Reports

Maximum Permissible Body Burden of Strontium-90

Abstract. The permissible body burden of Sr^{90} is discussed with respect to the mode of intake. It appears that the maximum permissible load may depend on the type of exposure, acute or chronic, the acute being the more serious.

The purpose of studying the distribution and metabolism of bone-seeking isotopes is to make it possible to derive the dose rates (local and average) to different parts of the skeletal tissue. In this way it may be possible in the end to establish values for the maximum permissible body burdens of various bone-seeking isotopes. This procedure includes a comparison of the derived dose rates with those judged to be necessary and sufficient for the production of various biological effects, such as malignant blood and bone changes. This seems at present to be a possible means of hazard evaluation, when lack of data makes direct comparisons difficult between the body burdens of different isotopes and the resulting biological effects.

The foregoing argument is general in that it applies to most bone-seeking isotopes. A general treatment of the principles for dose-rate calculations for such isotopes has recently been given (*1*). Specific isotopes have, furthermore, been treated in several works. In the following discussion (*2*) Sr^{90} will be chosen to illustrate the method proposed for estimating maximum permissible body burdens.

It has been calculated (*1*) that the skeletal tissues receive a dose rate of 2.6 rem/year (or 7.25 mrem/day) on the average, from a total body burden of 1 μc of homogeneously distributed Sr^{90}. This assumes a homogeneous dispersion of the Sr^{90} in the 7000 g of skeletal tissue (the standard man). A body burden of 1 μc of Sr^{90} is equivalent to 1000 S.U. (sunshine units, or μμc of Sr^{90} per gram of Ca).

It is obvious from several investigations that the assumption of a homogeneous Sr^{90} distribution is unrealistic, since Sr^{90} occurs both as a general diffuse labeling and in localized sites (reactive bone) of microscopic and macroscopic dimensions. If the dose rates are calculated in relation to the isotopic content of the reactive bone sites, where a great deal of Sr^{90} is found, more realistic data may be attained. It is therefore necessary to consider the geometrical distribution of these reactive sites.

The geometrical configuration may be accounted for by two extreme cases, the cylindrical geometry of the Haversian systems and the more irregular appearance of the labeling in spongious bone. Estimates show that spongious bone is often the more important tissue when high dose rates are considered. However, it is an impossible task to make exact dose calculations for the spongious bone. A simplified geometry has to be assumed, and this has been done in a recent monograph (*1*) in which a system of plane parallel slabs of reactive bone interspersed with regions of bone marrow is considered. It is found that a homogeneous contamination of the reactive bone slabs with 1 mμc of Sr^{90} per gram of bone may give maximum dose rates of 25 to 35 mrem/day to bone and bone-marrow cells, with corresponding average values of 15 to 20 and 12 to 16 mrem/day. It is now important to remember that the reactive bone constitutes a certain fraction of the 7000 g of bone tissue that the standard man is supposed to contain. This fraction varies with the state of growth and remodeling of the bone tissue. It thus differs for children and adults as well as for different bones and parts thereof within the same skeleton. It appears legitimate to assume a fraction of around 0.20 to 0.25 to be a representative average figure. Thus, 1400 to 1750 g of the skeleton is considered to be reactive. In adults it can be estimated that approximately half of the reactive bone is found as spongious bone where the major part of the blood-forming bone marrow is situated.

If the maximum permissible value of 1 μc of Sr^{90} is considered, the following dose rates are obtained: 7000 g of bone will receive more than 1.8 mrem/day and, on the average, 5.5 mrem/day; 700 to 900 g of spongious bone will, on the average, receive 10 mrem/day—in some parts, 21 mrem/day; 1500 g of red bone marrow will receive more than 1.8 mrem/day and, on the average, 7.5 mrem/day; 1100 g of red bone marrow will receive an average of 9 mrem/day —in some parts, 21 mrem/day.

The maximum-dose-rate values given above are based on one assumption which is obviously not fulfilled—namely, that of homogeneous labeling of the different reactive sites or "hot spots" in relation to each other. However, variations in the Sr^{90} concentrations are to be considered rather the rule than an exception. Regions of the same dimensions as the average range of Y^{90} beta particles (~ 2 mm) and containing a large number of hot spots may differ from the average in Sr^{90} concentration by a factor of 5 to 10. This implies a corresponding increase in the maximum dose rates to some parts of the bone tissue.

It should finally be pointed out that the simplified geometry used to depict the spongious bone may lead to dose-rate values that are too low in comparison with those for biological material. It is easy to conceive of geometrical arrangements (for example, bone lamellae meeting in a corner or inhomogeneous activity distribution within hot spots) which will give locally a two- to threefold increase in the maximal dose rate. A body burden of 1 μc of Sr^{90} acquired in one exposure may thus give dose rates on the microscopic level as high as 300 to 500 mrem/day to certain parts of the reactive bone tissue and the bone marrow.

It seems advisable to correlate the permissible body burden with the maximum local dose rates rather than with the average whole-body values. The production of bone and blood malignancies is probably dependent on the local microscopic conditions—that is, on the local dose rates. Thus, when we compare the dose rate of 300 to 500 mrem/day from 1 μc of Sr^{90} with the dose of 1000 rem which is considered after a relatively long period to be significant in the production of biological damage to bone tissue, it is apparent that this dose (1000 rem) may be attained within 10 years. This suggests a revision of the value for the maximum permissible body burden of Sr^{90} to 0.1 μc instead of the currently accepted value of 1 μc, which was derived from comparison with radium data.

The foregoing argument is concerned with acute or short-time poisoning with Sr^{90}. If Sr^{90} is taken into the body over a considerable period, the situation is different, as the pattern of isotopic localization becomes different. Such "chronic poisoning" conditions prevail today for

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Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper. (Since this requirement has only recently gone into effect, not all reports that are now being published as yet observe it.)

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* 125, 16 (1957)].

children born in recent years, as essentially all calcium available in the biosphere is, and will be, contaminated with Sr^{90} from weapon tests.

If in the first instance considered above a uniform contamination is assumed, 7000 g of bone will receive an average dose of 7.25 mrem/day. This dose rate is maximal to red bone marrow, which on the average receives 1.5 mrem/day. The degree of mineralization varies, however, and it is found, on comparing regions of the same dimensions as the average beta range ($\sim$ 2 mm), that there may be calcium concentrations which differ from the average by a factor of 2 to 3. This implies that certain parts of the bone and bone marrow may receive doses of around 15 mrem/day.

It is apparent, however, that a constant intake of Sr^{90} will not give a nonuniform contamination of the skeleton in the sense described above. The mechanism of remodeling and exchange gives rise to a biological half-life for Sr^{90} in the skeleton, and the radioactive decay has some influence, as well, on the equilibrium state. If we assume an effective half-life of 2700 days (7.4 years), the Sr^{90} concentration may be expected to vary from the average by a factor of about 2 for a 15-year period and by successively larger factors for longer periods. To some extent this fact is accounted for by the differences in mineralization. Therefore in the case of chronic poisoning with Sr^{90} a higher figure than 0.1 μc is tolerable as total body burden; tentatively, the 1 μc level may be considered to be tolerable.

Today the Sr^{90} contamination of the geosphere and the biosphere is steadily increasing. This corresponds to a situation with aspects that lie somewhere between those of acute and chronic Sr^{90} poisoning. Children in the 0- to 5-year age group are examples of individuals with chronic poisoning conditions. Adults above 20 years of age are more likely to be examples of acute poisoning.

It should finally be pointed out that the conditions described here in relation to Sr^{90} have their counterpart for other isotopes. For instance, it seems that the evaluation of the hazards from radium poisoning should take into account the difference between acute and chronic poisoning. This is the more advisable since the short range of Ra alpha particles will cause greater differences in the local dose rates than is the case with Sr^{90}.

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Notes

1. An extensive bibliography is to be found in A. Engström *et al.*, *Bone and Radiostrontium* (Almqvist and Wiksell, Stockholm, 1958).
2. This article is part 3 of a series on health hazards from fission products and fallout; for part 1, see K. Low and R. Björnerstedt, *Arkiv Fysik* 13, 85 (1957); part 2, by R. Björnerstedt, is in preparation.

27 October 1958

Release of Autonomic Mediators in Cardiac Tissue by Suprathreshold Stimulation

Abstract. Pharmacological evidence is presented supporting the theory that the increase in contractile strength of isolated cardiac muscle under suprathreshold stimulation is due to the release of an adrenergic mediator (norepinephrine). However, release of this material does not account for changes in contractile strength associated with changes in frequency of stimulation at threshold levels.

Whelan *et al.* have reported that during periods of suprathreshold stimulation (stimulation at voltages well above threshold) contractile force of isolated cat papillary muscle gradually increases, while that of the cat atrial strip gradually decreases, or first decreases and then increases (*1*). They tentatively attributed these alterations in force to release of autonomic mediators by the suprathreshold stimuli, release of acetylcholine mediating a decrease, and release of "one of the epinephrine compounds" mediating an increase. A similar postulate had been made previously by Nelemans (*2*) and by Ursillo (*3*) to explain force changes following short periods of tetanic stimulation of spontaneously beating frog heart and mammalian atria, respectively.

Several years ago, while working with isolated left atria, we encountered the same phenomena reported by Whelan (*4*). With guinea-pig atria at both 27° and 37°C, suprathreshold stimulation increased contractile strength (Fig. 1*B*), whereas with rat atria at 27°C, it produced either a decrease or a decrease followed by an increase. Since the decrease in contractile strength produced in rat atria could be blocked by atropine and potentiated by physostigmine, we concluded that it was mediated by released acetylcholine. However, we were unsuccessful in our early attempts to obtain convincing pharmacological evidence that the increase in contractile strength produced in guinea-pig atria was due to release of adrenergic mediator, since none of several adrenergic blocking agents, including dibenamine, available to us at the time produced a clear-cut blockade of the increases in strength elicited by epinephrine and norepinephrine.

During the past year we have returned to the problem of identifying the potentiating material released by suprathreshold stimulation of guinea-pig left atria, making use of two newer pharmacological agents. One of these agents is 1-(3′,4′-dichlorophenyl)-2-isopropylaminoethanol hydrochloride (DCI), which recently has been reported to be an effective blocking agent against both the inhibitory effect of sympathomimetic amines on certain smooth muscles and the stimulating effects of these amines on the heart (*5*). The second agent is reserpine, which causes a rapid and drastic depletion of the endogenous catechol amines (chiefly norepinephrine) of cardiac tissue when it is administered to animals at high dose levels (*6*).

Exposure of guinea-pig left atria to about 10^{-4} g of DCI per milliliter for 10 to 20 min effectively antagonized the positive inotropic action of epinephrine and norepinephrine (Fig. 1, *A* and *C*). The antagonism persisted for long periods after washout of the DCI, whereas certain undesirable side effects of DCI at the concentration used—such as de-

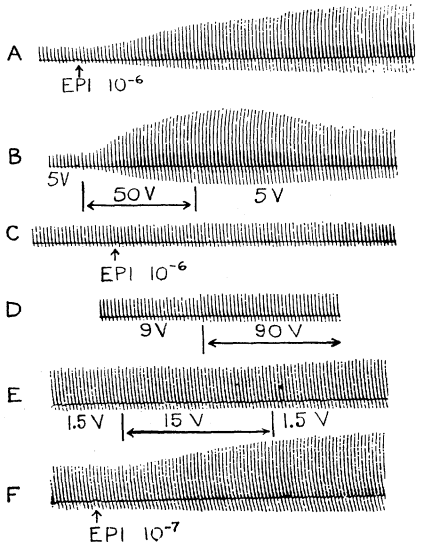

Fig. 1. Effects of suprathreshold stimulation and of epinephrine on contraction amplitude of isolated left atria of guinea pig under various conditions. Recordings were made with an ink-writing isotonic lever, exerting 1*g* tension on the atrium, which was suspended in 20 ml of oxygenated Krebs bicarbonate solution (*p*H 7.4) at 27°C. The stimulus was provided by a Grass 4C stimulator (biphasic pulse, 1 to 2 msec duration) at a frequency of 1 per second through Ag-AgCl electrodes. *A*, Effect of epinephrine on atrium from a normal guinea pig; *B*, effect of suprathreshold stimulation on the same atrium; *C*, effect of epinephrine on the same atrium after treatment with 10^{-4} DCI for 10 min; *D*, effect of suprathreshold stimulation on the same atrium after DCI treatment; *E* and *F*, effects of suprathreshold stimulation and of epinephrine on atrium from a reserpinized guinea pig.