Effects of Radium in Man

Pending more data, it seems advisable to lower the concentration level now permitted in the body.

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The maximum permissible concentration (MPC) for such radioelements as strontium and plutonium is indirectly based on the results of the studies of the effects of radium in man over the past 34 years (*1–12*). The first report relative to the establishment of the present MPC of radium of 0.1 microgram in the body was published by the U.S. National Bureau of Standards in 1941 (*13*). Seven individuals who had had from 0.02 to 0.5 microgram of radium in their bodies for periods of time varying from 7 to 25 years had no observed changes referable to the deposition of radioactive materials. Death attributable to the effects of radium occurred in patients having as little as 1.2 micrograms of radium. The MCP was set at 0.1 microgram, which incorporated a safety factor of 12.

The results of two large investigations, published recently, show that roentgenographic skeletal changes began to occur at concentrations of 0.4 microgram of total body radium, major skeletal damage at 0.7 microgram of total body radium, and bone tumors at 0.8 microgram of total body radium (*6, 10*). It is reassuring to find that it has not yet been necessary to change the MPC of radium of 0.1 microgram in the light of the large amount of information that has accumulated since the MPC was first established. However, the present data, accumulated over the past 34 years, on the effects of radium in man, when extrapolated to cover a period equivalent to a normal lifetime, indicate that "appreciable bodily damage" (*14*) may occur at, or below, the present MPC of 0.1 microgram.

It seems advisable to lower the present MPC of radium now, until information is available on the effects of radium in man for at least one life-span, for the following reasons: (i) the present information on the reliability of the MPC of 0.1 microgram of radium in the body is inconclusive (*14–17*); (ii) no information on the effects of radium in man retained in concentrations at or near the present MPC for a period longer than 40 years is available (*6, 10*); and (iii) the roentgenograph, the most sensitive clinical means for detecting skeletal damage, is an inadequate method for detecting histopathological changes (*11*).

The International Commission on Radiological Protection (ICRP) has recommended that the average dose rate to the gonads and total body be less than that provided by 0.3 rem per week. The ICRP and the National Committee on Radiation Protection and Measurement have now proposed to limit the accumulated absorbed dose to one-third the integrated basic rate. The mean radiation dose from the present MPC of radium of 0.1 microgram is calculated by the ICRP to be 0.56 rem per week (*14, 16, 18*). The term *permissible dose* is defined by the ICRP as the dose of ionizing radiation which, in the light of present knowledge, is not expected to cause appreciable bodily injury to a person at any time during his lifetime. The term *appreciable bodily injury* is defined as "any bodily injury or effect that a person would regard as objectionable and/or competent medical authorities would regard as being deleterious to the health and well-being of the individual" (*14*). The ICRP has recommended that exposure to radiation in the geographical neighborhood of controlled areas be limited to one-tenth of the occupational exposure, and that the exposure of the population at large should be of the order of the radiation in the natural background (*14*). Therefore, the discussion of the MPC of radium will be limited to discussion of utilization of that concentration for the MPC of occupational exposure.

Four means of interpreting the term *appreciable bodily injury* will be considered in this article—namely, microscopic skeletal changes, roentgenographic skeletal changes, major clinical damage, and neoplasia. The reliability of the present MPC will be discussed with regard to these four interpretations. When possible, an attempt will be made to determine whether "appreciable bodily damage" will be expected at any time during an individual's lifetime as a result of the fact that 0.1 microgram is currently established as the maximum permissible concentration of radium.

Radiation Dosimetry

The determination of radium content in the body is made by collection of radon in the breath and by the determination of the gamma ray activity from the decay of radon and its daughter products in the body (*4, 6–9*) (the error in such determination of total body radium probably does not exceed plus or minus 20 percent) (*9*). One of the difficult factors in the correlation of radium content with skeletal change is time of retention. The relationship of radium burden to time was not positively introduced as a factor until recently (*9*). Physical measurements of the retained radium were made from 10 to 35 years after deposition in the recent Boston-Chicago studies. It would, for example, be difficult to take time into consideration in making a comparison of the clinical effects of 1 microgram of radium in the body for periods ranging from 10 to 35 years in a large group of patients.

Estimates of the accumulated radiation dose from radium have been made from data obtained from 20 patients in a mental institution (*5, 7–9*). These estimates have been based on the expression of retention as an approximate power function of time, with an exponent of about -0.5. By utilization of this power function, the total accumulated radiation dose can be related to the radium burden at the time of measurement. The total dose is twice the product of the burden at that time and the time after injection (*19*). For example, if a patient was found to have 1 microgram of radium 20 years after administration, then

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the accumulated radiation dose, from the 1 microgram in the skeleton for 20 years, would be about 600 rads. The radium content of the mental patients at 1 year was about four times the radium content at 20 years. The total accumulated dose would be about 1200 rads. Thus, the additional 600 rads takes into consideration the radiation dose from the radium which was eliminated over a period of 19 years.

In the middle-aged patients, the loss of radium retained for 20 to 30 years should be small over the remainder of their normal lifetime. The available data on human beings show a decreasing coefficient of elimination of radium with time after administration (*9, 20*). For example, the mental patients cited above excreted only about 0.008 percent of the radium in their bodies per day about 20 years after administration. It would even be possible to disregard excretion over the next 20 years in these patients for purposes of dose calculations without the introduction of too large an error. If we assume that the above expression for retention as a power function of time is valid, then only about 20 percent of the radium in the patients at age 50 will be lost in the next 20 years. Therefore, subsequent calculations will be based on the above expression with a reasonable assurance that no large error will be introduced. Thus, the estimated accumulated radiation dose from 0.1 microgram of radium in a patient aged 70 years who had been given an unknown amount of radium at 18 years would be of the order of 300 rads (Table 1). The accumulated radiation dose from 0.1 microgram of radium maintained constant in the skeleton from 18 to 70 years would be of the order of 150 rads (Table 1).

Determination of the accumulated radiation dose permits a direct correlation of a quantity of radiation with skeletal damage during the time of retention. However, one of the major limitations is the variation of the retention of radium in the mental patients, from which data the mathematical expression of the accumulated radiation dose was derived. The retention of radium in these patients was determined 6, 12, 233, and 258 months after administration. Most of the values were within a factor of plus or minus 2 of the mean retention (*9*). However, the smallest amount of the injected dose of radium retained was about one-sixth as much, and the largest amount of retained radium about four times greater, than the mean retention in the 20 patients (*21*). The variation in retention should be kept in mind when the reliability of the estimates of the accumulated radiation is considered.

Estimates of the radiation dose in this article have been computed on the basis of an average energy dissipation of 11 million electron volts (Mev) for each atom of radium disintegrating (*22*). Only alpha radiation is considered, and since this radiation is primarily confined to the skeleton, no other organs are considered in the dose calculations. The accumulated dose from 0.1 microgram of radium in the skeleton of a 70-kilogram man (weight of skeleton, 7 kilograms) in one year is estimated to be about 3 rads. The value of 3 rads per year for 0.1 microgram of radium will be used in subsequent calculations.

Estimates of the mean radiation dose to the skeleton are based on the assumption that radium is uniformly distributed throughout the skeleton. This is obviously not a satisfactory assumption, because the radiation dose to bone in small areas of high radium concentration is many times the mean radiation dose (*23–26*). However, to correlate areas of maximum radium deposition with bone damage would be very difficult. The status of bone many years after radium deposition is the end-result of the pathological process rather than a concise picture of the relation between deposited radium and histology at the time of examination (*11, 25, 27*). Because of these limitations, the term *estimate* will be used in subsequent discussions in correlating either the total body content of radium or the accumulated radiation dose with skeletal damage.

Mesothorium Contamination

Mesothorium (Ra^{228}) is an isotope of radium which was used in the manufacture of luminous dials. In some of the workers in factories where luminous dials were made, the radiation dose from mesothorium was much greater than the radiation dose from radium (*6, 12*). Mesothorium has also been found as a contaminant of the radium solutions used medically. However, all information at present indicates that the mesothorium content of the radium solutions given

Table 1. Minimum radiation dose and skeletal change.

Patient	Latent period (yr)	Total body radium (μg)	Radiation dose* (rad)	Comments
		Roentgenographic change		
Skeletal roentgenographic changes characteristic of radium toxicity.	20	0.4	500	See *10*.
		Major skeletal damage		
Patient with lowest radium content.	22	0.7	1000	See *10*, and case history in text.
Mental patient with lowest radium content.	9	1.6	1300	Two patients of the series of 19 mental patients had major damage of the femoral heads. These patients were considered to have been given "pure radium" (See *10*).
		Neoplasia		
Radium-treated patient with lowest total body burden.	24	0.8	1100	Estimated accumulated radiation dose from mesothorium was 50 rads (See *6, 40*).
		Radiation dose		
0.1 microgram of radium, maintained constant from age 18 to age 70 years.			150	
0.1 microgram of radium found at age 70 years. Unknown amount given at age 18 years.			300	

* Estimated accumulated radiation dose from radium only.

medically were small. The initial mesothorium content of some of the radium ampules examined, which were prepared for medical use 25 years ago, could not have exceeded 0.66 percent (*9*).

The patients who received radium medically are the primary source of material utilized in this study for evaluation of the relationship between radiation dose from radium and skeletal damage. Therefore, the contribution of mesothorium to the accumulated radiation will be disregarded in the patients given radium medically when the mesothorium content is not reported. However, the radiation injury from mesothorium, when it is taken into consideration, will be considered equal to the injury from radium per unit dose of radiation delivered.

Microscopic and Roentgenographic Change as a Criterion for MPC

The present MPC of 0.1 microgram is probably already too high if the criterion for the MPC is microscopic change. Characteristic changes in skeletal roentgenographs have been found in connection with a total body radium content of 0.4 microgram. The skeletal roentgenograph is incapable of detecting microscopic changes in the skeleton, and undetected histopathological changes are probably occurring in patients who have a content of 0.1 microgram or less of radium.

Changes in skeletal roentgenographs in patients given radium have been described by numerous investigators (*2, 4–6, 10*). These characteristic, well-differentiated, and widespread changes observed throughout the skeleton are rarely found in any other disease process (*6, 10, 11, 28*). Greater reliance can now be placed on these roentgenographic skeletal changes as a result of studies on the correlation of the frequency of bone involvement with total body radium concentration within a certain dose range (*10, 11*). Thirty of the patients in the Chicago study who were given radium for medical reasons were selected because each of these patients had had a complete roentgenographic examination. They were arranged in order of increasing amounts of retained radium, from 0.5 to 14 micrograms, and the skeletal changes characteristic of the deposition of radioactive materials were tabulated in five bones (*11*). The frequency of involvement was expressed as a percentage of the total number of bones which could possibly be involved. Only 8 percent of the total number of bones were involved in 14 patients who had had between 0.5 and 1 microgram of radium. Fifty-five percent of the bones were involved in seven patients who had had between 1.1 and 2 micrograms of radium, and 65 percent of the bones were involved in nine patients who had had between 2.1 and 14 micrograms of radium.

It is well known that the roentgenograph is not capable of detecting microscopic changes in the skeleton (*29, 30*). Characteristic histopathological changes were found in bone specimens from two patients which were not demonstrated on roentgenographic examination (*11*). This is important for two reasons. First, it demonstrates that the skeletal roentgenograph, the most sensitive clinical device for detecting skeletal changes at present, is inadequate; and second, it suggests that roentgenographic changes which are considered "nondeleterious" (*31*) may represent more extensive skeletal damage than is now appreciated. The small changes in compact bone, detected roentgenographically, are about three to six times the diameter of a Haversian system (*11*). However, high concentrations of radium are usually found in a small percentage of individual Haversian systems (*23–26, 32*). The range of alpha particles in bone is of the order of 25 microns (*23*); therefore, if these skeletal changes are the direct result of alpha radiation coming from radium concentrated in the individual Haversian systems, it would be expected that skeletal changes would be primarily confined to one Haversian system. It is difficult to attribute these macroscopic areas of absence of compact bone to the highly localized alpha radiation within a Haversian system. Radium is also found diffusely distributed throughout bone (*25*); therefore, these changes may be the result either of more generalized damage from the diffusely distributed radium or of more generalized changes such as those which might occur from the effect of radiation on the blood supply.

Serial roentgenographs are available on about ten patients (*11*). Skeletal changes characteristic of radium deposition began to occur about 10 to 15 years after administration of radium. In most of these, a gradual progression of the skeletal change is seen with increasing time after deposition of the radioactive element.

Both microscopic and roentgenographic evidence of radium damage may be expected from less than 0.1 microgram of radium over a normal lifetime from the extrapolation of the results from the patients under observation. For example, the accumulated radiation dose to the skeleton of a patient who received an unknown amount of radium at age 30 and who was found to have 0.5 microgram of radium at age 50 years is of the order of 600 rads during the 20-year period. The total radium content will be about 0.4 microgram at the age of 70 years, and the estimated cumulative radiation dose to the skeleton will be about 950 rads (see Table 1).

Major Skeletal Damage as a Criterion for MPC of Radium

It seems that the importance of major clinical damage has not been fully appreciated in recent considerations of the toxicity of radium. Bone damage occurred as frequently as bone tumors in the 78 patients of the Boston-Chicago investigations (*6, 10, 11*). Seventeen of the 78 patients had major skeletal damage, whereas 15 of the 78 patients developed tumors. Destruction of the head of the femur has also occurred in patients with lower radium content than in radium-treated patients who have had bone tumors (*33*). Ten of the 50 patients given radium, and two of the workers in luminous-dial factories of the Boston-Chicago study had major destructive changes in one or both femoral heads. Four persons who had worked with luminous dials and one radium-treated patient had fractures of the femur (*6, 10, 11*).

The patient with the smallest total body radium content of either the Boston or Chicago series (0.7 microgram) to have major destructive changes was given twelve injections of radium in 1928 and four injections of radium in 1934. In 1950, aseptic necrosis of the right femoral head was found. In 1954, similar destructive changes were found in the other femoral head. The estimated accumulated radiation dose after 22 years was about 1000 rads (Table 1).

In spite of the fact that, as yet, age has not been shown to be a significant factor in major clinical damage, it is possible that major skeletal damage will occur with smaller amounts of radium than has been seen at present as the patients grow older. Some degree of generalized atrophy of bone frequently accompanies the onset of old age (*34*). The rate of calcium accretion also diminishes with age (*35*). Fractures of the femur in the aged are well known (*36*). It is therefore probable that major skeletal damage will occur at, or near, the MPC when the patients under study have had radium deposited in their skeletons over a normal lifetime (*33*). Major skeletal changes may be expected because of the combination of the effects of the increasing accumulated dose, the decreasing ability of the body to repair skeletal damage, and the atrophy of the skeleton in old age in these patients (see Table 1).

Bone Tumors as a Criterion for MPC

Extrapolation of the results of bone tumor induction from radiation beyond 40 years in man is more difficult than projection of either major skeletal damage or roentgenographic changes (*37–39*). Neoplasms were found in 15 of the 78 patients of the recent Boston-Chicago investigations (*6, 10*). Sarcomas of the bone were found in 11 of the 78 patients evaluated. There were seven sarcomas in the 50 patients who received radium and four sarcomas in the 28 who had worked on luminous dials. The patient with the lowest concentration of radium (0.8 microgram) to develop a bone tumor had received radium medically 24 years prior to the occurrence of the neoplasm. The total accumulated radiation dose from mesothorium was estimated to be of the order of 50 rads (*6, 40*). The total accumluated radiation dose from radium was estimated to be about 1100 rads after 24 years (see Table 1).

There is some suggestion that an inverse relationship may exist between radium content and tumor induction when the patients studied by Martland in 1931 are compared with the patients evaluated in 1951 (*2, 11*). There was a latent period for tumor induction of about five to ten years in three patients with contents of 6, 15, and 50 micrograms of radium. There was an average latent period of about 25 years in tumor induction in the eight patients in the Boston-Chicago investigations reported in 1951. The mean radium content in the eight patients was 3.4 micrograms. Little reliance can be placed on estimates of the minimum total body content for tumor induction over a normal lifetime from these meager data.

The available evidence at present suggests that cancer induced by radiation arises from a tissue environment that has suffered severe disorganization, either as a result of local radiation damage, of hormonal disturbance, or of other physiological change arising from radiation exposure (*38*). It may be possible that the neoplasms seen in the radium-treated patients arise from the atypical osseous tissue which is found many years after radioelement deposition (*11, 27*). "More work must be done before it will be possible to discuss with any confidence the mechanism of radiation carcinogenesis" (*38*).

Summary and Conclusions

It cannot be concluded from the present information on the effects of radium in man that the present MPC of 0.1 microgram of radium is permissible. The effects of radium deposited in man in concentrations at or near the present MPC for a period greater than 40 years is not known. Extrapolation of the present results to cover a normal life-time indicates that "appreciable bodily injury" may occur at or below the present MPC. It would seem advisable to consider lowering of the present MPC of radium until information becomes available on the effects of radium in man over a normal lifetime (*41*).

References and Notes

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