisotopic methods for detection and diagnosis of a variety of diseases, including cancer, heart disease and stroke. Many of these methods were predecessors of present techniques widely employed in nuclear medicine. The doses administered during these procedures produced risks that were outweighed by benefits received by the exposed patients as well as by the millions of patients who have subsequently experienced nuclear medicine procedures.

   William R. Hendee, Ph.D.

2. The statement was made that "American investigators frequently transgressed the standard of informed consent" which seemed at odds with the recollection of research that was presented during the hearing. What questions would you have liked to ask the witnesses?

   The nature of informed consent was far different in the 1940s, 1950s and 1960s from what it is today. I would have liked to have asked the witnesses three questions:

   1.) As you were developing radioisotopic procedures in the early years, did you have any reason to believe that you were subjecting your patients to moderate risks?

   2.) In your research with human patients in the early years, did you have any reason to believe that you were interacting with your patients in ways that were different from the ways other investigators were interacting with their patients?

   3.) In retrospect, do you believe that, given the context and ethical standards of the time of your early experiments, that you "transgressed the standard of informed consent?"

   William R. Hendee, Ph.D.

VAMC BOSTON

Question 1: In conducting radiation related research in the VA, what were the highest dosage levels to which your subjects were exposed? What was your understanding at the time as to what risks were entailed in such dosage levels? Can you recall whether you described those risks to the research subjects and, if so, how would you have described them?

The highest dose levels to which subjects were exposed were below the limits of Atomic Energy Commission regulations: 350 microcuries for potassium-42, 150 microcuries for sodium-24, 15 microcuries for sodium-22, and 300 microcuries for tritium. Those dosage levels were insignificant compared to environmental and body burden exposures from naturally occurring radionuclides. The risks to the subjects were described to the subjects in those terms.

Question 2: If by the term "informed consent" we mean freely given consent following a full and careful explanation of the research project, whether or not the subject is given a form and asked to sign it, did you conduct research in the VA which did not seek your subjects' informed consent?

No.

Question 3: Who was responsible for informing patients of the possible risks of participating in a particular study and who was responsible for determining this risk? How was the risk determined?

Physicians were responsible for informing patients about possible risks of participating in a particular study and for determining the risks. In patient studies the risk-to-benefit relationship was determined by the physician's knowledge of the patient's medical problem. Consideration was given to other radiation, such as x-rays, to which the patient might be exposed. For diagnostic studies and particularly for therapeutic procedures, such as iodine-131 administration for hyperthyroidism and thyroid cancer, patients were also informed about precautions to be taken and possible side effects, such as hypothyroidism.

Question 4: Do you agree with current restrictions and regulation of research involving human subjects? Has this trend of increasing protection gone too far?

Dr. Burrows agrees with current restrictions and regulations. The trend of increasing protection has been enabled by improved technology and increased sensitivity of radiation measurement procedures.

Question 5: Would you have had the cooperation of so many patients if the current restrictions had been in place back in the 1940s and 1950s?

Dr. Burrows is of the opinion that, had current restrictions for research been in place in the 1940s and 1950s, it is unlikely the restrictions would have discouraged or prevented patients from participating in research activities.

Question 6: Dr. Rothman cites the principle set forth at Nuremburg that calls for voluntary consent of research subjects and for the subjects to have "sufficient knowledge and comprehension of the elements of the subject matter involved as to make an enlightened decision." Would you comment on how one insures that patients have achieved that level of understanding?

Any level of patients' understanding will be dependent on patients' general knowledge and physicians' communication skills. For clinical research using tracer doses (which are not considered to be of physiological significance), patients can readily understand physicians' explanations.

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