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BIOLOGICAL BASES FOR MAXIMUM PERMISSIBLE EXPOSURES

by

Simeon T. Cantril, M.D.

(For inclusion in P.P.R. - Volume 20, Chapt. 2)

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BIOLOGICAL BASES FOR MAXIMUM PERMISSIBLE EXPOSURES

by

Simeon T. Cantril, M. D.

1. Introduction

1.1 Definition of Terms.

In the development of the science of radiotherapy, a special nomenclature has grown up, which, for the most part, is clear and unambiguous to the doctors and physicists engaged in the field. For special reasons, some of the quantities involved were defined in a manner different from that in which analogous quantities in pure physics would have been handled. The present project makes it a matter of general interest to correlate these two aspects. Some account of the terms used will therefore be given before proceeding to the main discussion.

Dose:

Webster defines dose as -

(a) The measured quantity of a medicine to be taken at one time or in a given period.

(b) A definite quantity of anything regarded as having a beneficial influence.

(c) Anything nauseous that one is obliged to take.

The radiotherapist presumably accepts definition (b) in considering the radiation effect on his patients, and definition (c) in considering the effect upon himself.

Webster's definitions are based on the simple picture of the swallowing or injection of a measured quantity of material. With rare exceptions such a quantity is retained by the body for a period long

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in comparison with the giving of the dose. The radiation case is quite different. When the body is subjected to x-radiation or gamma radiation some part of the incident energy is absorbed, but in general the major part is transmitted without interaction. It is assumed that the tissue is effected only by the energy absorbed. Dose, in the sense used in radiotherapy, refers then to the energy absorbed in the tissue. In principle, dose could be measured directly in terms of energy absorption per unit volume, but the practical difficulties are great, and it is better to determine dose indirectly by ionization measurements under certain prescribed conditions.

The Roentgen:

The ionization per unit volume of air in a sufficiently small cavity in an absorbing medium subjected to x- or gamma-irradiation is approximately proportional to the energy absorbed per unit volume in the medium at the same point. Although this relation would in itself provide a feasible method of dosimetry it was avoided in the setting up of international standards because it requires the use of an ionization chamber with "tissue walls." No general agreement about such a tissue wall could be reached. It was, therefore, decided to use the ionization inside an air-wall or air-equivalent wall cavity as the standard of reference. On this system the unit of dose, called the roentgen is the quantity of x- or gamma-radiation that produced 1 esu of quantity of electricity of either sign per 0.001293 gm of air (= 1 cu.cm. of dry atmospheric air at 0° C and 760 mm of mercury pressure) in such a hypo--thetical air-walled ionization chamber.

The merit of the system was that over the range of wave lengths used in radiotherapy, the energy absorbed per gram of soft tissue was

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sufficiently accurately the same as that absorbed per gram of air. The correlation broke down when the biological material concerned was either skin, which contains enough sulphur to give an important photoelectric contribution, or bone, in which the air-walled cavity gives an entirely erroneous picture of the energy absorption. With these exceptions it became common practice to state that the roentgen corresponds to an energy absorption of 83 ergs per gram of tissue or to the production of 1.61×10^{12} ion pairs per gram of tissue.

When neutron therapy began to be used it was found that the absorption of energy from neutrons in air was not proportional to that in tissue. Moreover while it had been relatively easy to make an air-equivalent material with respect to x- or gamma-rays, since this depended only on the electron density and the artificial matching of the photoelectric effect over a wide enough range, for measuring fast neutrons the hydrogen content of the chamber wall became the prime factor. So far the tentative methods of neutron measurement have used the following devices:

(a) A pure carbon wall, chosen because of its reproducibility. (L. H. Gray)

(b) The bakelite wall, coated with aquadag, of the customary 100 r Victoreen condenser r-meter. (The n unit of P. Aebersold)

(c) Pure water (presumably as ice?) Another generally available substance, but this time with approximately the correct amount of hydrogen. (L. H. Gray)

(d) Basic Dosimetry with different walls and chamber gases to deduce the tissue-equivalent dose. (L. H. Gray)

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(e) Paraffin wall with ethylene gas. (E. O. Wollan)

(f) The balanced double ionization chambers filled respectively with argon and a gas rich in H. (Wollan, Gamertsfelder, Parker).

In the meantime, many writers have used the term roentgen as synonomous with the absorption of 83 ergs per gram of tissue or the production of 1.61×10^{12} ion pairs per gram regardless of whether the primary radiation was x-rays, gamma-rays, beta-rays, alpha-rays, neutrons, or any radiation that produces ionization in tissue. This unit has been variously specified as the "tissue roentgen", the "roentgen-equivalent" or the "equivalent-roentgen". The latter two terms are misleading because the biological effect is certainly not equivalent, and as the "e" was used in Europe for a unit similar to, but not identical with the "r". We have preferred to use the expression "roentgen equivalent physical" (rep).

Another concept enters into the discussion when tolerance dose is considered in relation to varying radiations. The effect produced upon similar tissues by an equivalent amount of energy absorption from different types of incident radiation varies greatly. It is possible to produce the same biological effect with different radiations but it requires varying amounts of absorbed energy as measured physically. Using the roentgen as a standard unit, when a measured amount of radiation produces an effect similar to an x-ray effect from a known number of roentgens, that amount can be said to be biologically equivalent to that number of roentgens. The logical term to express this concept is "roentgen equivalent biological", abbreviated "reb". This, in speech, can be so easily confused with "rep", that we have adopted the abbreviation

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"rem" which can be understood to imply "roentgen equivalent man, mouse, mammal, or medium", depending upon the biological effect under discussion.

Dosage-rate:

By convention, dose per unit time is called dosage-rate. There is an alternative expression using exposure instead of dose, and exposure rate instead of dosage-rate. The essential point is to distinguish between dosage-rate and intensity. The former is essentially a measure of energy absorption per unit time; the latter is the energy flux. The relation between dosage-rate and intensity is therefore a function of the absorbability of the radiation in question. The more recent radiological literature has carefully observed this distinction, but the older papers frequently expressed intensity in terms of r per unit time.

Tolerance Dose:

For the present purposes, tolerance dose will be assumed to be that dose to which the body can be subjected without the production of harmful effects. It is not self-evident whether dose as used here refers to a total dose or to the elements of dose in a given period of time. This will be discussed later. We have taken the latter view and further specify that the given period of time shall be one day.

Tolerance dosage-rate:

Tolerance dosage-rate has to be interpreted as the dosage-rate that is continuously tolerable. We say that the daily tolerance dose is 0.1 r (in general). If one writes "The tolerance dose is 0.1 r per day", it is argued that this expression is dimensionally a dosage-rate, and that one should write "the tolerance dosage-rate is 0.1 r per day." There is here a difference in attitude which can be resolved only by a resumé of the manner in which tolerance dose has come into the literature.

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Tolerance dose versus tolerance dosage-rate:

The question of interpretation between dose and dosage-rate ultimately leads to far reaching differences of opinion concerning the permissible exposure of the body. The origin of the difficulty is closely related to the development of radiotherapy since 1928. The current International Recommendations for X-ray and Radium Protection read as follows:

"The evidence at present available appears to suggest that under satisfactory working conditions, a person in normal health can tolerate exposure to x-rays or radium gamma-rays to an extent of about 0.2 international roentgen per day or 1 r per week. On the basis of continuous irradiation during a working day of seven hours this figure corresponds to a tolerance dosage rate of 10^{-5} r per second."

It is clear that the persons responsible for these recommendations had in mind that it was immaterial whether the exposure was taken in equal daily amounts or whether it was averaged out over a week. The earlier writers frequently quoted the permissible exposure per month. In all this there was no restriction on the dosage-rate other than the implication that the exposures received were such as would normally arise in x-ray or radium work. The crux of the problem is then the normal mode of receiving unwanted radiation. This occurred in four principal ways:

(1) Fluoroscopists:

The fluoroscopist was exposed to short bursts of quite intense radiation (of the order of 10^{-1} r/sec. on the hands, and 10^{-3} r/sec. on the body).

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(2) <u>X-ray therapy technicians:</u>

In this case the technician was exposed to radiation for periods of about 5 to 30 minutes with intervals of the same order between treatments. Before the advent of self-protected tubes and special shielding, a typical dosage-rate for these exposures would be 10^{-4} r/sec. At the present time the exposure of x-ray technicians is so little that in general it adds nothing to our knowledge of tolerance.

(3) <u>X-ray therapy patients:</u>

It is debatable whether patients should be included because their exposure is received over a period of weeks rather than years. However, in therapy, a large portion of the body receives a dose of the order of one per cent of that delivered to the treated part. Since it would not be uncommon to deliver 4000 r to each of two or three fields, the body can receive 80 to 120 r in a few weeks, at a dosage-rate of about 10^{-2} r/sec. Such an irradiation is not without demonstrable effects, but it is believed to cause no permanent damage. A dose of this magnitude is a three year quota of daily tolerance doses. A study of patients subjected to repeated courses of x-ray treatment would be instructive except that most of the patients so treated would die too quickly of other causes.

(4) <u>Radium therapists and technicians:</u>

These men were exposed for periods up to one hour at irregular intervals, with a background of perhaps 2×10^{-6} r/sec. through the working day. The highest dosage-rate normally encountered would be about 10^{-3} r/sec.

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In all cases it appears that the exposures from which the present knowledge of tolerance was derived were given in relatively short bursts at dosage rates mainly in the range of 10^{-4} to 10^{-3} r/sec. This should be sufficient evidence that no special significance should be attached to a tolerance dosage-rate of 10^{-5} r/sec. The inclusion of this figure in the International Recommendations was, we believe, nothing more than a recognition of its convenience as a guide when protection measurements are made with a survey meter, calibrated in r/sec. All points at which the dosage rate is permanently less than 10^{-5} r/sec. can be considered safe.

On the whole, the exposure of personnel regularly employed in a radiation hazardous occupation will be more or less evenly distributed except for week-ends.* In addition a large body of information on repeated daily exposures of patients has been built up. For these reasons we restrict the meaning of tolerance dose to daily tolerance dose. This procedure is somewhat arbitrary. There is nothing magical about a period of one day, and it would manifestly be absurd to claim that 0.1 r can be delivered daily with any time distribution in the day, and that 0.2 r cannot be given every alternate day or 0.5 or 0.6 r every working week. Nevertheless there has to be some limit to the dose-time relation, and the daily limit is convenient. No restriction need be placed on the dosage rate at which daily general body radiation is received. Conditions should not exist in which the body can received the daily quota of 0.1 r in less than 10 secs., and this automatically limits the maximum

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*However, radium technicians in the larger institutions are frequently "on radium" and "off radium" in alternate months. It is fairly well established that freedom from radiation for four weeks gives the blood a chance to recover from potential damage.

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dosage-rate to about 10^{-2} r/sec. which differs by only a factor of 10 from the dosage-rates giving rise to our general knowledge of tolerance.

Of interest in the dosage-rate problem are the experiments reported by Curtis, Zirkle and co-workers(2). Two different gamma ray sources were used, and all variant factors were eliminated except the dosage-rate, which was 30 r/min. in one case and 4 r/min. in the other. The longest duration of exposure to produce lethal effects in mice was 4 hours. It was found that with this discrepancy in dosage-rate, there was nearly a 50% difference in lethal effect, in favor of greater effect for the higher dosage-rate.

In the above experiments both the dosage-rate and the total duration of the single exposure to produce death were necessarily variants, and it is of interest that so wide a variation in effect was shown. For other effects, as for example the production of erythema in the human skin, it has been shown that(3) when the exposure rate of gamma radiation varied from 12 to 1273 r/hour identical skin erythemas were produced in the same individual when the total dose remained constant, the duration of treatment constant (one week) and the intermittent exposures in all cases given at 24 hour intervals. The same was true when x-ray exposure-rates varied from 3.3 to 225 r/min.

1.2 The History of the Tolerance Dose.

A severe case of x-ray dermatitis was described in January 1896, only a month after the discovery of x-rays. It was not until 1902 that Rollins(4) attempted to formulate some idea of a tolerance dose. He suggested that "if a photographic plate is not fogged in seven minutes, the radiation is not of harmful intensity." In present day terminology

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this would amount to perhaps 10 - 20 roentgens per day delivered by soft x-rays. The early injuries from radiation were largely those of the skin, but the demonstration of the marked radio-sensitivity of the blood forming organs (1904-1905) and of the reproductive organs of animals (1903-1904) carried some warning that more serious damage than dermatitis could be anticipated. The first organized step to insure protection from x-rays was made in 1915 by Russ(5) who read a paper on protective devices before the British Roentgen Society. Definite action, however, was delayed. To quote from Henshaw(6) "Because of the war activity which existed then, this plan failed to bring forth important advancement. As a result of war demands, caution gave way to action and protective measures were again forgotten. The taking of increased risks at this time probably was a factor which contributed to an unfortunate development in 1919 to 1921, both in this country and in Europe, when a number of prominent radiation workers died of apparent irradiation injuries, particularly aplastic anemia. Unfavorable publicity developed, and definite action resulted."

The American Roentgen Ray Society formed a Committee in 1920 to recommend protection measures, which were formulated and published in September 1922. The British X-ray and Radium Protection Committee presented its first recommendation in July of 1921. The two sets of recommendations were quite similar and dealt largely with protective materials recommended for use in building x-ray and radium laboratories and apparatus.

At the first International Congress of Radiology held in London in 1925 the question of x-ray and radium protection was considered but no definite action was taken. At the second International Congress

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held in Stockholm in 1928 definite proposals were adopted and subsequently an International Committee on X-ray and Radium Protection was formed. The recommendations adopted by the International X-ray and Radium Protection Committee contained no reference, however, to a tolerance dose, merely stating that the known effects to be guarded against were: injuries to the superficial tissues, derangement of the internal organs and changes in the blood. The report of this Committee in 1931 likewise contained no statement of a tolerance dose but in two subsequent reports (1934 and 1937) the tolerance dose is stated as 0.2 roentgen per day(7).

It is of interest to search for the basis on which the above tolerance dose was established. From 1925 to 1932 various individuals published their own opinion on the tolerance dose. A somewhat detailed appraisal of the basis of these opinions is warranted here.

Mutscheller, in 1925(8) published a tolerance dose figure of .01 of an erytheme dose* per month, and to quote his publication, "Several typical good installations and fair averages were taken as a basis for calculating the dose to which the operators are now exposed during the time of one month. Thus it seems that under present conditions and standards accepted at present, it is entirely safe if an operator does not receive every thirty days a dose exceeding .01 of an erythema dose, and from the present status of our knowledge this seems to be the tolerance dose for all conditions of operating roentgen ray tubes for roentgenography, roentgenoscopy and therapy. This dose, however, is derived from the average of a limited number only of typical examples, and is perhaps not yet sufficiently checked biologically

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* An erythema dose is one which produces a perceptible reddening of the skin.

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and so it may happen that in the future this dose will have to be changed either to a larger or a smaller practical tolerance dose."
In 1928[9] Mutscheller again published the same tolerance dose figure, and in 1934[10] the same figure of .01 of an erythema dose was published for "rays of higher penetration " used for therapeutic application. The erythema dose for this quality of radiation was given as 340 roentgens. Hence his tolerance dose was then 3.4 r per month or 0.1 r per day.

Glocker and Kaupp[11] in 1925, and acting for the German Committee on X-ray and Radium Protection, published the same figure as .01 of an erythema dose which they took directly from Mutscheller.

Sievert[12] published in 1925 one-tenth of an erythema dose per year as a safe dose, based again upon the laboratory and hospital measurements.

Barclay and Cox[13] in 1928 published a figure of .00028 of an erythema dose as a daily exposure which could be tolerated without effect. They arrived at this figure in the following manner. Two examples of exposure were taken as a basis. One was an x-ray technician who had worked for six years and it was judged that the daily exposure which she received was .007 of an erythema dose. The second was a radiologist whose daily exposure was appraised at .0023 of an erythema dose. Barclay and Cox then arbitrarily took 1/25th of the daily exposure to which the x-ray technician was judged to have been exposed over the six year period, namely .007 of an erythema dose, and arrived at their tolerance figure of .00028 of an erythema dose per day. It should be noted that in both examples exposure was to soft x-rays and that the safety factor of twenty-five was purely arbitrary.

Failla[14] in 1932 published a report on the "tolerance intensity" to which his technicians had been subjected in operating a 4 gram radium

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installation. This was of the order of .001 of a threshold erythema dose per month (threshold erythema dose taken as 600 roentgens). The measurement of this intensity was done with photographic film by Dr. Edith Quimby. The longest term of employment had been four and a half years. No ill effects from this level of radiation had been noted in the technicians. He accordingly adopted .001 of an erythema dose per month (.6 r per month or .02 r per day) as the "tolerance intensity" for gamma rays. In referring to the previously published tolerance dose levels, Failla pointed out that they were based upon sofe x-ray radiation, having a lesser penetration than gamma rays and hence less potentiality for damage to internal organs. Since protection from soft x-rays is readily obtained, Failla suggested then that the figure of .001 of an erythema dose per month be accepted as tolerance for both x-rays and gamma-rays.

Kaye(15) brought together in 1928 the combined opinions on the tolerance dose and converted the figures to .001 of an erythema dose in five days as an average value.

The dependence of erythema on quality of radiation is illustrated by the following approximate values:

Quality	To Produce Erythema
Grenz rays	100 r
100 kv	350 r
200 kv	600 r
1000 kv	1000 r
Gamma rays (radium)	2000 r

Thus it may be seen that for soft scattered x-rays (which were those considered by Mutscheller), the erythema dose may be only 1/5 of that for gamma rays of radium which formed the basis of Failla's figure.

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The International X-ray and Radium Commission, acting for the International Congress of Radiology, set the tolerance dose at 0.2 roentgen per day in both 1934 and 1937 recommendation[7]. As an outgrowth of this International Commission there was formed in the United States an Advisory Committee on X-ray and Radium Protection which published its first proposals[16] in 1931 in the Bureau of Standards Handbook No. 15. Here the tolerance dose was set at 0.2 roentgen per day. In a later report of this American Advisory Committee (Bureau of Standards Handbook No. 20) the tolerance dose is stated as 0.1 roentgen per day, no explanation being given for this reduction in tolerance dose. In a subsequent publication in 1941 on the subject of Radiation Protection, Taylor[17] who is Chairman of the American Committee, referred to the safety value of 0.02 roentgen per day. This latter figure, however, is not the combined opinion of the American Advisory Committee but was published independently by Taylor.

Wintz and Rump in a League of Nations Publication in 1931[18] reviewed the various statements of tolerance dose and came to their own conclusion that the admissible dose is 10^{-5} r/second assuming an eight hour working day and 300 working days per year. This amounts to ~.25 r per day. They qualify this dosage-rate for persons remaining in proximity to sources of radiation giving off rays without intermission (radioactive preparations) by reducing it by a factor of 3 (i.e. 0.1 r per day). Both Failla and Wintz and Rump have thus specifically referred to gamma rays in defining their tolerance doses. The American recommendations[19] of 0.1 r per day refer to both x- and gamma rays.

The difficulties of establishing a tolerance exposure level can be ascertained from the history of its development. A clear cut experiment

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on a large scale is virtually impossible to conduct because there would always arise various degrees of abnormality (in blood levels) which would have no relation to radiation exposure. In this respect Taylor concludes: "Obviously, the determination of this tolerance dose is difficult and at best uncertain. The biologic factors differ too greatly among individuals to permit the use of a sharply defined tolerance. To be well beyond the danger limit, one must apply a generous factor of safety to the result of any physical measurements."

1.3 The Legal Status of the Tolerance Dose.

The legal status of radiation safety recommendations is discussed by Lauriston Taylor in his chapter on Roentgen Ray Protection in the "Science of Radiology"(20). He states that the "legal status of roentgen ray safety recommendations was brought up at the outset and it is important to note that in no country do such recommendations have a strictly legal recognition. The complications of this were early recognized and the British Committee, for example, felt that public opinion could be just as effective as word of law. Moreover by not having a legal status, the recommendations could remain flexible and be readily changed to suit changing conditions. Laws, once formed, change slowly and, in the matter of roentgen ray protection, such inflexibility may lead to complications.

"The method found by the British Committee to be most effective, in bringing about acceptance of the recommendation, was to put the power of inspection and approval in the hands of the National Physical Laboratory ..... "

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"In this country, the same conditions* did not exist, and, while recommendations have been accepted** there is neither legal status nor the authorization for a central laboratory to put weight behind an enforcement. The charter of the National Bureau of Standards does not foster any general outside inspection of activities, nor have funds ever been authorized for the purpose. This Bureau does, however, test and certify protective materials and concurs in the recommendations of the Safety Committee."

The National Bureau of Standards Handbook No. 20 on X-ray Protection(19) explicitly states in the first paragraph, "throughout these recommendations the word 'shall' is used to indicate necessary requirements, while the word 'should' indicates advisory requirements to be applied when possible." This is included under "General Recommendations" and is in line with Taylor's above statement that the Bureau of Standards does concur in the recommendations of the Safety Committee.

Again in 1932(21) in discussing the work of the American Advisory Committee on X-ray and Radium Protection, Taylor states that: "the question of the legal status of these recommendations has been frequently raised. They have none. The Committee feels that none is needed; that legislative enactment tends to stunt development and prevent healthy changes. We are free to admit that our present proposals may require changes in the future as they are developed. We wish nothing to interfere with the freedom for modification. I should be

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* A National laboratory with powers of inspection and approval.

** The recommendations of the American Advisory Committee have been accepted and published by the Bureau of Standards.

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pointed out, however, that lack of legal standing will probably not in any way detract from their legal value. They are a recognized set of recommendations, drawn up by qualified representatives of the art and freely distributed to those interested. A court decision involving x-ray protection would in all probability, for lack of another source, be guided by these recommendations, and persons ignoring them may be held liable for negligence."

Certain states have set up, through their Departments of Health and Industry, rules to cover the safety of workers engaged in luminous dial painting. New York has compromised on an allowable concentration of 10^{-10} curies of radon per liter in the working air. Massachusetts has prescribed that the whole body exposure to gamma rays shall be maintained at less than 0.1 r per 8 hour day. But in so far as we can determine, in no state are these Department rulings or recommendations actually law on the statute books. It would seem that the time is appropriate for some government agency to establish and enforce adequate rules for protection against radiations and radioactive elements used in industry. The advent of the atomic energy program further emphasizes this need. The enormous increase in the use of industrial radiography and luminous dial painting brought on by the war will continue in postwar years on a reduced scale but one that is still larger than before the war. Artificial radioactive substances will be in wide use in many phases of industry, chemistry and biology.

Considering the fact that radiation damage continues to be produced by industrial use of radiations, we are inclined to believe that laws are needed even though we may be in agreement with Lauriston Taylor that "legislative enactment tends to stunt development and prevent

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healthy changes." Legislation has protected the public from over-exposure to lead, benzol, carbon monoxide and a host of other toxins without interfering too seriously with progress.

1.4 Project Radiation Problems.

In the hasty development of the Plutonium Project the possibility of exposure to all kinds of radiations was magnified many fold over any which had existed heretofore in industry or the laboratory. The hazards due to roentgen and gamma rays were fairly well known from previous unfortunate experiences. The effects of exposure to beta and neutron rays arising outside the body were less well known. Enough was known of the biologic action to permit an estimation of tolerance doses and utilizing these shielding was constructed with a sufficient margin of safety. The hazards due to the fission products were largely unknown. There had been previous experience with limited quantities of radium and radon, and an extremely small amount of such radioactive elements as iodine, phosphorus and strontium. From the little that was known from these experiences the magnitude of the hazards to be encountered in dealing with tremendous quantities of radioactive fission products had to be deduced. The toxicity of uranium and its various compounds was not known with any degree of certainty and the dangers of plutonium were entirely unknown.

The traditional permissible doses upon which the safety of any radiation exposure had to be based were: the International tolerance dose, of 0.2 r per day of x- or gamma radiation; the American tolerance dose, 0.1 r per day; the tolerance concentration of radon in air, 1×10^{-14} curies per cc.; the recommendation of the Bureau of Standards

that 0.1 microgram of radium deposited in the body be considered as the maximum safe limit. No tolerance dose had been established for fast neutrons but as compared to x-rays they were known to be about 2.5 times as effective in producing skin changes in humans for equal energy absorption. Other effects on mammals showed the neutrons from 215 to 10 times as effective as x-rays.

The above seemed rather meager information. Without it however the protection program would have had no base levels on which to build. The problem then was to investigate the soundness of certain of these traditional levels, while proceeding to ascertain radiation tolerance for both radioactive substances and radiations yet unavailable in sufficient quantity for any considerable biologic assay. As these radioactive substances became available the experimental work was begun. As sources of external radiation were made available (i.e. slow and fast neutrons, intense beta ray beams) they in turn were used for biologic research to determine their effects and to check the validity of those factors of safety which had already been utilized in design and construction without waiting for biologic confirmation. Fortunately this necessary reversal of procedure did not result in major alterations, largely due to the factors of safety which were incorporated. But there were unexpected results from the biologic work which strongly emphasize the wisdom of knowing the degree of hazard beforehand. These will be discussed in a later section.

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2. The Biologic Aspects of the Tolerance Dose

Experience thus far has taught that certain fundamental biologic trends will influence the allowable exposure to radiation. This information has been gained through both therapeutic and experimental work with radiation. The problem of radiation tolerance is largely concerned with the radiosensitivity of tissues, and for that reason a discussion of radiosensitivity is briefly included here.

2.1 Radiosensitivity of Tissues.

1. Radiosensitivity. By radiosensitivity is meant the relative vulnerability to radiation of a tissue living in its normal physiological environment. Advances in the application of radiation to medical uses have come about largely by learning to adapt the techniques of exposure to take advantage of the varying sensitivities of different tissues.

Not only do different tissues have different radiosensitivities but also similar tissues in different environments respond differently. When animals are exposed to irradiation of the entire body there are not only marked differences in radiosensitivity of different species but there are also variations within strains of the same species. This is one of the obstacles in carrying over to man conclusions based on the biological effects of radiation found in the lower animals.

The problem is further complicated by various biological events which can alter the radiosensitivity of a given tissue. A few examples will serve to bring out certain of these factors which are known.

2. Rate of Growth. In general, the more rapidly growing and active cells tend to be the more radiosensitive ones in a given tissue.

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3. Cellular Environment. The composition of the medium or the environment of the cells comprising a tissue strongly affects the radiosensitivity. This is closely associated with the complex physiochemical alterations which must ensue within the cell when it is subjected to unnatural ionization. Whether the effect of the ionization is a direct one, taking place within the cell, or an indirect one resulting from alterations in the environment, is still largely a matter of conjecture, although evidence is accumulating to show that both mechanisms may be active. As an example of the effect of environment upon radiosensitivity one may cite the diminished effect of radiation upon otherwise extremely radiosensitive tissues when they are subjected to a reduced oxygen supply during the time of exposure. Likewise there is experimental evidence to show that a change in the acid-base relationship, affecting the permeability of cell membranes, can for certain tissues increase their radiosensitivity. Physical factors such as heat, cold or previous radiation may alter either the rate of growth or the environment of the cells, and thus produce a change in their vulnerability to ionization in them or in the medium in which they live.

4. Threshold and Non-threshold Effects. If one plots a dose-effect graph for various tissues subjected to radiation, there are in general two forms which the graph may take:

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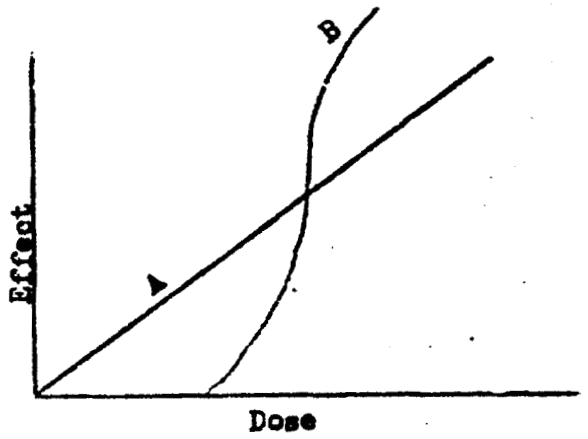

(A) Curve A illustrates the non-threshold case. The effect is directly proportional to the dose no matter how small or large. There is no initial threshold of dose which must be exceeded before an effect is obtained. To recognize a non-threshold effect, it must be readily observable or measurable. An example is the influence of radiation upon the germ plasm of Drosophila.

(B) Curve B illustrates a threshold effect. Here the effect is not measurable by present methods until a certain threshold of dose is exceeded. Threshold effects are not linear with dose. The effects of radiation upon the skin and the blood forming organs are examples. Until the dose reaches or surpasses the threshold, the first sign of skin effect (erythema) or of effect upon the blood forming organs (as reflected in the circulating blood) are not seen.

The majority of radiation effects are thought to be of the threshold type. It may be that as more delicate indicators are found to measure effects, more of them will be seen to be of the non-threshold type.

5. <u>Reversibility of Effects</u>. The reversibility of radiation effects is important, particularly in occupational exposure. By reversibility is meant the return of a tissue to its previously normal state after exposure is discontinued. The reversibility of any specific effect is dependent upon the reparative or regenerative properties of the tissue. Some tissues, such as skin, the blood forming elements, membranous linings of the body cavities or glands, and peripheral

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nerves are endowed with a special type of repair mechanism. Other tissues, such as brain, kidney and lens of the eye have no repair mechanism. In them, repair is by the formation of a scar, which does not take over the function of the original tissue which it replaces. The effects in such cases are said to be irreversible.

In order for an effect to be reversible, it must not produce injury beyond the limits of the normal capacity for regeneration. Otherwise the effect is permanent and may lead to complete destruction or exhaustion of the tissue.

Both the total dose and the total time over which it is given may affect the ability of the regenerative processes to function. If the total dose is excessive regeneration and repair may be impossible irrespective of the time over which it is administered. On the other hand, a total dose which will produce reversible effects, if given at a sufficiently slow rate to permit regeneration may result in irreversible damage to the tissues if given at a faster rate over a shorter period.

A tissue which has been irradiated may regenerate to a degree that it can carry on its normal function. Any latent damage may be undetectable by present methods. The tissue will however be more vulnerable to subsequent irradiation, and slower to regenerate. Bone marrow, for example, despite its remarkable powers of recovery will eventually be exhausted following repeated irradiation.

2.2 General Body Effects.

For the purposes of simplification, the general body effects will be considered from the standpoint of (1) external radiation

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and (2) internal radiation. Although the effects are similar in many respects the source and route of administration of radiation has some bearing on the tolerance dose.

Regular blood counts have been done on the workers of the Plutonium Project to establish the individual blood count level and to be able to follow any trends in blood count which might result from over-exposure to radiation. Dr. Jacobson's analysis of these studies, reported elsewhere, indicate however that for the degree of exposure encountered on the Project, the blood count is not a significantly early index. The analysis of blood studies made in irradiated animals also supports this conclusion. At best the leukocyte count serves as a means of detecting injury to the bone marrow when it has been subject to prolonged irradiation in excess of the permissible level. It may in some individuals reflect injury from a single exposure of penetrating radiation of the order of 25 - 50 r.

There has not as yet been developed a specific biologic test which is reliable in detecting the initial signs of injury resulting from general body radiation from an external penetrating source.

By internal radiation is meant radiation originating within the body. It comes from radioactive elements which get into the body by any means, such as ingestion, inhalation etc. Experience with internal radiation was obtained through studies of inhaled radon both in animals and man. Studies of the blood of workers concerned with separation of radium show an eventual effect upon the blood producing organs. The magnitude of the exposure can be correlated with the level of radioactivity of the expired air(24). Similar studies have been made upon

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the workers concerned with the preparation of mesothorium[23]. The late effects of continued inhalation of excessive amounts of radon are unfortunately known for man. The high incidence of lung cancer in the Schneeberg, Sazony, and Jachymov mines of Bohemia has been directly attributed by some workers to breathing air containing radon, which gives an alpha bombardment to the lung tissues. The reported incidence is high. In one report[24] out of a total of 89 deaths occurring in a period of ten years among 400 miners, 60 autopsies were obtained and 42 of the deaths were shown to be due to primary lung cancer. This was an incidence of 9.7 ± 1.5 per year per 1000, or about 30 times the normal expectancy. Of 48 mice kept for a year in the Schneeberg mine, 28 died, seven having developed tumors of the respiratory organs[25]. The average radon content of the air in these mines is of the order of 3×10^{-12} curies of radon per cc.

Lorenz questions the validity of these observations and does not ascribe the high incidence of lung cancer either in the workers or mice to the high radon content.

The radioactive gases which in the past have been an occupational hazard were the emanations from radium and mesothorium. The Plutonium Project brought us in contact with other radioactive gases (Xenon, Argon, Krypton), and the radioactive vapor (Iodine). The Xenon and Iodine problem will be more fully discussed in a later section.

Internal radiation from ingestion and deposit of radioactive material in the bodies of radium dial painters was first described by Martland[26]. The history of this occupational disease is well known. About 98 to 99 percent of the radium which was ingested through the habit of pointing

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the brushes in the mouth was excreted, but the remainder was deposited in the body, largely in the bones. As little as 1 to 2 micrograms fixed in the body has proven lethal. Here again the continued bombardment of bone marrow results either in a fatal anemia, atrophy of the bone or in the production of malignant bone tumors. The late signs of damage, anemia or malignant bone tumors, may be evident some years after exposure has resulted in the deposit of radium. It is possible, however, to detect radioactivity in the expired air as an early check on over-exposure, and this is done routinely by the more cautious plants producing luminous dials. There is apparently an initial compensatory activity of the bone marrow which attempts to keep pace with the tissue destruction produced by the continued alpha bombardment but eventually leads to bone marrow exhaustion and fatal anemia. Experience with radium poisoning in the luminous dial industry has led the Bureau of Standards to establish 0.1 microgram of radium as the limit which can be deposited in the body without resulting in later damage[27].

The hazards of internal radiation from ingestion, inhalation or trans-cutaneous passage and eventual deposit of radioactive materials in the body could not be overlooked as a major hazard for the Project. Studies on the absorption, deposition and excretion of the various fission products were done and are reported elsewhere by Dr. Joseph G. Hamilton and his associates. The tolerance value or maximum permissible amount of any fission product which could be safely taken into the body could not be set until a complete study had been made of the way the body handled that element and of the effects of the radiation from it. This had to be done separately and collectively for each fission product.

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The problem of the hazard due to plutonium did not receive early consideration. Until the fall of 1943 there was not a sufficient quantity of plutonium recovered to allocate the amount necessary for even tracer biologic work. As soon as the first micrograms could be spared for biologic assay, this was done, and the results of these early, as well as later experiments by Dr. Hamilton and his associates, as well as by Dr. Kenneth S. Cole and his associates, are reported in Volumes XXII and XXIII. They have formed the basis of our permissible levels thus far established for exposure to plutonium.

2.3 Skin Effects.

The effects of radiation on the human skin gave the first indication of any biologic effect of x-rays and gamma-rays. Becquerel, who carried a tube of radium in his vest pocket for demonstration purposes, developed a reaction of the underlying skin. X-ray dermatitis was in evidence within a few months after the discovery of x-rays.

The greatest number of radiation injuries has been to the skin both in x-ray and radium workers. Following the early wave of damage to the skin which came in the first fifteen years of x-ray and radium use there were more precautions taken to prevent skin damage. With special attention given to local protection, the number of injuries to the blood forming organs increased due to lack of complete protection. As emphasis was then placed on whole body protection, the skin injuries again assumed first place and at the present time they are still appearing in unnecessary numbers. The majority of these are physicians or dentists; a fewer number appears in radium workers.

The characteristic effect of large doses of x-ray and radium upon the skin is the production of a skin erythema. In this respect

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they are comparable to ultra-violet radiation except that the latent period between exposure and erythema is much more delayed, depending upon the dose, up to about four weeks with a single x-ray or gamma-ray exposure. As was previously noted, in general it requires a larger dose of shorter wave length radiation than of longer to produce the same effect. As the length of time over which the radiation is administered is increased, the dose required to produce an erythema becomes larger.

The erythema is the result of a dilation of the fine capillaries, venules, and arterioles supplying the skin. The mechanism is thought to be identical with the erythema produced by ultra-violet irradiation[28] having a wave length of about 300 micro-microns, which is the component of sunlight effective for this purpose. The stimulus which produces the blood vessel dilation is thought to be due to a local release of a "histamine-like" substance from the living superficial layers of the skin.

The skin is composed of essentially two layers of tissue - the epidermis which consists of the epithelial cells forming the protective covering of the body, and the dermis lying beneath the epidermis, which consists of the supporting connective tissue for the epidermis and carries the nutrient vessels, acessory organs and nerve supply. The thickness of the epidermis, or outer cellular layer, varies over the body but in general ranges from 0.07 to 0.12 mm. On the palmar surface of the hands and fingers, it averages 0.8 mm; on the soles of the feet 1.4 mm. In men accustomed to heavy labor, which produces a thickening of the skin of the hands, the epidermis may be considerably thicker. The outermost layer of the epidermis (stratum corneum) consists of dead,

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hornified, flattened cells. The thickness of this outer horney layer varies over the body, being thickest on the soles (.8 mm) and palms (.44 mm). On the backs of the hands and over the remainder of the body it is considerably thinner. As cells are lost from this outer layer by normal wear and tear, the underlying growing layer of the epidermis continues to furnish a new supply. There are no blood vessels within the epidermis - the fine capillaries nearest the surface lying directly beneath the epidermis. Thus erythema is produced below the epidermis.

Superficial injury of the skin is evidenced either by erythema or a desquamation of the epidermis, which, if the exposure has not been too severe, will eventually heal by growth of epithelium from the basal layer of the epidermis. More severe damage will injure the vessels in the dermis, resulting in prolonged ulceration, which may or may not eventually heal, depending upon the degree of injury sustained.

The thickness of the outer horny layer of the skin is of importance in relation to the penetrability of alpha and low energy beta-radiation. Since the alpha particles of uranium have a range in tissue of about .05 mm one would not expect skin injury from them. When the energy of alpha particles is greater (as those from a cyclotron) penetration in tissue becomes sufficiently great to produce skin injury(29).

The beta-ray penetration of tissue is discussed at some length in a report by H. M. Parker, which is to be found in Volume XXI. It is sufficient here to emphasize that beta-particles of the average

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energy associated with the long lived fission products will penetrate well below the skin, and hence there is real potentiality for injury if due caution is not exercised to avoid over-exposure.

The above discussion of erythema applies to radiation injury of a relatively acute type. The dose required to produce erythema is relatively high. As the time over which the dose is administered is lengthened (as in chronic occupational exposure) a considerably higher total exposure will be tolerated. Erythema may be an early sign only when the dose has been acute, but it may not appear at all when the exposure is spread over a period of years. Hence one cannot rely upon the appearance of an erythema to judge whether or not over-exposure is producing damage when the exposure is prolonged over a period of years. Other signs which should prove a warning are a loss of the normal skin ridges of the finger tips, loss of hair on the back of fingers and hand, cracking, brittleness or ridging of the fingernails, a loss of the normal sensitivity and an abnormal dryness of the skin.

The late evidence of injury appears as telangiectasis (a permanent capillary dilation), pigmentation, atrophy of the skin and its appendages (hair follicles, sweat and sebaceous glands) and skin thickening with the appearance of wart-like growths. The most serious late sign of damage is ulceration, which usually results from minor abrasions which fail to heal. Ulceration in many cases eventually progresses to cancer of the skin, which in some 25 percent[30] spreads beyond the hands and proves lethal. In some instances the wart-like growths (keratosis) become malignant, and hence when they have appeared

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they must be carefully observed. The time between onset of exposure to the recognition of skin cancer in one series was an average of nine years. The ages of these victims ranged from 28 to 60 years.

Stone and Larkin found that 110 "n" of neutrons produced by 16 mev deuterons produced a threshold pigmentation of the human skin appearing between the 4th and 19th day, which effect is also produced by 650 to 700 r of 200 kv rays*. Thus for the fast neutron exposure there is a ratio of effect varying by a factor of 6 for the human skin. For x-rays this is taken into account in the tolerance dose level for fast neutron exposure of 0.01 "n" (0.025 rep) per day.

Unfortunately, the workers who have in the past received skin injury have no record of the exposures received over a period of years. There is no general agreement on skin tolerance among radiologists or physicists who have medical experience. On inquiry from two professors of radiology of wide experience, the answers varied from 0.5 to 5.0 r per day of x-ray as tolerable to the hands. The Handbook (No. 18) on "Radiation Protection for Amounts up to 300 Milligrams" published by the Bureau of Standards in 1934 states that: "the safe general radiation to the whole body is taken as 1/10 r per day for hard x-rays, and may be used as a guide in radium protection. 5 r per day has been taken as the tolerance for the fingers. It must be emphasized that the calculation of radium dosage is not easy, and too great reliance is not to be put on the above figures."

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* The "n" is arbitrarily defined as a quantity of fast neutron exposure giving the same reading as one roentgen of x-rays when the measuring instrument is a 100 r Victoreen condenser chamber.

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This statement published in 1934 was fortunately overlooked when we were faced with the problem of setting a permissible exposure for skin - more particularly the hands. Although it is admitted that "the calculation of radium dosage is not easy," it can be done, and with reliable accuracy. We would also agree that "too great reliance is not to be put on the above figures," more particularly the 5 r per day allowed to the skin of fingers. In the opinion of those responsible for radiation protection on the Project 5 r per day was excessive. We were willing to admit that 1 r per day to the skin of hands would not be injurious if received occasionally when special work made this necessary. But in view of the uncertainties in the whole skin exposure problem, and the large number of workers who would be handling radioactive substances (uranium and fission products), it was thought advisable to place the skin exposure level on a par with general body exposure - 0.1 r per day. In retrospect after some four years of experience, this is admittedly conservative - but the error, if it does exist, is on the side of safety.

2.4 Effects on Reproductive Organs.

The reproductive organs may sustain damage either to the germ plasm or to the cells which carry the germ plasm (ova or sperm). To obtain a permanent sterilization of the female ovary requires a dose of some 400 - 600 r within the ovary. Sterilization in man is produced by 800 - 1000 r in the testes. There is a threshold dose which must be exceeded before any effect upon fertility becomes manifest.

Experiments reported elsewhere by Heston and Lorenz have already shown that continued exposure of female mice to 1 r per 8 hours daily

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produces ovarian follicular atrophy after approximately 540 r.

The effect of near tolerance levels of irradiation on the sperm count of dogs was undertaken by the Rochester Area of the Manhattan Project. The final results of this work, when published, may be of considerable interest.

The possibility of damage to the reproductive organs is the most discussed and feared hazard in the minds of most of those who work with radiation. The reasons for this keen interest in the subject can best be learned from Freud. The incidence of reduced sterility following occupational exposure is not known with any accuracy for work in the past. A study of birthrate for employees of the Hanford Engineer Works, made by Dr. J. A. Quigley, does not however show any evidence over a two year period. For the nation as a whole the birthrates for 1943, 1944 and 1945 were 21.5, 20.2 and 21.6 per 1000 population. For Richland, Washington the birthrate for a period late 1944 through 1945 averaged 37.3 per 1000 population. A relatively young population accounts for the factor in favor of the Richland area. No stimulating effect is implied.

2.5 Radiogenetic Effects.

In 1927 Muller[31] demonstrated that the mutation* rate of the fruit fly could be accelerated by exposure to x-rays. In the fruit fly radiation increases the rate of appearance of common mutations which occur spontaneously; it produces the uncommon ones only rarely. Single exposures of 30 - 40 r will double the mutation rate in the fruit fly; doses of 500 r are required to produce mutations in mice,

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* A mutation is an hereditarily transmissible abrupt alteration in germ plasm.

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and these appear in far lower incidence than in the fruit fly.

Work done at the National Cancer Institute on the genetic effects of radiation (reported elsewhere) has not elicited mutations or evidence of genetic change with exposures up to 8.8 r per day over many generations in mice. The only effect noted has been a decrease in litter size, which may be attributable to reduced sperm or ova.

Radiation-induced mutations have been found to have characteristics which bear on the practical consideration of radiogenetic changes possibly associated with occupational exposure. The most important of these is that there is a linear relationship between dose and increase in mutation rate. There is no threshold effect - the cumulation of exposure is thus additive. Furthermore, the magnitude of the effect is independent of the wave length and dosage rate of exposure[32]. These genetic studies (largely in the fruit fly) have lead to considerable discussion concerning their applicability to man in relation to tolerance dose. There are workers in the field who advocate a further reduction in the tolerance dose for x- and gamma-rays because of the non-threshold effect of x-rays upon the germ plasm of the fruit fly. Further concern is added to these fears by the possibility of even greater radiogenetic damage from heavy particle radiation (neutrons, protons, etc.) than from the more familiar x- and gamma-rays.

Mutations, whether spontaneous or produced by radiation, are about 90 per cent lethal or sublethal. This means that the offspring does not survive the gestation or hatching period, or dies shortly thereafter. The lethal mutations are either dominant or recessive. By dominant is meant that, for the exposed parent organism, the lethal effect appears in some of its direct offspring. By recessive is meant that the effect might appear only in some succeeding generation of the radiated subject. In man it would appear in near descendants only should cousins or near relatives intermarry. It has been calculated from the laws of genetics that some 5000 years would be required for

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a mutated gene to meet another mutated gene descended from the original mutation. This would indicate that we need not be too concerned about the recessive deleterious effects of mutations.

Our present knowledge of radiogenetics has been gained entirely from experimental studies in the fruit fly or other lower organisms, and to a lesser extent from mice. Actually very little is known about genetics in man, and still less about the effects which might be produced by exposure to radiation. As yet there is no convincing evidence to indicate that the present generations of radiation workers have produced offspring which differ from those of the general population. It can be argued, however, that succeeding generations or intermarrying may bring abnormalities to light. If experimental findings in the non-mammalian organisms are accepted as valid for man, then one can only escape some degree of radiogenetic effect by avoidance of all radiation exposure, including the natural radiation (cosmic, etc.).

This concept has lead Henshaw[6] to suggest that perhaps for the non-threshold reactions such as the radiogenetic ones, we should define rather a "tolerance injury" than a "tolerance dose."

3. The Dependence of Tolerance Dose on the Nature of the Radiation

3.1 Specific Ionization.

Experimental as well as clinical studies have shown that the biologic effect produced by the absorption of a given quantity of energy is dependent in part upon the nature of the incident radiation. The effects are produced in some manner by the ionization resulting from the impinging radiation, but the distribution of ionization is not the same for all qualities of radiation. A greater ion density

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along the path of an ionizing particle is associated with a more pronounced cellular or biological effect. The density of ionization per unit length of path is referred to as the specific ionization of a particular quality or type of radiation. One can then compare biological effects produced by equivalent energy absorption from x-rays, gamma-rays, neutrons, etc. A detailed and critical analysis of this phenomenon is reviewed by Zirkle. We refer to it here because it is convenient to consider tolerance dose from the point of view of the type of radiation involved rather than in terms of the specific effect on the various parts of the body as in the foregoing section. The evidence comes from the same sources and some repetition is inevitable.

1. <u>X-rays</u>. As our knowledge of permissible exposure has been derived almost exclusively from experience in hospitals, it is best founded for x-radiation. In particular the original choice of tolerance dose was founded on two cases, both involving the exposure of operators to scattered radiation only. The wave length of this radiation can be taken as 0.3Å. Hence its penetration in tissue is about 86 percent at 1 cm. deep and 25 percent at 10 cm deep. (These figures are derived from a consideration of the scattering contribution in a body subjected to wide beam irradiation. The corresponding figures from the absorption coefficient alone would be 80 percent and 8 percent respectively.)

The tolerance dose supposedly had a safety factor of the order of 20 - 40 for radiation of this type. Modern practice involves shielding the operator by lead screens, but it is permitted that directly transmitted radiation falls on the operator, up to the

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limiting tolerance amount. Under these conditions the net effect on the deeper seated organs may be different. This is especially the case with the modern high voltage machines. 400 kv. radiation is as common now as 150 kv. was when tolerance was first established. Penetration of this radiation is about 100 percent at 1 cm. and 50 percent at 10 cm. (90 percent and 30 percent respectively from the absorption coefficient) and we might consider its effect on the haemapoetic system as approximately twice as damaging.

Little has been written about the damaging effects of x-radiation generated in the range between 400 kv. and 1200 kv. Such hospital installations have in general been well protected and have not been operated many hours per day except in recent years. In this range of voltage there is little increase in the "percentage depth dose" for depths up to about 10 cm., for wide beam irradiation. The increased penetration of the primary beam is offset by the reduced contribution from scattering. It is also known that the effect of these radiations in therapeutic dosage is quite closely the same in deep tissue as that of the well studied 200 kv. radiations. As far as skin effects are concerned there are two familiar effects both of which indicate that for equal dose as usually measured, the damage by high voltage radiation should be less severe. It is reasonable to suppose that a tolerance dose established for 200 kv. radiation with a margin of safety of 10 or more will still be safe for x-radiation up to 1200 kv. The widespread industrial use of 1000 kv. radiation in the present war would give a fruitful source of study in a few years if the exposures were adequately recorded.

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2. Gamma Rays. Adequate experience with gamma radiation has been restricted to that from radium and its products, and again it is derived from handling in hospitals. It has long been accepted that the danger of exposure to gamma radiation exceeds that from x-radiation for two reasons: (1) x-rays can be "turned off" when not required, (2) the gamma ray penetration is higher. Wintz and Rump[18] who gave the first consideration to gamma ray exposure select a dosage rate of $1/3\ 10^{-5}$ r/second as against 10^{-5} r/second for x-radiation. The latter figure is based on an 8 hour day and the former apparently implies possible exposure to gamma-radiation for 24 hours per day. In the alternative expression of tolerance dose as a daily amount, Wintz and Rump would make no distinction. On the basis of penetration (94 percent a 1 cm., 58 percent at 10 cm. without backscatter) one might have a factor of 2 or 3 to represent the additional total body ionization.

It is commonly supposed that the effect of gamma-radiation on the body is greater than that of x-rays for equal surface dose solely on account of the greater penetration. It is assumed that the action of the radiation is entirely due to the secondary electrons liberated and that change of specific ionization over this range is not important. Hence the method of expressing tolerance dose in terms of the total ionization has recently gained favor, especially abroad. The unit employed for this purpose is the "gramme-roentgen." 1-gramme-roentgen corresponds to $1.6 \cdot 10^{12}$ ion pairs.*

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* Dose in roentgens is a measure of the ionization per cc, and is independent of the size of field or volume of tissue radiated (increased scattering, etc. is included in the measurement of 'r').

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Simple computations will show that there is more change in total ionization as a result of geometry than results from the change from soft x-rays to gamma-rays. For equal surface dose we have

	Relative total body ionization
Soft x-rays from large distance	1
Gamma rays " " "	2.5
Gamma rays from point source at 100 cm.	1.9
Gamma rays " " " " 10 cm.	0.6

Exposure to gamma-radiation from internal sources can be treated in terms of the ionization produced in tissue. In general the effect would be exceeded by that of the accompanying beta-radiation.

3. Beta Rays. There is no sound evidence on the permissible exposure of the body to beta radiation. The handling of strong sources was not common until the development of artificial radioactivity, especially by the cyclotron. (This is not strictly correct inasmuch as cathode ray tubes, e. g. Lenard tubes, have been widely used, and these are potent enough sources. With such an installation it is relatively easy to maintain adequate shielding at all times. Consequently there seems to be no record of damage by prolonged exposure to these radiations. The numerous cases of exposure, accidental or otherwise to stray beams for short intervals is not discussed here).

It is generally conceded that the effect of x-rays and gamma-rays on tissue arises from the electrons which are energized in tissue by these radiations. Hence, for equal ionization, beta-radiation should produce the same effect*, apart from a possible correction due to specific ionization differences. This has been

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* For a more detailed consideration on some of the physical aspects of the effects of beta-radiation on tissue, the reader is referred to Volume XIII, in which this is the subject of a report by H. H. Fewson.

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sufficiently well confirmed by experiments at therapeutic levels. One can therefore confidently state that an exposure to beta-radiation of 0.1 r/day will be safe. Since the external beta-ray effect is confined to the skin or to tissue within perhaps 1 cm. of the skin it is evident that beta-radiation will add little or no contribution to the general body effect. The experiments of Raper and Barnes(33) which are reported in Volume XXII or XXIII, show that for exposures to beta-radiation in the range of 1500 - 59,000 rep*, there was no effect upon the blood forming organs of rabbits when the peripheral blood was sampled.

Lethal effects, reported by Raper and Barnes, were produced by extensive burns. The LD50 for their beta-radiation varied from 2200 rep for baby rats to 17,500 rep for rabbits. The gamma-ray LD50 lethal effect varied from 310 r to 1270 r, and was not correlated with the size of the animal.

Damage arising from the ingestion or inhalation of beta active material is however another problem, since here the effect has to be assessed in terms of ionization with zero absorber, in contrast to external beta radiation where the factor of absorption is considerable.

4. Neutrons. The effects of prolonged exposure to low intensity beams of neutrons was unknown at the start of the project. Many effects of higher intensity neutron irradiation of biological materials have been compared with x-ray or gamma-ray irradiation. In this work the neutron dose has frequently been quoted in "n" units as the

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* Half value penetration in tissue 0.55 mm.

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reading of a particular Victoreen condenser chamber. The ionizing effect in the body of 1 "n" of fast neutrons can be considered equivalent to 2.5 rep. The biological effectiveness of neutrons relative to x-rays varies widely for different materials or for different conditions in the same material. According to Zirkle[34] the effects on mammalian tissues show effectiveness ratios ranging from 5 to 9 (in terms of r to "n"). From these figures it has become common practice to consider 0.01 n (0.025 rep) as a tolerance dose of comparable safety to 0.1 r for x-rays.

Experimental work reported by Zirkle, Raper, Riley and Stapleton on the biologic effectiveness of fast neutrons[35] indicated that for mice the LD50 exposure for fast neutrons, directly determined, was 91 n. The LD50 exposure of pure gamma-rays, indirectly determined from experimental data, was 812 r.

The effect of slow neutron radiation was originally considered to be due to gamma-ray emission from hydrogen capture, and the tolerance level for slow neutrons was originally based on the gamma-radiation internally emitted. Work reported by Zirkle[36] has however considerably altered this conception. He has found experimentally that when mice are subjected to combined slow and fast neutron exposure, the gamma-rays emitted from the mouse, both calculated and measured, amounted to only some 12 percent of the total lethal effect of his radiation components. Some 38 percent was found to be due to proton and carbon recoils from the reaction N^{14} (n,p) C^{14}. In a pure slow neutron exposure, about 75 percent

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of the lethal action would be due to this effect. In a larger animal (man) the gamma radiation from hydrogen capture would have a relatively larger effect.

On the basis of these experiments, the permissible exposure to slow neutrons has been placed at 0.025 rep per day (conversion gamma rays). In general however, the body would not be subjected to slow neutron irradiation without the admixture of gamma or fast neutron irradiation. The proton effect is however considerably larger than was originally envisaged, and is an excellent sample of the applicability of experimental biologic work carefully done.

5. Alpha Rays. For external radiation the penetration of natural alpha particles is well below the thickness of the "absorbing layer". The damaging effect is assumed zero unless the intensity is such as to physically burn the part. There is now some clinical evidence to substantiate this point as a disc of uranium metal has been worn in contact with the skin for several months. The observed damage was nil for this exposure corresponding to 250 rep/day.

Internally, the dose is computed in terms of the ionization produced. Since the increased biological effectiveness of neutron produced ionization is believed due mainly to the high specific ionization along the proton tracks, it is to be expected that alpha particles would be even more effective. A tolerance dose of 0.01 rep/day thus seems reasonable.

Since the effects are limited to the ingestion or inhalation of alpha ray emitters they are considered more fully in relation to plutonium hazards.

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6. Combined Radiations. The body will be exposed to more than one type of radiation simultaneously at various times during a career associated with radiation work. Theoretically the summation of the daily tissue ionization, properly weighted for the specific ionization factors of the components of the radiation exposure, should not exceed 0.1 rep/day. As a working policy the exact composition of the incident radiation will not be known at all times. From a protection standpoint however, a real effort should be made to analyze radiation exposure whenever possible, and to determine the gamma, beta, neutron (fast and slow) exposure in a particular operation. There is sufficient evidence to indicate the additivity of exposure to take these factors into consideration.

Zirkle and co-workers(35) have shown the additivity effect of a component beam of gamma-rays and fast neutrons. Their work was done on the acute lethal effect, and could thus not prove that these radiations were additive in producing all types of damage. To quote from their report: "It does, however, indicate a strong probability that this (the additivity effect) may be true, and this probability must be recognized in setting conservative standards of permissible exposure of personnel under conditions where both types of radiation are present."

Experimental work reported by Raper and Barnes on the additivity of gamma and beta-radiation, tended to show that for lethal effect there was some, but by no means complete, additivity of the lethal effects of the two radiations. It would seem that in this case the damage which produced death differed considerably for beta and gamma

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radiation, and that although death may be in a sense hastened by an additivity factor, the specific contribution of each which resulted in death was by a different mechanism.

Mention should be made of the importance of additivity in exposure of the skin of hands, when work requires close handling of sources which emit both beta and gamma radiation . Here the composite radiations will have additive effect for skin damage. In most instances one of the components is large in respect to the other, but in some instances where each contributes a significant degree of exposure, the exact amount of each radiation is of practical significance.

4. Specific Tolerance of Radioactive Materials

When handled in large quantities either in the laboratory or industrial plants radioactive materials are hazardous by reason of:

(1) Radiations from the outside - external radiation.

(2) Inhalation and deposition in the body with consequent radiations from within the body.

(3) Ingestion and deposition in the body with consequent radiations from within of radioactive poisons through carelessness, or contamination of sources of water supply.

(4) Contamination of skin or clothing, contributing to external radiation or wound contamination in case of an accident producing an open wound.

No description will be given of the protective measures taken to circumvent these hazards, as these are described elsewhere.

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4.1 Radium and Radon

Radium deposition in the body: 0.1 microgram

Radon concentration of atmosphere: 1×10^{-4} curie/cc.

4.2 The Radioactive Gases and Vapors.

The radioactive isotope of the noble gas Xenon was considered a hazard of possibly some magnitude, with disposal problems which would be difficult to surmount. Xenon is produced as a fission product, and as such has to be put into the atmosphere under the present operational program. The quantities of $Xenon^{133}$ are large, and considerable early work was done by Cole in attempting to determine its biologic effect. The radioactive isotope of Argon is made when Argon in the air is bombarded with neutrons. It appeared as a potential hazard only after operation of an air cooled pile reached a large scale, and air in quantity was irradiated.

Radioactive Iodine (I^{131}) is a fission product, and as a vapor comes into the general problem of the radioactive gases. Of all this group thus far considered, it has proven to be the most important one from the standpoint of health and protection.

A radioactive gas or vapor can be hazardous because: (1) it is inhaled and deposited in the body emitting radiations, (2) it contaminates the atmosphere and emits radiations that affect the body from without, (3) it commonly does both of these. Xenon and Argon (the two significant gases) have been found to be potentially hazardous from the standpoint of contributing to a radioactive atmosphere in which the subject is immersed. Iodine on the other hand, is, as a vapor, more hazardous because of inhalation and rapid deposition in the thyroid gland.

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(a) Xenon is absorbed preferentially in fatty tissue when inhaled. Earlier work done by Hamilton showed that when animals were exposed to a mixture of Xenon and oxygen, the Xe concentration in tissue was 0.1 to 2 times the Xe concentration in the inhaled gas mixture. The highest values were in fat and the lowest in blood. When the animal was released from the Xenon atmosphere, the Xenon was excreted via the lung.

Calculations made originally by Tollan(37) were based upon the radiation to the body from the outside when a subject was immersed in an infinite cloud of Xe^{133}. The half-life is 5.4 days; the average total energy of beta rays plus soft gamma rays is about 2×10^5 ev per disintegration, in which the beta component is about 2.5 times larger than the gamma. Penetration of the radiation into the body is not then significant. Considering the beta and gamma components as additive, and for immersion for a 24 hour period, an atmosphere with a concentration of about 2×10^{-11} curie/cc would give a daily exposure of 0.1 rep. Over a comparable period the lungs receive, by inhalation, an ionization equivalent to 0.1 r when the atmospheric concentration is about 3.2×10^{-9} curie/cc. The limiting factor is thus the external radiation, and the level of 2×10^{-11} curie/cc has been used as a permissible level. In actual practice this concentration has not been approached, and $Xenon^{133}$ has not been a hazard to personnel or the public.

(b) $Iodine^{131}$. Radioactive iodine had already been the subject of considerable research prior to the inception of the Plutonium Project(38). This had largely been done by Hamilton and associates

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at the University of California. Experimental data had accumulated referable to human absorption and excretion to a point where its use as an experimental clinical tool had been tried in certain disorders of the thyroid gland.

Iodine^{131} is a fission product liberated as a vapor in the extraction of plutonium from the mixed fission products. It is present in considerable quantity, and its half-life of about 8 days further adds to the difficulties of disposing of it. Under operating conditions the vapor was suitably discharged under regulated conditions into the upper atmosphere, but there was always the possibility of its descent to ground, and its eventual deposition over the surrounding countryside. Because of this it was necessary to fix upon a level of I^{131} concentration in the atmosphere such that people breathing the atmosphere would deposit in their thyroid glands no more than a tolerance quantity of I^{131}.

The original calculations made on the permissible atmospheric concentration of I^{131} were made by W. Cohn(39) in May 1943. Subsequent physical measurements and calculations have altered this original value (i.e. energy). The factors upon which the level is based are(40):

Average energy for I^{131}	0.21 mev
Respiratory rate	1 cubic meter per hour
Disintegration constant	0.087 day^{-1}
Thyroid radiation tolerance	1 r per day*
Thyroid mass	25 grams
Percent inhaled I^{131} deposited in thyroid gland	20 percent

* This value has been empirically judged from experience in radiation therapy when the normal thyroid gland has been included with the field of radiation in treating other organs (i.e. larynx). Myxedema (resulting from thyroid deficiency) is not seen clinically when the normal gland is irradiated, using doses up to 5000 to 8000 r in four to eight weeks.

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By calculation, utilizing the above data, the permissible equilibrium amount of I^{131} in the thyroid is about 2 micrograms; the daily increment is 0.17 microgram; the permissible daily intake is 0.85 microgram. The permissible atmospheric concentration of I^{131} for a 24 hour breathing period is thus calculated as 3.5×10^{-14} curie per cc.

As a further extension of this problem, a permissible concentration of I^{131} in drinking water (assuming this to be a sole source of I^{131}) is:

$$\frac{\text{Permissible daily intake}}{\text{Water consumption (L)}} = \frac{0.85}{3} \text{ microcurie/liter} = 0.28 \text{ microcurie/liter.}$$

Since the monitoring of personnel for I^{131} deposition was done on a large scale at Hanford Engineer Works, it became necessary to establish a counting rate which would correspond to a deposition of 2 microcuries (the permissible accumulated total). This was done by Healy[40] and for the particular thyroid counters in use this was approximately 750 counts per minute, when the counter was held against the most favorable position over the neck. Thus in actual practice not only the atmospheric concentration but also any possible thyroid deposition was monitored.

4.3 Mixed Fission Products in Drinking Water.

The basic biologic research underlying the fission product tolerances from the standpoint of internal deposition was done by Hamilton (University of California) and Cole (University of Chicago)

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and their co-workers. These studies are reported elsewhere and their particulars will not be summarized here. Studies in absorption (gastro-intestinal, pulmonary, parenteral), excretion and deposition were many, and were necessitated by the unknowns which would potentially arise as hazards to personnel.

The toxic effect of internally deposited fission products is due practically exclusively to their beta radiation. Since the ranges of beta rays in tissue are small, it was assumed (as a working basis) that all the beta radiation emitted in the tissue was absorbed in situ. The extent to which an ingested, inhaled or injected fission product deposited in a specific tissue depended upon its chemical properties and physical form, which also regulated the degree of absorption into the blood stream, and eventual deposition in tissue. The rate of radioactive decay, relative to rate of excretion, was important as well.

From a practical standpoint under working and operating conditions, and excluding I^{131}, the hazard of internal deposition of any one or a mixture of fission products was not great other than by gross carelessness or accident. In view of the problems relative to waste by-product disposal, it was of interest to fix upon a permissible level for mixed fission products in drinking water. As a public health problem this aspect of waste disposal was carefully considered and handled. Monitoring for possible unexpected eventualities was established, and a tolerance value of 1.2×10^{-9} curie per cc was calculated to be a permissible level for consumption of 3 liters of water daily(41). In actual practice no water used for drinking has been found to approach this level.

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4.4 Plutonium Tolerance Levels.

The entry of plutonium into the body can, under laboratory or industrial conditions, result from ingestion, inhalation, or direct entry into the tissues by lacerations or abrasions resulting from accident. The permissible amount of plutonium that could be fixed in the body was originally established by calculations using the allowable radium deposition of 0.1 micrograms as the base. The plutonium deposition level was thus initially established as 5 micrograms, and was based upon comparisons of half-life, the number of rays emitted in a complete chain and the energy of the alpha rays from plutonium and radium.

1. Air Concentration. The first working level was that originally proposed by H. M. Parker[42] for concentration of plutonium in the atmosphere. The original permissible level of 5×10^{-10} microgram per cc. was derived from the following assumptions:

(a) that plutonium as fine dust particles or droplets was deposited uniformly over the lung surface (8×10^5 cm^2).

(b) 50 percent of the inhaled plutonium is retained in the lung.

(c) the damage from the retained plutonium would be to the finest passages (alveoli, bronchioles) by alpha irradiation.

(d) for alpha ray radiation the tolerance dose was taken as 0.01 rep per day.

From the above Parker calculated that 0.64 microgram of plutonium deposited evenly throughout the lung tissue would give a dose to the lung of 0.01 rep per day. Assuming that there was no

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elimination of the retained plutonium, an air concentration of $\sim 5 \times 10^{-10}$ microgram would, at the end of two years, have built up to an amount which would give a dose of 0.02 rep per day to the lung at the end of the second year. For the first year the tolerance amount (0.64 microgram) would not have been reached. It was thought that 0.01 rep increasing to 0.02 rep per day during the second year would not be harmful.

The above provisional level of 5×10^{-10} microgram/cc of air was thus accepted as a working basis until biologic research could give more precise data. Actually this was not obtainable until almost one year later, when experiments had been analyzed. It was found by Hamilton that about 20 per cent of the plutonium originally inhaled was eventually deposited in the skeleton; the largest fraction ($\sim$50 percent) was trapped in the upper air passages and eliminated. About 25 percent remained in the lung some of which was more slowly eliminated by ciliary action. The absorption of plutonium from the lung was quite dependent upon the particular compound. The oxide is not absorbed at all and the nitrate is quite readily absorbed.

It should be noted that the original air concentration level of 5×10^{-10} microgram/cc was one based upon pulmonary injury from radiation and did not consider absorption through the lung and deposition in the body. Based then upon the later data of absorption and excretion, the previously established level would result in about 0.1 microgram per year being deposited in the skeleton if the plutonium inhaled was in compounds similar to those used experimentally. In industrial practice it was found that suitable protective measures

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could keep the working atmosphere below 5×10^{-10} microgram/cc by a factor of 10 or more. Hence the original tolerance value for atmospheric concentration was retained in use.

2. Deposition in Body. More detailed account is given elsewhere of the biologic work, both in animals and man, which formed the basis for appraising the hazard of plutonium deposition in the body.

As was previously stated, based on a comparison with radium, 5 micrograms was calculated to be the maximum allowable amount of plutonium that could be fixed in the body. Since acute experiments, producing readily recognizable and measurable injury seemed the quickest way of answering the pressing question, these were undertaken by the biologists, using radium again as a "control".

The rather surprising results of these experiments were that, rather than being less toxic by a factor of 50, plutonium and radium, when given parenterally, produced death in about 30 days, using equivalent weights of the two elements. The ratio for lethal action was then (for 30 days) not $\frac{Pu}{Ra} = 50$, but rather 1. As these experiments were extended in time the ratio $\frac{Pu}{Ra}$ became larger, yet even for 150 days it was about 5.

In July 1945, the Manhattan District, acting through Colonel Warren, based upon data briefly summarized above, set a provisional allowable deposition in the body of 1 microgram accumulated total[43]. It was stated that this level would be reviewed in December 1945, relative to subsequent experimental data. The level of 1 microgram was the maximum allowable amount for deposition. The level adopted at Hanford Engineer Works was 0.5 microgram, since operating conditions and protection

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made this lower level achievable without added facilities. Subsequent revision of the 1 microgram level has not as yet been made.

Nickson has described elsewhere the present methods now in use to detect plutonium deposition. These were based upon urinary excretion, the excreted amount serving as a basis for calculating the amount present in the body at the time. The amount excreted is a measure of (1) the amount deposited and being excreted from the deposition and (2) that which is passing through the body, being excreted without deposition. Conservatism adds to safety by assuming rather that plutonium excreted via the urine stems from that deposited.

3. Concentration in Drinking Water. The absorption of plutonium by the gastro-intestinal tract was not known in the earlier period when it was being handled in relatively small quantities and before biologic data was available. Radium salts were known to be absorbed rather easily 0.5 - 2 percent. Experiments (described elsewhere) in both animals and man have resulted in finding a fairly uniform absorption by ingestion of about 0.05 percent.

The problem of a possible ingestion hazard from drinking water, although remote, arose from waste disposal operations and the necessity to monitor water sources in the vicinity of the plutonium producing plants. A calculation of permissible plutonium concentration in drinking water at Hanford Engineer Works was made by Parker[44]. This was based upon the Hanford deposition level allowable in the body of 0.5 microgram, and a long range conservative view assumed that the recipient would work in the plant for thirty years of his seventy year span. Utilizing the 0.05 percent absorption figure, the

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tolerance concentration for drinking water in the working areas was calculated to be about 2×10^{-5} microgram per cc if at the same time the drinking water in the residence district was contaminated to the extent of about 10^{-5} microgram per cc. Under actual monitoring conditions an amount less by a factor of about 100 is readily detectable, and would give ample warning should any significant contamination arise.

4. Summary. From the above discussion it can be seen that plutonium is a highly toxic element, and is a hazard which greatly complicated the design, cost and speed of plutonium production. Substances of equal or greater toxicity have been encountered heretofore. Radium, because of its radon gas problem, is a more toxic substance. Yet the quantity of plutonium to be produced has magnified the hazard beyond that of the radium industry. Fortunately we had the previous misfortunes of the radium industry as a warning and as a guide to allowable limits of exposure. It must be assumed however that there is much to be learned which is as yet unknown of the biologic and toxicologic properties of plutonium. Further research is essential to establish beyond question the safe limits of exposure. It would seem at this writing that these have not been exceeded in the present project. Time will furnish the answer.

5. The Applicability of Animal Experimentation TO Radiation Tolerances in Man

In reviewing the subject of radiation tolerances from the historical viewpoint, it is striking that evidence from animal experimentation played so little part in those levels established up to 1942. These were:

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X and gamma radiation	0.1 r/day
Radon concentration in atmosphere	1×10^{-14} curie/cc.
Radium deposition in the body	0.1 microgram

Each of these above levels had been established by adding a safety factor to an amount which had been observed to produce injury when exceeded by a factor in each case less than 10. Human misfortune rather than animal experimentation formed the basis for these values.

The past literature is surprisingly lacking in animal exposure carried on with radiation at tolerance or near tolerance levels. This might be explained as:

1. Radiologists had not given much attention to the subject as a whole. The problem had been relegated to a few committees of the various societies.
2. For the radiobiologist experiments within the tolerance range require long periods of time and large numbers of animals to complete. They are therefore costly and time consuming. There may have been the feeling too that research into other fields offered more fruitful paths, since "tolerance" for mice, rats, rabbits or fruit flies still was not "tolerance" for man, and could never be proven to be so.

With awakened interest in radiation tolerances occasioned by the Plutonium Project, the radiobiologists were asked to investigate many phases of radiation tolerances, and to study the problem from the standpoint of applicability to personnel protection.

In judging that a certain level of radiation cannot be tolerated, one must look for the earliest signs of an injury which is lasting and damaging

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to the economy of the organism. This implies that we can establish normal standards within fairly well defined limits and can also control other noxious agents or mechanisms which might either directly or indirectly produce injury confused with those resulting from radiation. These restrictions interfere with observations on large groups of people, and are not so readily controlled. Within limits, then, we might conclude that animal experimentation could approach the problem from the standpoint of radiation injury with more likelihood of controlling the extraneous factors which produce alterations in leukocytic levels, weight, fertility, longevity, or whatever index we may wish to follow.

Animal research also has the advantage of being able to sample the body elements and functions more completely by selective autopsy. It can also follow the animal to his death, either natural or radiation-induced.

The most important advantage of animal research however lies in the possibility of exposing the organism to known quantities and qualities of radiation. We have seen the contributions made in the study of slow neutron irradiation by Zirkle and co-workers. Their findings had not been anticipated, and considerably altered the conceptions of safe levels of exposure to radiation of this type. A similar contribution was made in helping to fix a level of plutonium deposition below the threshold to produce injury.

Histopathologic, metabolic or other studies may uncover, through animal experimentation, indices of earlier radiation damage unsuspected from our present clinical or laboratory methods.

These in the main are the contributions which we might hope to gain from animal experimentation relative to radiation tolerances.

The important question arises, however, as to how far we can trust animal experiments when the information must be carried over to man and

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his protection. Several instances in which this transposition has broken down have already come to light. Evans has found that rats will tolerate quantities of deposited radium which would be lethal to a man. Studies on the tolerance of skin in animals cannot be applicable to man because of the very great difference between the skin of man and various laboratory animals. Nor is it expected that a group of men could submit to a daily exposure of 8 r per day of gamma radiation up to a total dose of 1350 r without serious impairment of hemopoietic function as evidenced in the circulating blood, as has been done with a group of inbred mice (CH-2311).

These observations, though at variance with animal research, do not invalidate all results obtained in animals. They indicate rather that we must look to animal research for as precise information as it can give on qualitative and quantitative effects in the animals. From there on it is a matter for observation, experience and judgment to use the information in evaluating human reactions. The more precise the animal research, the more valuable will be the information to those interested in radiation protection.

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6. Tolerance Levels for Radiations and Radioactive Materials

Hazard	Permissible Tolerance
External gamma and x-radiation	0.1 r per day
External beta radiation	0.1 rep per day
Fast neutron radiation	0.02 rep per day
Slow neutron radiation	(0.025 rep per day) (conversion gamma rays)
Internal alpha radiation	0.01 rep per day
Radium deposition in the body	0.1 microgram*
Radon concentration in atmosphere	1×10^{-14} curie per cc.
Radioactive Xenon^{133} in atmosphere	2×10^{-11} curie per cc.
Radioactive Iodine^{131} in atmosphere	3.5×10^{-14} curie per cc.
Mixed fission products in drinking water	1.2×10^{-9} curie per cc.
Plutonium concentration in atmosphere	5×10^{-10} microgram per cc.
Plutonium deposition in the body	1.0 microgram**

* Accumulated total.
** Accumulated total. Hanford Engineer Works level 0.5 microgram.

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