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SOME GUIDELINES FOR STUDIES INVOLVING INTERNAL ADMINISTRATION
OF RADIOACTIVE MATERIALS TO HUMAN VOLUNTEERS

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The Health and Safety Laboratory of the U. S. Atomic Energy Commission's Idaho Operations Office provides a routine invivo whole body counting program for the protection of the nearly 6,000 employees at the National Reactor Testing Station in southeastern Idaho. During the five-year period from 1961 through 1965, 7,134 invivo determinations were made. Foreign activity has been detected 4,625 times on 2,278 individuals including follow-up measurements made on the same individuals when significant exposure has occurred. In all, a total of 41 different radionuclides have been detected in humans, in addition to the naturally-occurring potassium-40 and cesium-137. Virtually all of the exposures have been received inadvertently during the routine performance of their duties. The exposures have generally occurred from inhalation of particulate matter of unknown particle-size distribution under uncertain circumstances.

Of the 4,625 times that foreign radionuclides have been observed in humans, not more than a half dozen have involved activities greater than about 1 uc. In perhaps 95% of the cases, the activity present was less than 0.1 uc., most of which was eliminated within a very few days. Since the maximum permissible body burden of most beta-gamma emitters is several microcuries or greater for continuous exposure, such levels are of very little physiological significance to the host. As a matter of fact, to save the time and expense of reducing the complex gamma spectra either manually or by a computer program, body burdens lower than about 0.1 uc. are merely recorded qualitatively as being present and are not even quantified. Yet, in almost every case, because of the extreme sensitivity of modern instrumentation, we have been able to determine the mode of excretion from the body, the effective half-life of the specific nuclide involved, and other valuable information from such minute and physiologically insignificant quantities of radioactive materials. This information is of particular importance because it has been obtained on actual human beings under practical conditions and consequently is much more informative and realistic than other data of this kind which is usually obtained by extrapolation from animal data. For example, one of the most important pieces of information derived to date from our routine whole body counting program has been the general philosophy that urinalysis is grossly inadequate as a routine monitoring technique for internal contamination in humans where inhalation of insoluble particulates is concerned. Since our experience has also indicated that inhalation of insoluble particulates is the most likely source of contamination to be encountered around operating reactors, routine urinalysis has been abandoned in our laboratory as a monitoring technique except for determination of the organ dose from systemically deposited nuclides or detection of certain specific soluble nuclides which are known to be absorbed by the body and excreted in the urine. I wonder how much longer we would have continued using a technique for detection and assessment of internal contamination in humans that does not give

the protection we had thought if instruments and techniques for direct measurement of gamma-emitting nuclides on humans had not been developed.

In view of the significant accumulation of very valuable information concerning the metabolic characteristics of a large number of radionuclides that has been obtained from the minute quantities of materials received inadvertently, deliberate exposure of human volunteers to similar minute quantities of radioactive materials under controlled conditions would permit a marked increase in the rate of accumulation of such fundamentally important biological data. Almost every dose calculation that I have ever made, or have heard others describe, has contained an apology or a hedge that the validity of the answer depended on whether or not certain assumptions used in the calculations were correct. In many cases, those assumptions were guesses at best, or were derived by extrapolation from animal data and their validity is certainly open to question when applied to humans. Most of the actual human data presently available was obtained from evaluation of human accidents involving intake of radioisotopes. In view of the extremely minute quantities of materials required and the very high sensitivity of modern instrumentation for their detection, why do we continue to penalize ourselves with half truths and calculations that at times border on the ridiculous when far better data is available for the taking from direct human studies without significant harm to the individual volunteer? Others have also pointed out this need for research programs involving humans to provide better data than is presently available for assessment of the dose received from internally deposited radionuclides (1). I would like to suggest a "Principle of Comparability" that it is both logical and prudent that we should be willing to place at least as much at risk to understand the fundamental effects of internal radiation on humans as we do routinely in developing a nuclear technology. In other words, exposures that are acceptable for day-to-day operation of a reactor should also be acceptable for studies to determine the effect of internal emitters in man.

The use of human subjects in scientific experimentation has generated much controversy concerning the ethics involved, particularly in the medical profession. Throughout much of recorded history, men of medicine have set down principles of good conduct to guide them in their relations with their patients. Many of these precepts apply directly to human studies involving radioactivity. Though by no means the oldest of pagan medical oaths, the oath of Hippocrates is the best known and the most enduring. Traditional and modernized versions continue to be used as a profession pledge of ethical behavior. When the American Medical Association was founded in 1847, it adopted the oath of Hippocrates in its pagan form. At the same time, it adopted a code of medical ethics published in 1803 by the English physician, Thomas Percival. In 1947, the first General Assembly of the World Medical Association appointed a committee to draft an updated wording of the Hippocratic oath. After minor changes, this was adopted in 1948 at Geneva by the second General Assembly as the "Declaration of Geneva." After World War II, the Nuremberg Code of Ethics in Medical Research was framed by a task group of the American Medical Association to guide the allied military tribunal in the prosecution of 23 Nazi physicians accused of brutal experiments on political prisoners. This code is perhaps the one most frequently quoted where human experimentation is concerned. Most recently, another code of ethics on which work was started following World War II was adopted by the Eighteenth World Medical Assembly in June of 1964 in Helsinki, Finland, as the Declaration of Helsinki. According to Dr. Harry S. Gear, Secretary General of the World Medical Association, recommendations in the Declaration of Helsinki "are offered to all medical men and their colleagues in other disciplines, who undertake scientific and clinical investigations involving human beings." The House of Delegates of the American Medical Association has since endorsed the Declaration of Helsinki as an ethical guide to clinical medical investigation. Representatives of the American Medical Association are currently meeting with members of

the American Federation for Clinical Research and the American Society for Clinical Investigation in an effort to prepare a modern code of ethics for human experimentation.

The Helsinki Declaration outlines very strict rules for nontherapeutic clinical research and seems to be particularly pertinent to the type of studies being proposed. The nature, purpose, and risks must be explained to the subject, the subject must be fully informed and must give his free consent, and the patient must be in such mental, physical and legal state as to be able to exercise fully his power of choice. Consent should be obtained in writing and be witnessed. The investigator must respect the right of each individual to safeguard his own personal integrity and, at any time during the course of clinical research, the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating teams should discontinue the research if in his judgment, it may, if continued, be harmful to the individual. The concept of valid informed consent is a particularly fundamental and important one, yet often requires a level of knowledge and freedom from constraint that is impossible to achieve with people that are ill, children, or those mentally incapable of comprehending the meaning and consequences of the scientific and technical principles involved. Inability to convey the necessary information and understanding does not in any way lessen the requirement for valid informed consent.

Several items from the Nuremberg Code would seem to be particularly pertinent to our proposed studies. The first item says "The voluntary consent of the human subject is absolutely essential." Item 6 points out a nearly self-evident point of logic that "The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment." Item 10 says in part "During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage,"

The official position of the United Kingdom has been greatly clarified recently by a statement of their Medical Research Council in their annual report for 1962 and 1963. The statement deals primarily with medical investigations in general but is directly applicable to work with radiation and radioactive materials. The council emphasizes the importance of proper safeguards both in procedures contributing to the benefit of the individual and, more specially, in procedures in which the individual concerned does not benefit directly from the investigation. Again, particular importance is attached to obtaining the individual's true consent, by which is meant "consent freely given with proper understanding of the nature and consequences of what is proposed." Provided that these safeguards are ensured, the council clearly endorsed the concept of investigations involving volunteers, and concludes that "After adequate explanation, the consent of an adult of sound mind and understanding can be relied upon to be true consent." They further emphasize the responsibility on the professions, on the heads of investigating departments, and on individual investigators, to ensure that the conduct of all these investigations is irreproachable. The more obvious requirements that the experiment should be conducted only by technically qualified persons exercising the highest degree of skill and care throughout all stages of the experiment, and that no experiment should be conducted where there is any reason to believe that serious injury or death would occur are implicit in all of the codes of ethical conduct.

One of the greatest retarding influences on the accumulation of human data has been the feeling, particularly prevalent in some of the earlier codes, that experimentation must not be carried out on human subjects unless the subject himself expects to benefit. For example, the doctor can combine clinical research with professional care, the objective being the acquisition of new

...knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient. Not only is this contrary to the spirit of sacrifice for the good of ones' fellow man so prevalent in many parts of the world but is totally unrealistic and undesirable when governed by sound ethical and moral principles. The proposed guide lines acknowledge and accept the spirit of both the Nuremberg Code and the Declaration of Helsinki but we submit that it is entirely appropriate for human subjects to accept small risks to themselves to help develop information that will be of value to others. Specifically, when the subject himself does not stand to benefit by the experiment being performed, the internal dose permitted shall not exceed the occupational exposure permitted workers in the atomic energy industry, as specified in Title 10 Part 20 of the Code of Federal Regulations for licensees and in AEC Manual Chapter 0524 for AEC and Contractor personnel.

The pertinent values are 3 rem per quarter or 5 rem per year for the whole body or 10 rem per quarter and 30 rem per year for the thyroid. For the sake of simplicity and to eliminate the need for factual information concerning which organ is critical, which may itself be the principle reason for the experiment, the higher levels permitted for single organs other than the thyroid are not permitted at present and the dose received is considered to be to the whole body. Although the 3 rem per quarter for whole body may be averaged over 13 weeks, the basic unit proposed for a single exposure is 0.3 rem for the first week, a value only slightly larger than the average value of 0.23 rem permitted for each of 13 consecutive weeks. An extensive table of activities required to produce a dose of 0.3 rem per week to the critical organ from a single exposure has been published (2) and is most helpful and convenient in determining the maximum permissible dose to be used as well as for administrative checking. Another significant point in this connection is that these values and the equations from which they were calculated have been prepared by a well known authority in the field of internal dosimetry, have been published in the open literature and are easily available to others. Another similar and more recent paper entitled "Radiation Doses from Administered Radio Nuclides" is also very useful (3). However, published information tends to become outdated and all final calculations of dose must reflect the most recent methods and information recommended by the Federal Radiation Council and the International Commission on Radiological Protection.

One of the significant differences between doses administered from external or internal sources is the inability to terminate the latter on demand by removal of the source. Both common prudence and most of the medical codes suggest that the long-term dose commitment should be restricted to permit either the experimenter or the volunteer to reconsider his decision to continue the test. Consequently, limitations are imposed on the effective half lives that can be employed at a given level of activity so that more than one opportunity is presented to stop the experiment before even a 1-year's maximum permissible dose will have been committed irrevocably.

A summary of the maximum permissible intake for a single exposure as a function of half life and dose received is given in Table I. Obviously, when the half life is less than that shown in the table, the dose received will also be less than that shown. Specific guide lines are as follows:

1. The quantity of radioactive nuclides to be taken in a single day shall not exceed that required to deliver a dose to the critical organ of 0.3 rem for the first week after exposure as given in columns 5 and 8 of the published table (2), for ingestion and inhalation, respectively. These values have been chosen to permit integration of the dose received over a time period of one week. Where necessary, the values must be updated to reflect the latest information available.

2. The maximum level of 0.3 rem in the first week may be used only with radionuclides having an effective half life in the critical organ shorter than 18 days so that the dose will not exceed the second limitation of 1.25 rem in the first quarter. The dose of 5 rem per year permitted by AEC Manual Chapter 0524 is permitted but only for four separate tests so that the dose can be terminated within a reasonable length of time (one quarter) if either the subject or experimenter should so decide. This limitation also ensures that the total integrated dose will not exceed approximately 5 rem for a maximum of four tests per year.
3. Nuclides with effective half lives longer than 18 days can be used provided the quantities are reduced to limit the long-term commitment. Nuclides with effective half lives in excess of one year are not employed in any case. With nuclides having half lives from 18 days up to 13 weeks, the values given in the published table (2) are reduced by the factor 4.3 so that the dose per year will not exceed 1.25 rem. Again, four tests per year are permitted to restrict the yearly dose to 5 rem and the total integrated infinity dose to only slightly more. For nuclides with half lives of 13 weeks up to one year, only one-tenth the quantity mentioned in the table is permitted per test and only one test is permitted per year to keep the dose for the first year down to about 1 rem and the total infinity dose down to about 2 rem. Use of nuclides with half lives in excess of one year is not likely to be necessary and is undesirable because of inability to terminate the exposure within a reasonable length of time.
4. Nuclides for which the thyroid is the critical organ can be used in quantities three times that specified in the table as permitted by AEC Manual Chapter 0524. Corresponding increases permitted by Manual Chapter for "other organs" can be utilized if the critical organ is known with some assurance. Otherwise, the dose should be limited to that permitted for the whole body.
5. If the source is encapsulated in polyethylene tubing or other impervious material that will not be released in the body and will be eliminated in about 24 hours, the maximum activity used and the number of experiments performed can be adjusted such that the dose received does not exceed 0.3 rem per week or 5 rem per year to that part of the gastrointestinal (G.I.) tract deemed to be the critical organ. As pointed out in the footnote to the table in reference 2, the values given in columns 4 and 7 for a dose rate of 0.043 rem per day may be considered as maximum permissible values for continuous exposure when the G.I. tract is the critical tissue. Consequently, either a single experiment at 7 times this value or 7 experiments at this value could be performed each week. If the source strength is sufficiently high or the nuclides sufficiently long lived to constitute any significant hazard to others if the capsule should be opened, the source will be recovered and properly disposed of after termination of the study.
6. Chemical toxicity is to be considered specifically in each case, and will become a limiting factor when the threshold limit is reached. For example, a solution of methyl iodide containing radioactive iodine tracer could be more toxic chemically than radiochemically if the specific activity were sufficiently low. Both the chemical and radiochemical purity of the activity being administered must be established beyond question.

Since many volunteers will inevitably be obtained from our own subordinates, we must be particularly careful to avoid any suggestion of coercion or mandatory participation as a condition of employment. Consent forms may not even be distributed for signature until the potential volunteer has been

contacted, the experiment to be undertaken thoroughly explained and his consent freely given. Similarly, to avoid any adverse public reaction, the general philosophy of human studies being carried out in a given laboratory must have been discussed openly with and concurred in by the local medical authorities without the slightest suggestion of attempted subterfuge. Each specific experiment must be approved by at least two reputable scientists with administrative responsibilities and authority in the organization, one of whom must be a medical officer, and must be carried out openly by the experimenters acting as a group rather than any single individual going it alone. In our laboratory, the Chief of the Medical Branch approves the medical qualifications of the volunteer and assures that all necessary medical aspects of the proposal have been reviewed adequately. The Chief of the Analytical Chemistry Branch approves the project from the standpoint of chemical and radiological toxicities. After the study has been completed the radiation exposure data is entered on the consent form and filed in the individuals medical record.

The above guide lines reflect the maximum quantity of radioactive materials that can be used only with good and sufficient justification and are thought to be relatively conservative. Even so, as a general philosophy, the actual quantity to be used in any given experiment shall not exceed the smallest quantity necessary to achieve the intended results.

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Table I. Radiation Guides for Human Studies
Involving a Single Exposure

Effective Half-life	Fraction of Columns 5 or 8 ^a	Tests per Year	Maximum Dose Received, rem.				
			<u>First Week</u>	<u>First Year</u>		<u>Total</u>	
				1 Test	Max.	1 Test	Max.
18 days	1	4	0.3	1.29	5.16	1.29	5.16
13 weeks	1/4.3	4	0.069	1.25	5.00	1.33	5.32
1 year	1/10	1	0.03	1.15	1.15	2.3	2.3

^aTable in Ref. 2