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AEC LICENSING OF RADIOISOTOPES FOR CLINICAL RESEARCH

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Although I am a member of the Advisory Committee on Medical Uses of Isotopes of the Division of Licensing and Regulation of the Atomic Energy Commission, the opinions expressed herein are those of the writer speaking as an individual, and do not represent official policy of either the AEC or the Advisory Committee.

The established policies of the AEC are embodied in the Federal Register in 10 CFR 30 with which you are all presumably familiar. The decisions and actions of the Advisory Committee contribute to the making of regulations, but it is neither possible or desirable to attempt to spell out what the position of the Committee will be in a particular case. As a preface let me review briefly some of the history of the Subcommittee on Human Applications of the Isotopes Branch which was the precursor — so to speak — of the present Advisory Committee. The original group (usually dubbed the Subhuman Committee) first met on June 28, 1946 at Oak Ridge. Because the quantities of radioisotopes available were limited, the initial functions of the Subcommittee were, first, to recommend the relative production effort to be devoted to isotopes for therapy and diagnosis; and second, to make recommendations to the Isotopes Branch for the allocation of available materials for clinical use. As the demand for isotopes for medical use increased, production also increased so that allocation as such soon ceased to be an important problem. In 1948 the Subcommittee formulated certain broad objectives and criteria for their role in the authorization process. At this point I wish to make it quite clear that the role of the Subcommittee, and of its product the Advisory Committee, is to appraise applications and to make recommendations with respect to the human use of isotopes for the guidance of the appropriate agencies of the

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AEC. Authorizations have now been replaced by Licenses to possess By-Product Materials, which are issued by the Division of Licensing and Regulation in accordance with the provisions of 10 CFR 30, and internal rules, the making of which is a prerogative of the Licensing Division.

At the present time the principal objective of the Committee's appraisal as it applies to clinical research is to prevent unnecessary exposure to radiation. First of all we are obligated to protect patients and volunteer subjects from indiscriminate use of radioisotopes. The determination that a proposed use is indiscriminate involves a value judgment based on experience. In my view a use is indiscriminate when the purpose can be accomplished just as well or better by some other method than the use of a radioisotope. It is indiscriminate if inadequate or inappropriate instrumentation necessitates the administration of excessively large doses of the radioisotope. It is also indiscriminate if the design of the experiment requires a superfluous number of doses, or an unnecessarily large number of subjects. Finally, a use is indiscriminate when the object of the experiment itself is trivial.

Aside from purely ethical considerations the judgment that a proposed use is indiscriminate has the effect of protecting a patient or a volunteer subject from unnecessary exposure to radiation.

Second, we want to protect — as far as possible — people other than the subjects of clinical research from unnecessary exposure to radiation. In this context the "other people" include paramedical and laboratory personnel as well as individuals who have no way of knowing that they are exposed to any radiation in excess of the natural background.

The simplest way to accomplish our principal objective is to ascertain that the individual user who applies for a license has sufficient knowledge and experience to use radioisotopes properly in clinical research and to handle them safely under all circumstances. The central themes of the appraisal process are simple and can be stated as follows: Is the applicant's training and experience adequate for the research project he wants to perform? Will the person who knows he is to receive radioisotopes be exposed to more radiation than is necessary for the purpose of the experiment? Is the experiment and the radiation exposure justifiable? Will other people be exposed to radiation unknowingly, inadvertently or accidentally? We say in effect that an untrained or ignorant investigator is more likely to misuse radioisotopes than a trained one: and we say that we believe all unnecessary exposure to radiation should be avoided. We also say — in effect — that if an accident can happen, it will happen: so that proposed uses which are particularly liable to lead to accidents are sure to be disapproved. In my own institution — The University of Chicago Hospitals and Clinics — we are very sensitive to the possibility of accidental contamination of laboratories and quite regularly refuse to approve proposed uses where there is even a small probability of environmental contamination as a result of an accident or a technical error in the handling of sources of radioactivity.

In order to make the necessary value judgments, the Advisory Committee — or any other committee — needs to know four things:

(1) The design of the experiment.

(2) The calculation of exposure dose (or absorbed dose) of radiation expected from the radioactive material administered under the conditions of the experiment.

(3) The resources of the laboratory supporting the clinical study,

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(4) The extent of the applicant's experience in clinical research, and in the use of radioisotopes.

Most of us are particularly interested in the mathematical aspects of the applications. I think it is perfectly proper to insist that a clinical investigator be able to demonstrate his ability to use physical constants, formulas, and physiological data in a meaningful and accurate manner. It is good exercise for anyone to carry out the whole calculation of expected dose to a target organ and to the total body on the basis of one or more assumptions. Any competent scientist should want to do the calculation himself, and would not accept a set of published figures without verification, if for no other reason than to eliminate the possibility of a typographical error or a misplaced decimal point. Some applicants develop novel computations which are of interest and often revealing. Others are willing to sign their names to transcriptions of calculations that can be easily recognized as the published work of others — often identifiable by the errors they contain! I — for one — am suspicious of the integrity of such a person, and I am very reluctant to approve or to recommend the issuance of a license for human use in clinical research. Integrity is easy to recognize even though it is difficult to define, and I do not believe that anyone who lacks integrity should engage in clinical research with or without radioisotopes. Similarly I am hesitant to approve a clinical research proposal where microcuries and millicuries are confused, where the arithmetic is wrong, and where the units of radiation or exposure or dose are expressed in incorrect or inappropriate terms. This aspect of appraisal is really very simple: if a man makes one kind of mistake, why be surprised if he makes others? If he is careless with figures, why expect him to be careful with radioactivity? Obviously a perfectly accurate application is no guarantee that the radioisotopes will be used properly — but at least the uncertainty is not so great as it is when the application is carelessly prepared, misspelled, ungrammatical and inaccurate.

Although our Committee is not charged with the protection of patients and volunteers from the hazards associated with inappropriate or incompetent clinical research we can protect them from unnecessary exposure to radiation by the denial of a license.

There are five problem areas in clinical research where the present Advisory Committee and its predecessors have sought to develop guidelines on which all reasonable people will agree. Up to the present time there continue to be interesting differences of opinion in each area. Before I discuss these problems, I wish to repeat that the views expressed are my own. The extent to which they are shared by my colleagues varies.

1. *Experiment in a pregnant woman where a live baby is expected:*

I take the position that a radioisotope should be used in clinical research in pregnancy *only* when there is a very good reason to think that the mother will benefit from the results of the study. At the present time we have no convincing information on the extent to which embryogenesis or fetal development may be affected by small amounts of radiation. Likewise we have no reliable data on which to base a tolerable or a permissible dose of radiation to a fetus. It is fatuous to claim, as is done in some application, that a particular use of a radioisotope entails no more exposure to radiation than an x-ray examination of the maternal pelvis. If the design of a particular experiment involved only whole-body gamma radiation equivalent to several times the natural background I would be hard put to deny it approval on a rational basis. It happens that I

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cannot recall a radioisotope application where reliable calculations predicted only whole-body exposure on the order of 0.3 mr per day. In my own institution we have urged clinical investigators to use stable isotopes as tracers if they want to work with healthy pregnant women. We do not approve the use of radioisotopes.

I have what some may consider a non-rational basis for my strict attitude in this case: sooner or later a woman who has volunteered for a clinical research study using radioisotopes will deliver a child with a visible congenital defect. In fact the odds that this will happen are about 1 in 50. Someday one of these unfortunate mothers will attribute the event to the radioisotope used and she will have no difficulty at all in finding scientific opinion to support her allegation. An unpleasant court action will certainly follow — and there is a good possibility that two important activities will suffer: clinical research, and the use of radioisotopes in medicine. I prefer to avoid such a situation entirely by denying to myself and to my associates the opportunity to use radioisotopes in any amount for clinical research in any normal pregnancy.

2. *Experiments in healthy children.*

My objection to the use of radioisotopes in clinical research in 'normal' children less than one year old has the same basis as my objection in the case of healthy pregnant women. If it can be clearly shown that a neonate will benefit from a clinical research study using radioisotopes then I would approve it. For older healthy children there is a strong policy recommendation of the National Committee on Radiation Protection which implies that any exposure to radiation in addition to natural background and medical diagnostic radiation should be avoided prior to age 18. Furthermore, 10 CFR 30 specifically prohibits occupational exposure of anyone less than age 18. There are, then, legal and quasi-legal reasons for refusing to approve clinical research using radioisotopes in this age group. In the case of minors there is also an ethical problem. They cannot volunteer any more than they can sign a permit for a surgical procedure, so that permission to use a normal minor as a subject for clinical research must be obtained from a parent or a legal guardian. I can also imagine circumstances where a parent might grant permission; and I can also imagine circumstances where inducements might be offered so that the best interest of the minor child was compromised.

The question sometimes arises of using mentally-retarded institutionalized children as physiological normal controls for clinical research. In most circumstances I am opposed to this on moral as well as scientific grounds. In contrast I would approve a well-designed clinical research project directed to any aspect of mental retardation since there is no other possible way to learn about it except to study affected children. In either case one is confronted with the well-recognized fact that clinical research presents difficulties that do not exist when the subjects are animals. The fact that radioisotopes are used, or are not used, has no bearing on the matter. Everyone who engages in it realizes that clinical research is more difficult and demands different experimental conditions than obtained with laboratory animals.

3. *The amount of radioisotope that may be used:*

Any discussion of the size of a tracer dose of any nuclide runs the risk of degenerating into a *numbers game*. Some clinical investigators would like a committee — the Advisory Committee, or the NCRP, or some other committee — to publish a schedule of permissible doses for clinical research so that an in-

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vestigator would know what he could, and what he could not, do. In my view such an attitude is non-scientific and I am pleased that none of the Committees have obliged. My own guidelines are fairly simple: In normal subjects the dose of radioisotope should not be any more than is needed to accomplish the purpose of the experiment by yielding data which are statistically significant at a stipulated level of confidence. The only reservation I make is that the dose should not be sufficiently large to cause radiation injury. As a rough approximation I am willing to accept the assumptions of the NCRP that whole-body injury will not occur when the absorbed dose of gamma-radiation is less than the MPD as defined in Handbook 52. In the case of individual radionuclides the single dose should not exceed several times the maximum permissible body burden as listed in Handbook 69. When the life expectancy of the subject of a clinical study is limited (and our Committee has defined *limited* as less than one year) I see no reason to limit the amount of radioisotopes administered provided that the result of the radiation is not the production of painful complications or the exacerbation of the life-limiting condition. This point of view is particularly applicable to experimental therapy with radioisotopes, and is primarily humanitarian rather than scientific — which is the way I think it should be. Parenthetically I am not happy about the definition of limited life expectancy: I rarely can be sure that a patient will live no longer than one year. In my own thinking I consider life expectancy 'limited' when I am reasonably sure that the patient will die of the disease, and when the disease has produced sufficient impairment that the patient is increasingly incapacitated for the activities of daily life.

4. *Carbon-14*

At one time (1950) the Subcommittee on Human Applications placed a limit for specific compounds containing carbon-14 of 5 microcuries in normal subjects, and 200 microcuries in patients with a life expectancy of less than one year. This action was motivated by concern that carbon-14 might be incorporated to a significant extent into genetic material and might affect it adversely. It was also motivated by some of the strong reaction to the possibility of hazard from carbon-14 produced by tests of nuclear weapons. At present there are two divergent opinions which influence appraisal of clinical research projects. The ultraconservative view which is derived from the arguments of the ban-the-bomb people states that carbon-14 incorporated into molecules of DNA has a long biological half-life, and that as an atom of carbon-14 disintegrates the molecule of DNA is altered with potentially serious consequences. The uncritical persons tend to visualize a mutation with each disintegration, and thus a considerable increase in the occurrence of mutations well in excess of the spontaneous rate — which, parenthetically, is known only to a first approximation. If the increased incorporation of bomb-produced carbon-14 is bad, certainly we should be cautious about giving reactor-produced carbon-14 to normal subjects in clinical research. A contrary view is based on experiments with mice, and other laboratory organisms, and is considerably more permissive. In the case of mice single doses of formate-C^{14} (equivalent to a single dose of 300 to 500 mc given to a man) result in labelling of DNA as a result of incorporation into purines. In cells of the liver and brain where the turnover of DNA is slow, the number of carbon-14 atoms that disintegrate per year is such that about 5 molecules of DNA per million are involved. If each such event led to a definite mutation at one locus, the rate might be 5×10^{-6}. This value may be compared very approxi-

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mately with the spontaneous rate of mutation per gene per generation which is reported to be about 10^{-6}. Granting that the data and the assumptions have some validity it does not seem to me that ordinary tracer doses of carbon-14 are hazardous. Another approach to evaluating the problem is to consider the whole-body beta-irradiation from uniform distribution of the carbon-14, and the absorbed dose in target organs where concentration of the radionuclide can be estimated. This is the method used by the NCRP in Handbook 69. The values cited there apply to occupational exposure to radiation, but they can be manipulated in a consistent fashion to obtain estimates of dose with almost zero probability that radiation injury will result.

My own opinion takes all these factors into consideration as well as the fact that carbon-14 labelled compounds are usually expensive. I do not believe anyone will ever want to give enough carbon-14 to really affect genetic material, or to cause detectable whole-body radiation injury. In fact, few of us can afford to give enough carbon-14 to exceed the values listed in Handbook 69. Accordingly I appraise clinical research applications on the basis that no more radiocarbon should be given as a single dose than is needed to obtain statistically significant results for the radioassays proposed. Similarly, the number of repeated doses should be no more than the number required by good experimental design. As a matter of fact the considerations that I apply to carbon-14 are exactly the same as I apply to other radioisotopes.

5. *Tritium labelled thymidine:*

This useful material can be employed profitably in many types of clinical research. Some workers have expressed concern that the incorporation of the labeled thymidine into DNA may cause genetic injury in the same way that was postulated for carbon-14. The experimental data available are confusing to say the least, and the only information which provides me with a reasonable guideline is the experience with cultures of HeLa cells. It has been reported that an effect can be detected when the concentration of thymidine-H^3 in the medium exceeds 0.02 microcuries per ml. By simple extrapolation this is equivalent to a steady body burden of about 1 millicurie in an adult subject. One can introduce substantial safety factors and still be able to use satisfactory amounts of thymidine-H^3 in clinical research. This value — one millicurie — is interesting for it is about one-half of the amount that is usually stated to be the permissible body burden, and is about the amount required to measure conveniently total body water. I have not come to any firm decision about the problem of thymidine-H^3, but at present continue to apply the same criteria that I use in the case of carbon-14 labelled compounds and other radionuclides: namely, use the smallest amount that will provide significant radioassay data using technics that are appropriate and sophisticated.

To recapitulate, with few exceptions an experienced clinical investigator who has taken the time and made the effort to become thoroughly familiar with radiobiology will seldom submit an application for a license which will be recommended for disapproval by our Advisory Committee. Tracer technology fascinates many people and unfortunately there are some physicians who do not believe that special training is needed to use radioisotopes as research tools. As a matter of fact all the phenomena that can be studied using tracers, and all the phenomena that make radionuclides useful in medical research are implicated in the problem of safe-handling: half-life, energy, turnover, selective localization, radiobiological effects, and so on. When isotopes are used intelligently and

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imaginatively they are of inestimable value. Carelessly used, or used by a person lacking in fundamental information, the results are sure to be uncertain, and the possibility of harm is too great to deny. Equally serious is the likelihood of an incident, or incidents, which can only discredit in the minds of many the legitimacy of using this powerful tool in research. I can summarize briefly by saying that the principal objective of the AEC's licensing procedure is to reduce the possibility of unnecessary exposure to radiation.

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