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STRONTIUM-90 IN BONE: A CASE STUDY IN AGE-DEPENDENT DOSIMETRIC MODELING*

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Abstract—There is an increasing need for age-dependent dosimetric models, and it would be desirable to develop these models in such a way that the uniformity and basic features of the standard man models are retained. Unfortunately, available data concerning the age-dependent retention of nuclides would rarely permit the identification of compartments, uptake fractions, and clearance times using the empirical fitting methods that characterize the development of many adult models. However, in cases where compartments can be made to correspond to physically identifiable processes or subsections within an organ, it may be possible to combine relatively extensive information concerning the development of the human body with generally sparse nuclide-specific information to construct age-dependent compartmental models. In some cases there may be sufficient data to identify trends with age within compartments using empirical fitting techniques, provided the compartments have already been identified on physical bases. To obtain models that describe changes in a continuous manner from birth through adulthood, it may be necessary in many cases to modify existing adult models to consider fewer (or more easily identifiable) compartments. In this article we describe an age-dependent model for retention of ingested ^{90}Sr in bone that exemplifies these concepts.

INTRODUCTION

THERE is considerable evidence that the rate of uptake or removal of a radionuclide by the body can vary significantly with age. This is perhaps most extensively documented in the case of ^{90}Sr, which has been measured in tens of thousands of human skeletons and has been the subject of numerous animal experiments since the early 1950s (Ku62; SM66; SM72; ICRP72; Kl79). Attention was focussed on this nuclide for several years because it was considered to be potentially the most hazardous of the long-lived fission products whose inventories were beginning to grow as a result of the American and Russian nuclear weapons-testing programs.

The large quantity of data collected for ^{90}Sr has been incorporated in the development of several age-dependent models describing the metabolism of that radionuclide (for example, [La57; Ku62; Ri67; Pa73; Kl79]). However, with the exception of such models for ^{90}Sr and a few other radionuclides and recent models that describe translocation of nuclides through the respiratory or gastrointestinal tracts (Cr81a; Cr81b; Ho79), dosimetric methods have been developed primarily for an average adult. This is not only because of the complexity inherent in radiation dosi-

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metry and the lack of adequate data for different age groups, but also because of the emphasis traditionally placed on occupational exposures.

With the increased attention now being given to potential radiation exposures to the general public, there is a growing need for dosimetric models that incorporate age dependency. Moreover, it is desirable to develop these models in such a way that the uniformity and basic features of the standard man models are retained for all age groups. The basic problem, of course, is that available data concerning the age-dependent retention of nuclides are too sparse to permit identification of compartments and their uptake fractions and clearance times using the empirical fitting methods that characterize the development of most adult models.

The present paper represents a case study in age-dependent modeling, since we are examining, for the special case of ^{90}Sr, the extent to which basic human anatomical and physiological information can be used to develop a mechanistic metabolic model that applies from birth through adulthood. Clearly element-specific information must enter any such model at some point, and in the final analysis age-dependent metabolic modeling must be carried out for each element on an individual basis. However, as indicated by the model developed in this article, workable age-dependent metabolic models may be obtainable in some cases with considerably less reliance on element-specific data than has been displayed in the development of standard man models. We have chosen to consider ^{90}Sr because of the large amount of data available to evaluate the approach discussed here.

Our model for ^{90}Sr is consistent in spirit with the ICRP alkaline earth model for adults (ICRP72), in that compartments correspond to physically identifiable processes or subsections within the skeleton, and behavior of ^{90}Sr is studied in terms of behavior of the better known element, calcium. Valuable information was gained also from earlier age-dependent models for ^{90}Sr, particularly those of Papworth and Vennart (Pa73), Bennett (Kl79) and Langham and Anderson (La57).

SKELETAL COMPARTMENTS

In terms of the functions of the skeleton, bone is often divided into two categories, structural bone and metabolic bone. "Structural" refers to the mechanical function of the skeleton, and "metabolic" refers to the function of the skeleton in the regulation of extracellular calcium levels, particularly in blood plasma.

The skeleton will be viewed as consisting of 3 compartments, with 2 compartments associated with structural bone, which we shall identify with bone volume, and the third compartment defined largely in terms of metabolic bone, which we shall identify with bone surface. We shall examine the dynamics of the bone surface compartment in terms of a pool of skeletal calcium in rapid exchange with the calcium in blood plasma. This pool of rapidly exchangeable calcium will be thought of as a transfer compartment between blood and bone volume. Within bone volume lie the more massive compartments comprised of hard, compact bone and soft, spongy bone. We assume that the 3 compartments consisting of compact bone, cancellous bone, and bone surface are present at all ages, although the parameters describing the metabolism of those compartments are allowed to change continually brom birth to death.

DEVELOPMENT OF THE MODEL

Bone volume

The metabolism of ^{90}Sr is affected to a large extent by gains and losses of calcium by bone volume, and much of our discussion will deal with changes in this predominant mass of the skeleton. Bone surface will be treated as a transfer compartment between bone volume and blood. Parameters for bone surface (and even the very nature of bone surface) are considerably more uncertain that the corresponding entities for bone volume, and our notion of bone surface can be described more easily following the development of our model for bone volume.

There are 2 principal physical compartments of bone volume that we consider in our mathematical description of the uptake and removal of ^{90}Sr by the skeleton. For con-

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venience, we shall refer to Compartment 1 at all ages as compact (or cortical) bone and to Compartment 2 at all ages as cancellous (or trabecular or spongy) bone.

In the mature skeleton these 2 bone types are reasonably distinct in terms of both appearance (Fig. 1) and retention of strontium. However, in the non-adult, it appears that these 2 compartments become less and less differentiated with decreasing age, particularly in terms of uptake and retention of strontium. In fact, we assume that there are no differences in uptake and retention properties between the two compartments until some time during the second year of life and that differences remain fairly small throughout childhood. For the maturing skeleton it may be better to conceive of Compartments 1 and 2 as "cortical bone and its precursors" and "cancellous bone and its precursors", respectively, with emphasis on the final bone type rather than on the precursor. For example, bone originally laid down as spongy bone but later transformed to cortical bone by either a compactification of trabeculae or a filling in of interstices between trabeculae (En63; Bl75) would be considered as part of Compartment 1 throughout its existence.

The hard, compact cortical bone is found largely in the shafts of the long bones, where it surrounds the marrow cavities. Spongy bone, which is made up of a network of fine interlacing partitions (the trabeculae), is found in the vertebrae, in the majority of the flat bones, and in the ends of the long bones. The trabeculae enclose cavities containing either red or fatty marrow (Va75).

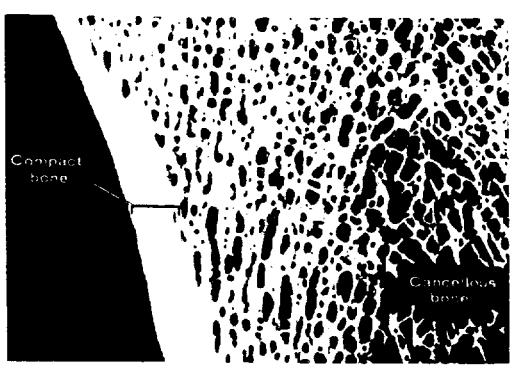

FIG. 1. A section of the tibia illustrating the compact bone and the trabeculae of the cancellous bone. (From Bl75 by permission of the publishers.)

Compact and cancellous bone are usually distinguished in terms of their surface to volume ratios, which tend to be much larger for cancellous bone. For example, results of Beddoe, *et al.* (Bed76; Bed77) indicate that the surface to volume ratio for cancellous bone in adults may be about 7 times as large as for compact bone, and a large difference is also suggested by those results for young childredn. In ICRP20, which was written before the results of Beddoe were available, a factor of 4 was used for adults (ICRP72; Ll71), and this factor of 4 plays an important role in various components of the ICRP model. In particular, it is assumed that the removal rate for calcium from cancellous bone must be 4 times the removal rate from compact bone, since the bone formation rate per unit area of surface is assumed to be the same for both bone types.

In the present model no use is made of surface to volume ratios, and the removal rates for calcium from compact and cancellous bone are determined independently of one another. We note that, for persons past the age of 40, the estimated removal rate for calcium from cancellous bone is approximately 7 times the rate for compact bone.

It should be kept in mind that the distinction between compact and cancellous bone represents an average for the entire skeleton. Surface to volume ratios vary significantly within bone types, and the distinction between compact and cancellous bone may not be readily evident at some points in the skeleton and at some stages of development. Since we shall assign a single uptake or turnover rate at a given age to an entire compartment, our model represents a gross oversimplification of the real system, and we can only hope to approximate averages of a variety of uptake and turnover rates at fixed ages within these compartments.

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Measurements have indicated that compact bone comprises about four-fifths of the adult skeleton and cancellous bone about one-fifth, by volume, by mass, and by calcium content (ICRP72). There does not appear to be much information available concerning changes in the relative fractions of the two bone types during development of the skeleton. In one study (Vi69), radiographic techniques were used to estimate cortical thickness at the midshafts of various bones in subjects between 1 and 90 yr of age. Obviously, accurate estimates of the total mass of cortical bone in the skeleton cannot be obtained from a study of this type. However, with the assumptions that bones are regular cylinders and that changes in cortical mass at the midshafts of the studied bones are representative of changes in cortical bone for the entire skeleton, it would appear from the extensive data of Virtama and Helela (Vi69) that the mass of cortical bone does not have a significantly different rate of increase from that of the total skeleton, particularly after the age of 5 or 6 yr. In this analysis account was taken of the fact that the mass of a unit volume of cortical bone (that is, a unit volume as estimated from a radiograph) may increase significantly through about age 17 (Col70; Si62).

On the basis of these considerations we have assumed that, at all ages, compact bone comprises 80% and cancellous bone the remaining 20% of the mass of the bone volume. The error inherent in this assumption probably increases with decreasing age below age 20; fortunately, this error will be largely negated by other assumptions in the model. In particular, we assume that there are only small differences in the uptake and turnover rates of ^{90}Sr in compact and cancellous bone during the first few years of life, so that the concentration of ^{90}Sr in the skeleton does not depend strongly on the relative masses of the two compartments at early ages.

Age-dependent changes in skeletal calcium

Chemically, ^{90}Sr behaves much like calcium and tends to accumulate in the skeleton. We assume throughout that the removal processes of the skeleton cannot distinguish between a calcium atom and a strontium atom, although this point is debatable (Sh72). It is generally agreed, however, that there is some discrimination against ingested ^{90}Sr before it reaches the skeleton (probably by the gut and kidney, and possibly by the bone itself [Ne58; Com67; Va75]), with the discrimination factor depending on age (Com67; Kn67). In our model this discrimination factor k is taken to change with age t according to the formula

$$k(t) = 0.7 \exp(-1.2t) + 0.2.$$

The function k was chosen simply as a convenient approximation to data obtained in several studies of the observed ratios of strontium to calcium in diet and in the skeleton (Com67; Kn67; ICRP72). It may be reasonably accurate for newborns and for persons more than about 2 yr old, but it should be regarded as describing only the general trend of the discrimination factor for the intervening ages where the change is rapid.

The mass of skeletal calcium is increased during childhood and early adulthood due to bone modeling, and there is a continual turnover of skeletal calcium throughout life due to bone remodeling. (Modeling refers to resorptive and formative processes associated primarily with growth and remodeling refers to bone turnover, which is assumed to cause no changes in quantity.) Most of the skeletal growth has occurred by age 20, and it is generally assumed that the mass and turnover rates of the skeleton remain constant after this age. There are, however, significant skeletal changes after age 20, as evidenced by radiographic studies of age-dependent changes in cortical bone (Vi69; Wo67) and by tetracyline studies of bone formation rates (Fr69). In particular, it appears that skeletal modeling may continue until the latter part of the fourth decade, although annual increases in skeletal mineral may be relatively small after age 20 (Fr69). The mass of the skeleton probably changes very little from age 35 to age 45 of 50, after which there is a continual bone loss (Vi69; Wo67; Ga64).

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Conclusions drawn concerning the actual rate of change of bone calcium during adulthood seem to depend on the bones chosen for study and the methods used. Furthermore, it is not evident whether these changes occur uniformly for compact and cancellous bone, although there is some indication that bone loss, at least, does occur uniformly for the two compartments (Vi69). As indicated earlier, we shall assume that the relative masses of compact and cancellous bone remain constant throughout life, and hence, in effect, that losses and gains of calcium always occur uniformly in the skeleton.

According to Mitchell, *et al.* (Mi45), the mass of calcium $C(t)$, in grams, in the human skeleton at age t yr (for t less than or equal to 20) is roughly approximated by

$$C(t) = 28.0 + 86.828t - 16.5105t^2 + 1.5625t^3 - 0.04114t^4.$$

This curve is based on data derived for boys between 5 and 17 yr of age, and extrapolations were made to birth and to age 20. Hence considerable errors may be involved at some points. In fact, dietary information described by Durbin (Dur70) suggests that calcium accretion during the first year of life for modern U.S. infants may be 20% greater than the amount indicated by this function. However, for lack of any better model for the change of skeletal calcium in nonadults, we have used Mitchell's function and the rate of change $C'(t)$ of calcium as a function of age implied by this function. Because Mitchell's function would imply that $C'(t)$ is negative at age 20, we have assumed that (1) holds only until age 19.3. (Here and elsewhere is this article, insignificant digits are retained for purposes of internal consistency in the model.)

From age 19.3 to age 55, the amount of skeletal calcium is estimated as

$$C(t) = -0.3070t^2 + 23.35t + 742.2,$$

and after age 55 as

$$C(t) = 1098 \exp[-0.01(t - 55)].$$

This would imply that the skeletal calcium increases by about 100 g from age 20 to the late 30s and then starts decreasing by amounts which are negligible for a few years but which reach approximately 1% per yr by age 55. It is assumed that the rate of decrease remains at 1% per yr after age 55. (See Table 1). None of these estimates is expected to have much accuracy on a year-by-year basis. Our intent is simply to characterize the general trend in the change in skeletal calcium with age. Changes for ages above 19.3 are particularly suspect since they are based on relative values in cortical volume near the mid-shafts of various bones as estimated from radiographic measurements, with the estimated amount of skeletal calcium at age 19.3 used as an initial value. Thus it is assumed that, for ages greater than 19.3, changes in skeletal calcium are proportional to changes in cortical volume as estimated from radiographs. Estimates for ages from 19.3 to 55 were based on the data of Virtama and Helela (Vi69) for the humerus, radius, femur, second metacarpal and second metatarsal, and the estimated bone loss for ages greater than 55 was based on a combination of studies (Vi69; Ga64; Wo67).

Removal rates from compact and cancellous bone

It appears that the age of the skeleton is the primary determinant of its chemical reactivity and hence of its rate of modeling and remodeling (Ne58). Young bone is more vascular and hydrated than older bone, so that the rate of mineral acquisition or exchange tends to be highest in young children. In the adolescent, modeling and remodeling rates are decreasing, and an increasing proportion of the skeleton is becoming mineralized and relatively inert. In the adult, most of the skeleton has become fully mineralized and is largely unreactive. Although the fraction of the skeleton which is reactive and hence available for remodeling decreases with age, the total amount available for exchange may not change a great deal throughout skeletal development (Ne58). In fact, as we shall see, the hypothesis that the total amount of calcium replaced in the skeleton per unit time be

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*Table 1. Estimated changes with age (yr) in skeletal calcium**

Age	Skeletal calcium (g)	Rate of change of skeletal calcium (g/yr)
0	28.0	86.8
1	99.8	58.3
2	147.5	38.2
3	178.7	25.5
4	200.6	19.2
5	219.0	18.3
6	238.8	21.9
7	263.9	28.9
8	297.4	38.4
9	341.2	49.4
10	396.3	60.8
11	462.7	71.8
12	539.3	81.2
13	624.3	88.2
14	714.6	91.7
15	806.3	90.8
16	894.4	84.5
17	973.1	71.7
18	1035.3	51.5
19	1073.2	22.9
20	1086.4	11.1
25	1134.1	8.0
30	1166.4	4.9
35	1183.4	1.9
40	1185.0	-1.2
45	1171.3	-4.3
50	1142.2	-7.4
55	1097.8	-10.4
60	1047.1	-10.5
65	996.0	-10.0
70	947.4	-9.5
75	901.2	-9.0
80	857.3	-8.6
85	815.5	-8.2
90	775.7	-7.8

*Insignificant digits are retained throughout for internal consistency in the model.

invariant with age during skeletal development is in reasonable agreement with estimates of the calcium turnover rate for cortical bone implied by tetracycline studies (Fr69).

In the remainder of this section, the term "removal rate" will refer to the rate of elimination of ^{90}Sr from the body due to both the biological process of bone remodeling and to radioactive decay (a factor of approximately 0.025 per yr). It is assumed that, except for radioactive decay, the removal rate for ^{90}Sr from bone is the same as that for calcium. Removal of ^{90}Sr due to bone loss in older persons is not included in our estimates of strontium removal rates but is considered separately in our model. In general, we assume that bone loss in older persons does not affect the concentration of ^{90}Sr in the skeleton (although it does affect the total quantity of ^{90}Sr in the skeleton), since ^{90}Sr is assumed to be lost uniformly during bone loss due to aging and in the same proportion as skeletal calcium.

For compact bone we assume a removal rate (per yr) at age t of $0.975 \exp(-0.110t) + 0.025$ for t between 1.5 and 35 yr, followed by a linear increase to 0.062 at age 44; after this age the removal rate is assumed to remain constant. These values are based on turnover rates derived from bone formation rates found in tetracycline studies (see Table 3 of the paper by Frost (Fr69)), with data points placed at the mean of the sampled ages in each age category. The expression for ages 1.5–35 is a fit to the decreasing data for that age range, and the linear increase for ages 35–44 is used simply for lack of better information for that age range. The formation rates given by Frost are for the typical cubic millimeter of compacta in the sixth human rib and apparently represent percentages per yr of compact bone being remodeled (ICRP72). In ICRP20 (ICRP72), where a single value of 2.5% per yr was used as the rate of turnover of compact bone at all ages, it was suggested that the turnover rate for compact bone in the rib may be higher than the average for the compact portion of the skeleton as a whole. We note, however, that for ages greater than 30, the turnover rates implicit in our values are never much greater than the ICRP20 value, and they are even lower at some ages. Even if the turnover rates suggested by the results of Frost are not representative of compact bone in general, they are probably indicative of the relative turnover rates at different ages.

Cancellous bone is assumed to have a removal rate (per yr) at age t of $0.912 \exp(-0.064t) + 0.025$ for t between 1.5 and 35 yr; the removal rate is assumed to increase linearly from 0.12 per yr at age 35 to 0.28 per yr at age 44 and to remain constant after 44. These rates for cancellous bone were based largely on turnover rates found by Bennett (Ben72a; Kl79) for the vertebrae; Bennett's values were derived from fits to ^{90}Sr concentrations measured in human vertebrae and represent ages 0–19, with a single value being given for

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adults. We have assumed that the change in the removal rate for cancellous bone follows the same pattern as that for compact bone, which simply means that the curve for ages 1.5–20 was assumed to continue through to age 35, and the change from age 35 to 44 was assumed to be analogous to the change for compact bone. Since a vertebra is not totally cancellous bone but contains a small amount of compact bone, our implied turnover rates for cancellous bone may underestimate the actual average values.

The removal rate curves for the two compartments intersect at approximately 1.5 yr. Prior to that age the skeleton is assumed to be undifferentiated in the sense that different types of bone do not have different removal or uptake rates. The removal rate (per yr) from birth to 1.5 yr is assumed to be $104.3/C(t) + 0.025$, which is derived from the removal rate at age 1.5 together with the assumption that the total amount of calcium replaced in the skeleton per unit time does not change between ages 0 and 1.5. (Recall that $C(t)$ is the mass of skeletal calcium at age t.) This assumption leads to a turnover rate for age 0.33 yr that is consistent with bond formation rates for that age (as a mean age) found from tetracycline studies (Fr69).

The biological removal rates for calcium or strontium from the two compartments as a function of age, as well as the removal rate for the total skeleton which would be implied by the assumption that the total calcium turnover per unit time is constant as function of age, are given in Table 2. Note that, as indicated earlier, through the period of rapid growth (up to age 20) the removal rate estimated for cortical bone from the tetracycline studies is not too different from that for the entire skeleton derived from assuming a turnover pool of constant mass.

Uptake rates of compact and cancellous bone

The fraction of ingested ^{90}Sr eventually taken up by the bone is assumed to be equal to the fraction of ingested calcium taken up by the bone times the discrimination factor $k(t)$ defined earlier. Moreover, the uptake fraction as a function of age for calcium is assumed to be controlled by the changes in skeletal calcium:

$$C'(t) = -(0.8a(t) + 0.2b(t))C(t) + m(t)A(t)$$

where $m(t)$ is the uptake fraction for calcium, $a(t)$ and $b(t)$ are the removal rates for calcium from compact and cancellous bone, respectively, and $A(t)$ is the average amount of calcium per yr ingested at age t. Therefore, $m(t)$ would be given by

$$m(t) = ((0.8a(t) + 0.2b(t))C(t) + C'(t))/A(t).$$

The total uptake $u(t)$ of ^{90}Sr by bone volume at age t is estimated from $m(t)$ by the formula

$$u(t) = k(t)m(t).$$

The uptake fractions $r(t)$ and $s(t)$ for ^{90}Sr by Compartments 1 and 2 are estimated by decomposing $u(t)$ into the components dictated by the hypothesized turnover rates and growth rates of the respective compartments. Thus,

$$r(t) = 0.8k(t)(a(t)C(t) + C'(t))/A(t)$$

and

$$s(t) = 0.2k(t)(b(t)C(t) + C'(t))/A(t).$$

In calculations of $m(t)$, $r(t)$ and $s(t)$, the calcium intake rate $A(t)$ was assumed to be 365 g per yr at all ages. Also, calcium losses due to aging were assumed not to affect $m(t)$, $r(t)$ and $s(t)$; that is, $C'(t)$ was taken to be zero at ages for which there is a net loss of calcium from the skeleton.

The fraction of ingested ^{90}Sr eventually reaching bone volume as a function of age is given in Table 3, along with the estimated fractions allotted to compact and cancellous bone, and the discrimination factor used at each age. Note that our assumptions imply a gradual decrease in calcium and strontium uptake for older persons; this is consistent with experimental results (Sm72). For ages 40 and above, the estimated fractional uptake rates of strontium by bone volume are reasonably consistent with the single value of

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Table 2. Estimated removal rates for calcium from bone volume expressed as fraction of total calcium (age in yr)

Age	Removal rate for compact bone*	Removal rate for cancellous bone*	Removal rate for skeleton assuming amount removal per unit time is constant†
0	3.725	3.725	3.725
1	1.045	1.045	1.045
2	0.782	0.802	0.707
3	0.701	0.753	0.584
4	0.628	0.706	0.520
5	0.563	0.662	0.476
6	0.504	0.621	0.437
7	0.451	0.583	0.395
8	0.404	0.547	0.351
9	0.362	0.513	0.306
10	0.325	0.481	0.263
11	0.291	0.451	0.225
12	0.260	0.423	0.193
13	0.233	0.397	0.167
14	0.209	0.372	0.146
15	0.187	0.349	0.129
16	0.168	0.328	0.117
17	0.150	0.307	0.107
18	0.135	0.288	0.101
19	0.121	0.270	0.097
20	0.108	0.254	0.096
25	0.062	0.184	0.092
30	0.036	0.134	0.089
35	0.021	0.097	0.088
40	0.029	0.184	0.088
45	0.037	0.255	0.089
50	0.037	0.255	0.091
55	0.037	0.255	0.095
60	0.037	0.255	0.100
65	0.037	0.255	0.105
70	0.037	0.255	0.110
75	0.037	0.255	0.116
80	0.037	0.255	0.122
85	0.037	0.255	0.128
90	0.037	0.255	0.134

*Per year.

†Used in model only up to age 1.5.

0.042 for adults derived by Papworth and Vennart (Pa73).

It is common in internal dosimetry to estimate a fraction f_1 of nuclide absorbed from the gastrointestinal tract into the blood and a fraction f_2' taken from the blood by the organ. Here the combined fraction $u = f_1 \times f_2'$ was estimated. For many situations, available information may be such that it is convenient to estimate age-dependent values of f_1 and f_2' separately.

BONE SURFACE

Compared with bone volume, there is relatively little information available with which to construct or evaluate the bone surface compartment. However, we thought it would be instructive to indicate where differences with age might arise in this compartment.

There is a continual acquisition by the skeleton of calcium from blood and a continual exchange of calcium between the skeleton and blood. For every ion added to the skeleton, there may be thousands or even millions of ions exchanged between blood and skeleton. This constant interchange of calcium between bone and blood serves to maintain a relatively constant calcium ion concentration in the plasma (Bl75; Gu71).

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Table 3. Estimated uptake fractions for strontium by bone volume, and estimated discrimination factor between calcium and strontium (age in yr)

Age	Fractional uptake by bone volume	Fractional uptake by compact bone	Fractional uptake by cancellous bone	Discrimination factor
0	0.471	0.377	0.094	0.900
1	0.183	0.146	0.037	0.411
2	0.111	0.089	0.023	0.264
3	0.092	0.072	0.019	0.219
4	0.084	0.065	0.018	0.206
5	0.081	0.063	0.018	0.202
6	0.081	0.063	0.019	0.201
7	0.085	0.065	0.020	0.200
8	0.092	0.070	0.022	0.200
9	0.100	0.076	0.025	0.200
10	0.111	0.083	0.028	0.200
11	0.121	0.090	0.031	0.200
12	0.131	0.097	0.034	0.200
13	0.139	0.103	0.037	0.200
14	0.145	0.106	0.039	0.200
15	0.147	0.106	0.041	0.200
16	0.144	0.103	0.041	0.200
17	0.136	0.096	0.041	0.200
18	0.122	0.084	0.038	0.200
19	0.101	0.067	0.034	0.200
20	0.088	0.056	0.031	0.200
25	0.058	0.034	0.024	0.200
30	0.038	0.021	0.018	0.200
35	0.024	0.012	0.013	0.200
40	0.039	0.015	0.024	0.200
45	0.052	0.019	0.033	0.200
50	0.050	0.019	0.032	0.200
55	0.048	0.018	0.031	0.200
60	0.046	0.017	0.029	0.200
65	0.044	0.016	0.028	0.200
70	0.042	0.015	0.026	0.200
75	0.040	0.015	0.025	0.200
80	0.038	0.014	0.024	0.200
85	0.036	0.013	0.023	0.200
90	0.034	0.013	0.022	0.200

concerning the precise mass and location of the portion of skeletal calcium that is in rapid exchange with extracellular calcium, much evidence indicates that this pool may consist of at most a few grams of calcium lying near the bone surface (Bl75; Gu71; ICRP72). In the description of the ICRP adult alkaline earth model (ICRP72), it was suggested that this pool could be identified with the skeletal calcium lying within 1 μm of the anatomical surfaces of bone, that is, the endosteum, the periosteum, the surfaces of trabeculae, and the surfaces of haversian and Volkmann canals. Studies involving radioactive tracers have indicated that the readily exchangeable calcium may not be uniformly distributed near the bone surface but may be located principally in areas of present and recent sites of bone formation or absorption (Bl75; Gu71). Because of the continuous maturation process, calcium laid down in recent weeks would probably have closer contact with circulating fluids than other skeletal calcium.

Estimates of the mass of calcium in the exchangeable pool are usually less than 10 g for adults, and a value of 4 g was used in ICRP20 (ICRP72). We shall estimate the mass of the exchangeable pool of calcium, which we shall refer to as the bone surface compartment, by assuming that the particular mass at any age is proportional to the amount of skeletal calcium deposited each day at that age; the proportionality constant is obtained from the assumption that the average of the varying masses between ages 30 and 80 is 4 g. Hence the mass of calcium in the bone sur-

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face compartment at any age is assumed to depend on the amount of skeletal growth and renewal at that age, and the masses are normalized to the ICRP adult value, which we assume is an average value for ages 30–80. These assumptions lead to estimates of 3–10 g of calcium for the mass of this surface compartment for most ages, although the estimates are slightly higher for periods of rapid growth and remodeling and slightly lower during the mid-30s, when turnover rates may be lowest (Table 4). The proportionality constant derived from our assumptions is 20.6 days; this would imply that the bone surface compartment in our model corresponds in terms of mass, to the amount of calcium deposited in bone within a period of approximately three weeks. Once again, considering the assumptions on which these estimates are based, it can only be hoped that the correct trend has been identified.

We conceive of the bone surface as a transfer compartment between blood and bone volume. That is, calcium (or strontium) is pictured as passing from blood to bone surface and from there to bone volume, and calcium leaving bone volume is pictured as passing through bone surface before reaching blood. Technically, this view may not be too accurate, since some calcium atoms may pass directly from bone volume to blood or vice versa. For practical purposes, however, this view does not introduce any problems because the rapid transfer between blood and bone surface would result in approximate equilibrium of ^{90}Sr in the two pools. (This assumes that bone surface does not discriminate between calcium and ^{90}Sr).

Table 4. Estimated changes with age (yr) in mass (g) of exchangeable calcium in bone surface (estimates made only for illustrative purposes)

Age	Mass of exchangeable calcium in bone surface
1	9.2
4	8.4
7	8.7
10	11.4
13	14.4
16	14.8
19	10.4
22	7.7
25	6.0
28	4.7
31	3.6
34	2.8
37	3.1
40	4.0
43	4.8
46	5.0
49	4.8
52	4.6
55	4.4
58	4.3
61	4.1
64	4.0
67	3.9
70	3.8
73	3.7
76	3.6
79	3.5

Calcium is removed from bone surface due to its deposition in bone and to its clearance to blood in route to excretion from the body. Removal rates for these two processes may be used to estimate an age-dependent removal rate for calcium on bone surface. The rates for deposition of calcium in bone were given in an earlier section. In order to retain internal consistency in the model, it was necessary to assume that calcium removed from bone volume is destined to be excreted from the body. Hence recirculation is not considered explicitly, and at best a crude approximation is obtained for the amount of calcium excreted. (Calcium losses due to the aging process were not included since that calcium was assumed not to pass through the bone surface compartment.)

With the given assumptions, the removal rate constant for calcium from the bone surface, when rounded to one decimal place, was calculated to 0.1 per day for all ages. This value agrees with the removal rate of calcium from blood, soft tissue, and bone surface used in the ICRP adult model for alkaline earths (ICRP72). In that model, a removal rate of 0.25 per day was assumed for ^{90}Sr. In the present model there is assumed to be no difference in removal processes from the bone for calcium and strontium, so that the removal rate of 0.1 per day is also used for ^{90}Sr.

MATHEMATICAL DESCRIPTION OF THE MODEL

For an individual born at time T, the amount $Q(t)$ of ^{90}Sr in a skeletal compartment at age t is described by the differential

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equation

$$dQ/dt = B(t)A(t)D(T+t) - L(t)Q(t),$$

where $B(t)$ is the fraction of ingested ^{90}Sr taken up by the compartment at age t; $A(t)$ is the amount of calcium ingested per yr at age t; $D(T+t)$ is the concentration of ^{90}Sr per g calcium in diet at time $T+t$; $L(t)$ is the sum of the radiological decay constant and the biological removal constant for the compartment at age t.

If there is an initial amount $Q(0)$ in the compartment at birth, this differential equation is equivalent to the integral equation

$$Q(t) = \left[\exp\left(-\int_0^t L(s)\,ds\right)\right] \times \left[Q(0) + \int_0^t B(w)A(w)D(T+w) \times \exp\left(\int_0^w L(s)\,ds\right)dw\right].$$

For ease of exposition, we have in many places omitted reference to units, and in our examples we refer only to "relative concentrations".

COMPARISON OF MODEL ESTIMATES WITH MEASUREMENTS OF ^{90}Sr IN HUMAN BONES

Measurements of ^{90}Sr in human bones have been made in various countries for several years. Extensive data are available for San Francisco and New York and for Great Britain beginning in the early 1950s (Kl79; Pa73; ICRP72; UN77), and we shall compare our model estimates with these data. Data for New York and San Francisco are almost entirely for the vertebrae, and British data prior to 1966 are largely for the femur. In our comparisons, the vertebrae are assumed to be representative of cancellous bone and the femur is assumed to be representative of the entire skeleton. Measurements of ^{90}Sr in different bones have suggested that the distinction between compact and cancellous bone types is superfluous for very young children and not too important for adolescents (Fl66; Br64). Our model also would indicate that the distinction between bone types is unimportant for very young children under essentially any intake pattern but that the small differences in ^{90}Sr concentrations previously measured in different bones of adolescents may be associated principally with chronic intake patterns such as those experienced up to this time.

Strontium-90 in diet

Estimates of the age-dependent intakes of ^{90}Sr during the years of interest were based on survey results of ^{90}Sr concentrations (per g Ca) in total diet and in milk. Approximate values for both the intake of calcium in total diet and the fraction of this calcium contributed by milk as a function of age are given in Table 5 (ICRP75; Dur70; Kl79).

Estimated concentrations of ^{90}Sr per g calcium in the average diet in New York and San Francisco (Kl79) and in the average

Table 5. Calcium intakes used in model estimates (age in yr)

Age	Annual intake of calcium (g)	Fraction of dietary calcium from milk
0	150.0	0.984
1	354.0	0.836
2	307.2	0.688
3	318.3	0.540
4	329.4	0.525
5	340.5	0.510
6	351.6	0.496
7	362.7	0.481
8	373.8	0.466
9	387.0	0.451
10	387.0	0.436
11	387.0	0.423
12	387.0	0.409
13	387.0	0.396
14	387.0	0.382
15	387.0	0.368
16	387.0	0.355
17	387.0	0.341
18	387.0	0.328
19	369.0	0.314
20	345.0	0.300
25	342.0	0.300
30	342.0	0.300
35	342.0	0.300
40	342.0	0.300
45	333.6	0.300
50	325.3	0.300
55	317.3	0.300
60	309.5	0.300
65	301.8	0.300
70	294.4	0.300
75	287.1	0.300
80	280.0	0.300
85	273.1	0.300
90	266.3	0.300

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national diet in Great Britain (Pa73) in recent years are shown in Table 6. All except one of our comparisons of model predictions and measured concentrations are for the period 1958–65, which includes the years of most rapid change of ^{90}Sr in diet, and for that period it was assumed that the ratio of the ^{90}Sr to calcium quotient in the total diet to that in milk is 1.5 for the United States and 0.9 for Great Britain. These ratios are taken from the 1977 UNSCEAR Report (UN77) and are averages for several years. For comparison with British values and with recent U.S. values, it would probably be justifiable to simplify matters by assuming a ratio of 1.0.

Comparison of observations and model predictions

For the kind of chronic exposure considered in the examples that follow, the activity of ^{90}Sr in the surface compartment contributes little to the concentration in the total skeleton, and we are not sure to what extent ^{90}Sr in bone surface at death would be left intact. Hence for simplicity our estimates of ^{90}Sr in bone in the following discussion have been made under the assumption that compact bone comprises a full 80% and cancellous bone a full 20% of the skeletal calcium at all ages, and (in effect) that ^{90}Sr is deposited directly from the blood into one of these two compartments.

Table 6. Estimated concentrations of ^{90}Sr per gram calcium in food in Great Britain, New York and San Francisco in selected years

Year	Great Britain	New York	San Francisco
1953	0.7		
1954	1.1	1.0	0.4*
1955	1.9	1.9	0.7*
1956	2.9	5.0	1.9*
1957	3.9	5.5	2.1*
1958	5.9	6.4	2.4*
1959	9.0	13.4	5.0*
1960	6.4	13.7	5.1*
1961	6.2	10.4	3.6
1962	9.9	9.8	4.1
1963	22.8	18.7	9.4
1964	25.9	29.5	13.8
1965	17.9	26.0	11.6
1966	12.1	20.3	8.3
1967	8.8	15.7	6.3
1968	7.6	14.8	4.0
1969	6.8	13.0	4.2
1970	6.1	12.0	4.0
1971		12.1	4.4
1972		11.3	3.6
1973		9.6	3.2
1974		8.9	2.9
1975		8.5	3.3
1976		7.9	2.8
1977		7.8	2.8
1978		7.4	2.8

*Estimated as 0.37 times New York values.

The ^{90}Sr concentration in newborns has been found to be approximately proportional to the concentration in the adult diet during the last few months of pregnancy (Ku62; Le67; Ll79). In this model we estimate the concentration of ^{90}Sr in the skeleton of the newborn as $0.15 \times D$, where D is the most recent estimate of ^{90}Sr in adult diet before birth. This estimator seems reasonably accurate for U.S. data but tends to overestimate slightly for British data.

In Fig. 2 model predictions based on reported ^{90}Sr concentrations in diet through 1964 are compared with measurements for the 3 British cohorts born 1958–60, respectively. The indicated observed values were read from graphs in a paper by Loutit (Lo67). Despite the errors introduced in model input in terms of ^{90}Sr in total diet and the ratio of the ^{90}Sr to calcium quotient in total diet to that in milk, model predictions appear to agree well with observations in this case.

Predictions for San Francisco for the years 1963–65 and for New York for the year 1964 are compared with actual measurements in Figs. 3 and 4. The scatter in data from one age to the next for older children suggests that there may be a nontrivial experimental error involved. However, the general pattern in the observed values is evident, and it would appear that the model predictions for San Francisco and New York are also in reasonable agreement with observed values despite the uncertainties in model input. It should be pointed out that our model is not completely independent of the observed values being considered here, since one parameter in our model (the age-dependent removal rate for calcium in cancellous bone) was based to a large extent on values estimated by Bennett using data which included that considered here, and the age-dependent discrimination factor used may have been influenced in some way by these data.

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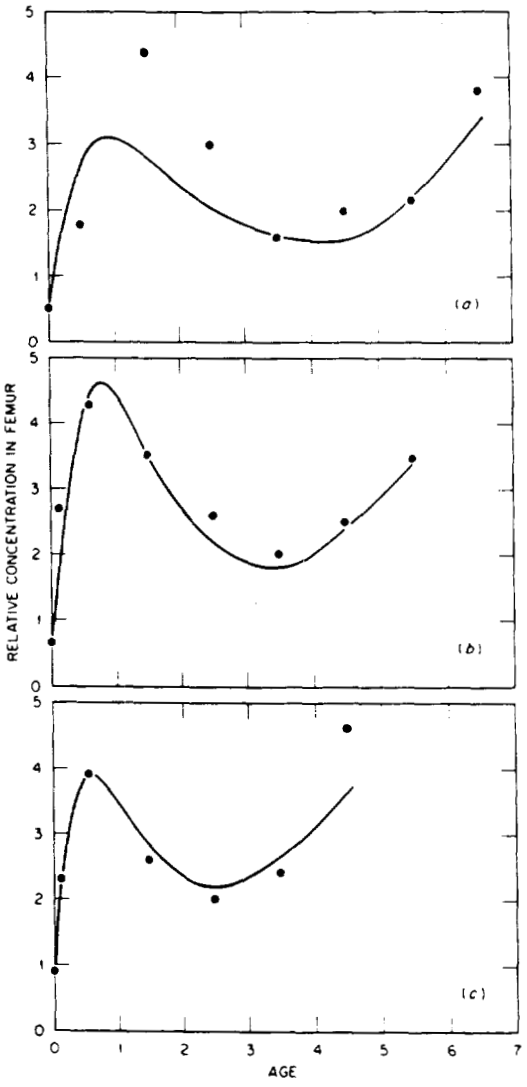

FIG. 2. Comparison of measured and predicted (curve) concentrations of ^{90}Sr in femur for British cohorts born in 1958 (a), 1959 (b) and 1960 (c) (age in yr).

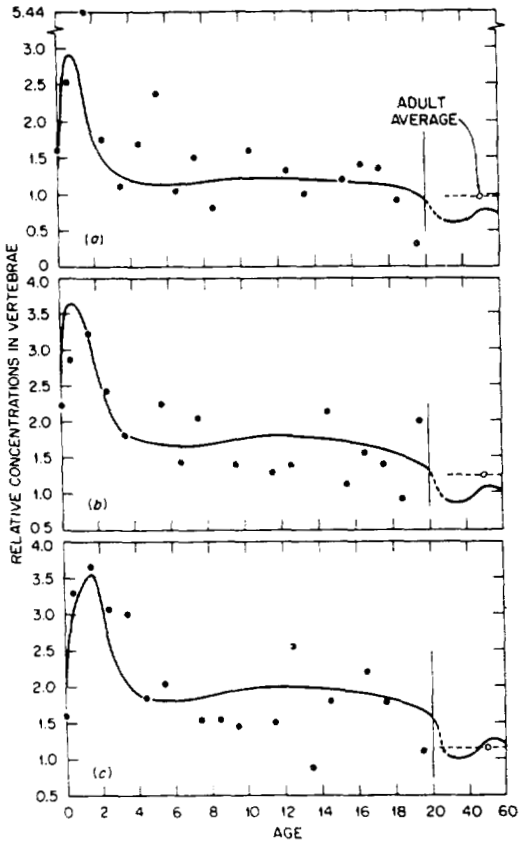

FIG. 3. Comparison of measured and predicted (curve) concentrations of ^{90}Sr in vertebrae for San Francisco populations in 1963 (a), 1964 (b) and 1965 (c) (age in yr).

Highest concentrations of ^{90}Sr in bone are generally measured in infants. In order to allow a more detailed comparison of model predictions with measurements for the first 18 months of life, a kind of "cohort curve" was formed by combining available data for children born in San Francisco from 1968–71 and dying there during that period at age no greater than 18 months (Ri69; Hasl70; Ben71; Ben72b). This forms a relatively large data set that might be representative of a cohort exposed to a relatively constant concentration of ^{90}Sr in food because the measured concentration of ^{90}Sr in food in San Francisco varied only slightly during that period (Table 6). Comparisons of model predictions and measurements for San Francisco for the late 1960s had indicated that the ratio of the ^{90}Sr to calcium quotient in the total diet to that in milk was dropping during that period, so values ranging from 1.0 to 1.5 were tested. Estimates obtained from the model using the two extreme values are shown in Fig. 5. The

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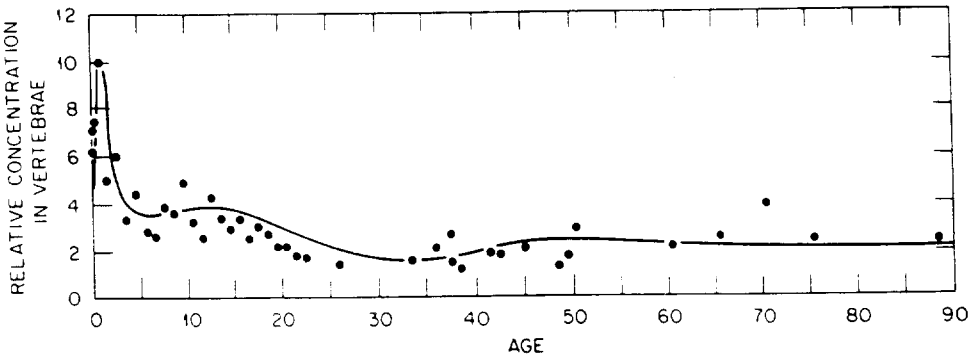

FIG. 4. Comparison of measured and predicted (curve) concentrations of ^{90}Sr in vertebrae for New York population in 1964 (age in yr).

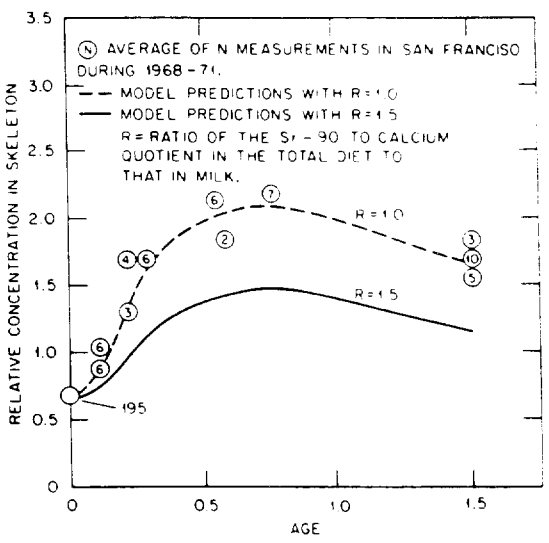

FIG. 5. Measured (circles) and predicted (curves) changes with age (yr) for infants in constructed San Francisco "cohort" during period 1968–71.

predicted curve corresponding to each value seems to have the appropriate shape, but a particularly good fit is obtained using a ratio of 1.0.

SUMMARY AND CONCLUDING REMARKS

The sparcity of nuclide-specific information for different age groups generally precludes the development of age-dependent metabolic models using the empirical fitting techniques that characterize most standard man models. However, in cases where compartments can be made to correspond to physically identifiable processes or subsections within an organ, it may be possible to combine relatively extensive information concerning the development of the human body with generally sparse nuclide-specific information to construct workable age-dependent models. In some cases there may be sufficient data to identify trends with age within compartments using empirical fitting techniques, provided the compartments have already been identified on physical bases. To obtain models that describe changes in a continuous manner from birth through adulthood, it may be necessary in many cases to modify existing adult models to consider fewer (or more easily identifiable) compartments.

In this article we have described an age-dependent model for retention of ingested ^{90}Sr in bone that exemplifies these concepts. The compartments used correspond in essence to those in the ICRP alkaline earth model, except that diffusion (which does not appear to be crucial, at least as a separate component) was omitted for simplicity. As far as possible, estimates of changes with age were based on general physiological con-

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siderations, and nuclide-specific data were used only to supplement information concerning the body's metabolism of calcium. For some components of the model, functions derived from empirical fitting procedures were used to describe trends with age, but none of the components themselves were products of fitting procedures.

The interdependence of physiological processes was taken into account wherever possible. For example, the uptake fractions for ingested calcium and ^{90}Sr were estimated in terms of the total calcium deposited in and removed from the skeleton. This represents only a first approximation to the actual situation, since both elements are probably redeposited in skeleton to some extent after being removed from that organ. However, we chose not to treat recirculation in the model explicitly, for several reasons. In particular, it is difficult to determine to what extent recirculation is already hidden in some components of the model, such as estimated half-times of compartments and the discrimination factor used. More generally, we felt that adequate information was lacking to treat recirculation explicitly.

It should be apparent that, even in the most favorable situations, age-dependent modeling will involve a large number of assumptions that presently find only weak support. However, we believe there will generally be much larger uncertainties arising from the assumption that the world is filled with average adults.

REFERENCES

Bed76 Beddoe A. H., 1976, "Measurement of Trabecular Bone Structure in Man", *Phys. Med. Biol.* **21**(4), 589.

Bed77 Beddoe A. H., 1977, "Measurements of the Microscopic Structure of Cortical Bone", *Phys. Med. Biol.* **22**(2), 298.

Ben71 Bennett B. G., 1971, "Sr-90 in Human Bone—1970 Results for New York City and San Francisco", USAEC Rep. HASL-243, I-99.

Ben72a Bennett B. G., 1972, "Fallout ^{90}Sr in Diet and Human Bone", *2nd Int. Conf. on Strontium Metabolism* (Conf. Pres., C. L. Comar), p. 457 (Springfield, VA: TIS).

Ben72b Bennett B. G., 1972, "Sr-90 in Human Bone—1971 Results for New York City and San Francisco", USAEC Rep. HASL-257, I-51.

Bl75 Bloom W. and Fawcett D. W., 1975, *A Testbook of Histology* (Philadelphia: Saunders).

Br64 Bryant F. J. and Loutit J. F., 1964, "The Entry of Strontium-90 into Human Bone", *Proc. Roy. Soc. B.* **159**, 449.

Co170 Colbert C., van Hulst H. and Spruit J. J., 1970, "A Phalangeal Atlas: An Application of Radiographic Photodensitometry", *Proc. Bone Measurement Conf.*, Chicago (Edited by J. R. Cameron), p. 224, AEC Conf. No. 700515.

Com67 Comar C. L., 1967, "Some Principles of Strontium Metabolism: Implications, Applications, Limitations", *Strontium Metabolism* (Edited by J. M. A. Lenihan, J. F. Loutit and J. H. Martin), p. 17 (New York: Academic Press).

Cr81a Crawford D. J. (to appear) "Identifying Critical Human Subpopulations: Radioactivity in the Lung", *Phys. Med. Biol.*

Cr81b Crawford D. J., "An Age-Dependent Model for the Kinetics of Uptake and Removal from the G.I. Tract", (submitted to *Health Phys.*).

Dur70 Durbin P. W., 1970, "Average Milk and Mineral Intakes (Calcium, Phosphorus, Sodium and Potassium) of Infants in the United States from 1954 to 1968; Implications for Estimating Annual Intakes of Radionuclides", *Health Phys.* **19**, 187.

En63 Enlow D. H., 1963, *Principles of Bone Remodeling* (Springfield, IL: Thomas).

Fl66 Fletcher W., Loutit J. F. and Papworth D. G., 1966, "Interpretation of Levels of Strontium-90 in Human Bone", *Brit. Med. J.* **2**, 1225.

Fr69 Frost H. M., 1969, "Tetracycline-based Histological Analysis of Bone Remodeling", *Calc. Tiss. Res.* **3**, 211.

Ga64 Garn S. M., Rohmann C. G. and Nolan P., Jr., 1964, "The Developmental Nature of Bone Changes During Aging", *Relations of Development and Aging* (Edited by J. E. Birren) (Springfield, IL: Thomas).

Gu71 Guyton A. C., 1971, *Textbook of Medical Physiology* (Philadelphia: Saunders).

HASL70 1970, "Sr-90 in Human Bone—1969 Results", USAEC Rep. HASL-227, II-10.

Ho79 Hofmann W., Steinhausler F. and Pohl E., 1979, "Dose Calculations for the Respiratory Tract from Inhaled Natural Radioactive Nuclides as a Function of Age—I", *Health Phys.* **37**(4), 517.

ICRP72 International Commission on Radiological Protection, *ICRP Publication* 20 (Oxford: Pergamon Press).

1169242

ICRP75 International Commission on Radiation Protection, 1975, *ICRP Publication* 23 (Oxford: Pergamon Press).

Kl79 Klusek C. S., 1979, "Strontium-90 in Human Bone—1978 Results for New York City and San Francisco", USDOE Rep. EML-363, I-125.

Ku62 Kulp J. L. and Schulert A. R., 1962, "Strontium 90 in Man V", *Sci.* **136**(3516), 619.

Kn67 Knizhnikov V. A. and Marei A. N., 1967, "Strontium Metabolism in Man", *Strontium Metabolism* (Edited by J. M. A. Lenihan, J. F. Loutit and J. H. Martin), p. 71 (New York: Academic Press).

La57 Langham W. H. and Anderson E. C., 1957, "Strontium-90 and Skeletal Formation", *Sci.* **126**(3266), 205.

Le67 Lenihan J. M. A., 1967, "Studies in Strontium Metabolism I: Correlation of Strontium-90 Levels in Fetal Bone and Maternal Diet", *Strontium Metabolism* (Edited by J. M. A. Lenihan, J. F. Loutit and J. H. Martin), p. 57 (New York: Academic Press).

Ll71 Lloyd E. and Hodges D., 1971, "Quantitative Characterization of Bone: A Computer Analysis of Microradiographs", *Clinical and Related Research* **78**, 230.

Lo67 Loutit J. F., 1967, "Strontium-90 from Fallout in Human Bone", *Strontium Metabolism* (Edited by J. M. A. Lenihan, J. F. Loutit and J. H. Martin), p. 41 (New York: Academic Press).

Mi45 Mitchell H. H., Hamilton T. S., Steggerda F. R. and Bean H. W., 1945, "The Chemical Composition of the Adult Human Body and its Bearing on the Biochemistry of Growth", *J. Biol. Chem.* **158**, 625.

Ne58 Neuman W. F. and Neuman M. W., 1958, *The Chemical Dynamics of Bone Mineral* (Chicago: University of Chicago Press).

Pa73 Papworth D. G. and Vennart J., 1973, "Retention of Sr-90 in Human Bone at Different Ages and the Resulting Radiation Doses", *Phys. Med. Biol.* **18**(2), 169.

Ri67 Rivera J., 1967, "Predicting Strontium-90 Concentrations in Human Bone", *Strontium Metabolism* (Edited by J. M. A. Lenihan, J. F. Loutit and J. H. Martin) , p. 47. (New York: Academic Press).

Ri69 Rivera J., 1969, "Sr-90 in Human Vertebrae—Results for 1968", USAEC Rep. HASL-210, I-76.

Sh72 Shimmins J. and Smith D. A., 1972, "Discrimination Between Calcium and Strontium in Bone Uptake and Loss", *2nd Int. Conf. Strontium Metabolism* (Conf. Pres., C. L. Comar), p. 389 (Springfield, VA: TIS).

Si62 Sissons H. A., 1962, "Age Changes in the Structure and Mineralization of Bone Tissue in Man", *Radioisotopes and Bone* (Edited by F. C. McLean, P. Lacroix, A. M. Budy), p. 443 (Oxford: Blackwell Scientific).

SM66 *Strontium Metabolism*, 1966 (Edited by J. M. A. Lenihan, J. F. Loutit and J. H. Martin) (New York: Academic Press).

SM72 *2nd Int. Conf. Strontium Metabolism*, 1972, CONF-720818 (Conf. Pres., C. L. Comar) (Springfield, VA: TIS).

Sm72 Smith D. A., Aitken J. M., Anderson J., Shimmins J. and Nordin B. E. C., 1972, "The Skeletal Uptake of Sr-85 in Relation to Age and Bone Loss in Women", *2nd Int. Conf. Strontium Metabilism* (Conf. Pres., C. L. Comar), p. 413 (Springfield, VA: TIS).

UN77, UNSCEAR, 1977, "*Sources and Effects of Ionizing Radiation*", (New York: United Nations).

Va75 Vaughan J. M., 1975, *The Physiology of Bone* (Oxford: Clarendon Press).

Vi69 Virtama P. and Helela T., 1969, "Radiographic Measurements of Cortical Bone—Variations in a Normal Population between 1 and 90 Years of Age", p. 293, *Acta Radiologica, Supplementum.*

Wo67 Wolanski N., 1967, "Changes in Bone Density and Cortical Thickness for the Second Metacarpal Between the Ages of 3 and 74 Years as a Method for Investigating Bone Mineral Metabolism", *Acta Anat.* **67**, 74.

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