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R. Hattner

Harold M. Frost

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MEAN SKELETAL AGE: ITS CALCULATION, AND THEORETICAL EFFECTS ON SKELETAL TRACER PHYSIOLOGY AND ON THE PHYSICAL CHARACTERISTICS OF BONE*

R. HATTNER, B.S.*** AND H. M. FROST, M.D.****

INTRODUCTION

In this report mean skeletal age will be defined, methods of calculating it given, and applications of this idea to skeletal tracer physiology, bone remodelling and bone physical characteristics discussed.

Some peculiarities of the physical characteristics of bone that are probably related to the present theme will be discussed later in this text.

It is known that bone seeking tracer ions such as Ca^{45} transfer from blood to bone and conversely.[2,5,22] Some of the tracer seems to become immobilized in the stable skeletal mineral mass, some appears to remain highly mobile, and some of the skeletal mineral seems to be unavailable to the tracer.[2,31,34,35] Only part of the tracer transfer between bone and blood occurs as the direct result of, and is therefore driven by, bone resorption and formation. The other part of the transfer seems to be due to a group of processes that are physical-chemical in nature and are not driven directly by bone resorption and formation.[31] Unknown factors at present are (a) the proportionality between tracer transfer that is cell mediated by resorption and formation, and the transfer that is not,[27] and (b) the nature of the major rate determining physical-chemical transfer systems. This ignorance impairs present ability to interpret tracer-based studies of skeletal physiology in animals and in man.

Before accurate interpretation of tracer based skeletal physiological studies can be made the following problems must be solved and characterized quantitatively: (a) the amount of mineral deposited as an essential part of bone formation per day;[2,40] (b) the amount of mineral solubilized by bone resorption per day;[2,13,40] (c) normal and pathological changes in mean skeletal age;[13] (d) the relationship between mean skeletal age and mean skeletal diffusion impedance;[13,14] (e) the relationship between

*From the Orthopedic Research Laboratory.
***Wayne State University, College of Medicine.
****Associate Orthopedic Surgeon.

mean skeletal diffusion impedance and tracer transfer; (f) the nature of changes in crystallite size, in the nonapatite mineral phase and in surface composition of the mineral, and their effects on tracer fixation;[26,31,36] (g) the effect of the microanatomy of bone on mixing between blood and lacunar fluids,[17] and the effect of osteocytes on this mixing.[13]

This report concerns mean skeletal age.

MEAN SKELETAL AGE

The mean skeletal age is the weighted mean (according to size) of the ages of all the moieties of bone which comprise the skeleton. All skeletons are composed of many separate bits or moieties of bone formed at separate times and welded together at and by cement lines.[20,29,39] Bone remodelling is responsible for the fact that the chronological age of the person is different from the mean age of his skeleton. This is true because at any moment there are moieties of bone just completed, others completed weeks, others months and others years before the moment of observation. If there were no remodelling then the mean age of the skeleton would be the same as the owner's chronological age. If remodelling were infinitely fast the mean age at any moment would be zero.[13] These two hypothetical situations establish the limits between which real mean ages are to be found, and also indicate that the mean age is determined by the remodelling rate.

SKELETAL MEAN MINERALIZATION DENSITY

Bone remodelling is the bone resorption and formation which normally occur throughout life in the lamellar skeleton. Bone formative activity occurs in physically discrete and accurately measurable sites termed *foci*.[13] The new lamellar matrix formed by lamellar osteoblasts spends the initial 14 days of its life unmineralized while, presumably, chemical and steric changes are going on in it which will enable it to mineralize.[10] When this matrix begins to mineralize it deposits roughly 70 per cent of all the mineral it can ever accept in the first 4 days, and roughly 20 per cent of its potential mineral load in the first day.[1,10,30,38] Additional mineral is added daily, weekly and monthly at progressively decreasing rates.

In other words mineralization of new lamellar bone matrix decreases in rate with time and so is a function of time or the age of the matrix. The highest mineral densities observed are found in the oldest extra Haversian bone in cortex.[29] As far as is now known the mineralization of lamellar bone is progressive with time, and not regressive, at least in normal bone.

It is intuitively evident that just as a skeleton has a mean age, so it must also have a mean mineralization density which is the weighted average of the mineralization densities of all of the moieties of bone in the skeleton.

Therefore the mean mineralization density is a function of mean skeletal age.

MEAN MINERALIZATION DENSITY AND TRACER DIFFUSION

On theoretical grounds diffusion of tracer into and out of the skeleton should be affected by (among other things) the mineralization density of the bone. This effect should be such that with increasing mineralization density there should be an increasing resistance to diffusion and conversely. Term resistance to diffusion *diffusion impedance.*[14]

We believe that the diffusion impedance which characterizes high mineral density bone (meaning by density grams of inorganic solids per ml. of matrix, absolute bone volume) is a major determinant to skeletal tracer uptake, that the bulk of this uptake is isoionic exchange, and that diffusion impedance is a rate limiting factor which sets an upper bound to the amount of tracer that can diffuse through a given path length of bone in unit time with unit serum concentration of tracer.[13,28] If this were true it could immediately be predicted that tracer uptake would be least in the most highly mineralized bone, and maximum in the most poorly mineralized bone. Such are the empirically observed facts.[11,14,34,35]. These facts have previously been explained in terms of effects of crystal size, surface effects of trace elements and so on. Certainly such effects probably do play a role in governing the rate of tracer transfer between bone and blood. It is our opinion that these effects have been assigned exaggerated importance however.

The diffusion path through bone for the average tracer ion is roughly 5 microns, assuming good mixing between lacunar and perivascular fluids.[16] In this text specific ion effects are ignored, and for this reason nothing will be said about the peculiarities of certain tracers such as plutonium, yttrium or strontium.[23,24]

If mean skeletal age is a determinant of mean skeletal mineralization density, and mean density is a determinant of mean skeletal diffusion impedance, and diffusion impedance is a determinant of tracer transfer between bone and blood, then mean skeletal age is a determinant of skeletal tracer physiology. While there seems to be little reason to question this line of reasoning, the *importance* of the effect of mean skeletal age on tracer transfer into and out of the skeleton remains to be empirically established.

CALCULATION OF MEAN SKELETAL AGE

In histological material we have noted that the distribution of sites of bone remodelling activity is not uniform from person to person. In one mode of distribution, sites of remodelling are spread evenly through the bones examined and the newer bone is avoided. This is arbitrarily termed *linear distribution* of remodelling activity because its curves plotted against time are the results of linear functions. In another, commoner mode of remodelling distribution the newer bone is as likely to be remodelled as its proportional amount is to the whole amount of bone present. This is termed *probabilistic distribution.* There is yet a third but less common mode which will be referred to in the Discussion.[15]

These observations indicate that there are several mechanisms governing the distribution of remodelling activity, and that in some people an unbalanced predominance of one may occur.

The effect of a given amount of remodelling activity on skeletal mean age and on the physical characteristics of the bone is significantly affected (on paper!) by the mode of distribution of remodelling foci.[13] Accordingly two models for calculating the mean age are presented, one based on linear distribution, the other based on probabilistic distribution.

In the following models it is assumed that the adult skeleton is being dealt with, that the amount of bone in this skeleton remains constant during the period of observation and calculation, and that the specified bone formation rates remain constant during the period of observation.[33,37] It is furthermore assumed that the mean age of the skeleton at the beginning of observation is zero. Some of the computational complications avoided by these assumptions will be dealt with in separate publications. A table of the symbols used is given at the end of this section of the text.

LINEAR REMODELLING DISTRIBUTION

In this model it is assumed that only the oldest bone is selected as the site for new remodelling activity. A given amount of new bone formed implies that previously a like amount of older bone was removed to create space for the new. Amounts of bone are in terms of absolute bone volume and here given the symbol V.[8,13]

The mean age (T_{mo}), of any amount of original bone (V_o) remaining after (t) years is (t). This may be written in symbols

$$T_{mo} = t \tag{1}$$

Make (k) the bone formation rate and equal to the decimal part of the original amount of bone duplicated as newly formed bone per year.[8,13] It will be assumed that the bone resorption rate equals the formation rate so that a given amount of bone formed is matched by a like amount resorbed. This corresponds closely to events in real adult skeletons. Under these circumstances the amount of new bone formed in any span of (t) years is the original amount (V), times (t) times (k), or:

$$V_n = Vkt \tag{2}$$

where (V_n) is the amount of new bone formed in time (t).

It is intuitively evident that the mean age of the new bone in equation (2) is (t/2), since at that moment half of the new bone would have been formed before, and half would be formed afterwards. This is true only as long as the bone formation rate and the total amount of bone remain constant, and only as long as new bone is not itself subject to remodelling. The same result may be derived from the mean value theorem of calculus applied as follows:

$$T_{mn}\Big]_{t_o}^{t} = f(x)\Big]_{t_o}^{t} = \frac{1}{t\text{-}to}\int_{t_o}^{t} f(x)\,dx \tag{3}$$

where (T_{mn}) is the mean age of the new bone, (t_o) is time at the start, and (t) at the end of the period of observation. Integration of equation (3) yields:

$$T_{mn} = \frac{1}{t\text{-}to}\left[\frac{T^2}{2} - \frac{T_o^2}{2}\right] \tag{4}$$

where (T) and (T_o) are the ages at times (t) and (t_o) respectively. By setting (T_o) equal to zero and cancelling out one obtains

$$T_{mn} = \frac{t}{2} \tag{5}$$

Any time after the beginning of observation the whole bone will be composed of two parts: the original bone remaining unremodelled (V_o), and the new bone formed since the beginning of observation (V_n). The mean age of the whole amount of bone (V) will thus lie somewhere between the extremes of the mean ages of the old bone and of the new. Divide the amounts of original and new bone by the total amount, and call these fractions the volume-fractions. If these are multiplied by their respective mean ages and the sum of the two products taken the result will be the mean age of the whole bone. In symbols:

$$T_m = \frac{Vo}{V}t + \frac{Vn}{V} \cdot \frac{t}{2} \tag{6}$$

The amount of new bone is calculated according to equation (2). The amount of original bone remaining is the whole bone minus the new, or

$$V_o = V - V_n \tag{7}$$

The adult skeleton does not increase in amount (in fact the converse is true) with time no matter how fast or how long bone formation occurs, because there is a like amount of resorption. To make equation (6) valid it is necessary to impose a constraint accounting for the fact that the amount of old bone remaining cannot be less than zero:

$$V - V_n \geqq 0 \tag{8}$$

Furthermore the amount of new bone cannot exceed the total amount of bone originally present, leading to another constraint in the form of another inequality:

$$V_n \leqq V \tag{9}$$

This is equivalent to saying that when the whole bone is composed of new bone the mean age reaches an asymptotic (constant) value which is identified by this inequality:

$$T_m \leqq \frac{1}{2k} \tag{10}*$$

By substituting equations (2,7) into (6) one obtains

$$T_m = \frac{V\text{-}Vkt}{V}t + \frac{Vkt}{V} \cdot \frac{t}{2} \tag{11}$$

This may be simplified to obtain, with the necessary constraints:

$$T_m = (t\text{-}kt^2) + \frac{(kt^2)}{2}$$

Where: $V_o \geq 0$; $T_m \leq \frac{1}{2k}$ (12)

*In limit form: $\underset{Vn \rightarrow V}{\text{Lim}} (T_m) = \frac{1}{2k}$

In figure 1 a graph of mean skeletal age over a four decade spread of bone formation rates is shown. The calculations are listed in Table I. The calculations are made from equation (11).

PROBABILISTIC REMODELLING DISTRIBUTION

In this model it is assumed that new bone is as likely to be remodelled compared to old as the fractional volume of new bone is to that of the old. Thus if there is 15 per cent new bone in the whole bone, 15 per cent of the remodelling activity will occur in the new bone. The rate of aging of the old bone is still (t) so that its mean age is still the age at the moment of observation. Because the new bone in this model also undergoes remodelling, the remodelling of the old bone becomes progressively less efficient, and its decrease in amount with time is nonlinear. Derivation of an equation for calculating the mean age in this remodelling distribution mode may be approached as follows:

When a substance is removed at rate (k) with respect to time, the amount remaining at any time (t) is given by the expression

$$V_o = Ve^{-kt} \quad (13)$$

where the symbols have their previous meaning and (e) is the base of Naperian logarithms. Note that the bone formation rate (k) is used here in the sense that it destroys original bone rather than in the sense that it creates new bone. The

Table I

	Age Years	5	10	20	30	40	50	60	70
k									
1.0	Tm	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Tmn	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
.1	Tm	3.75	5.0	5.0	5.0	5.0	5.0	5.0	5.0
	Tmn	2.5	5.0	5.0	5.0	5.0	5.0	5.0	5.0
.01	Tm	4.87	9.5	18.0	25.5	32.0	37.5	42.0	45.5
	Tmn	2.5	5.0	10.0	15.0	20.0	25.0	30.0	35.0
.001	Tm	4.98	9.95	19.8	29.5	39.2	48.7	58.2	67.5
	Tmn	2.5	5.0	10.0	15.0	20.0	25.0	30.0	35.0

Mean skeletal age values based on the linear model in the text and calculated according to equation (11). The mean ages are in years; the curves reach asymptotes for bone formation rates of 1.0 and 0.1. (k) = bone formation rate, or the decimal part of the bone duplicated as newly formed bone per year. Tm is the mean age of the whole bone, while Tmn is the mean age of the new bone only.

proportional amount of the whole bone composed of new bone at any time will then be the whole amount of bone minus the old bone or

$$V_n = V - Ve^{-kt} \tag{14}$$

The mean age of the old bone remaining unremodelled is still

$$T_{mo} = t \tag{15}$$

The volume-fraction of the old bone remaining is still $\frac{Vo}{V}$, as in equation (6), and its age-volume-fraction is still $\frac{Vo}{V}t$. If the mean age of the new bone is T_{mn}, then the mean age of the whole bone is still

$$T_m = \frac{Vo}{V}t + \frac{Vn}{V}T_{mn} \tag{16}$$

The problem remaining is to calculate the mean age of the new bone. This is the moment in time when equation (14) has half of its value at the moment of observation. Identifying by T_{mn} the moment in time considered to be the mean to be the mean age of the new bone we write, using equation (14):

$$\frac{Vn}{2} = V\text{-}Ve^{-kT_{mn}} \tag{17}$$

By progressive rearrangements and simplifications we obtain:

$$\frac{Vn}{2} = V(1\text{-}e^{-kT_{mn}})$$

$$\frac{Vn}{2V} = 1\text{-}e^{-kT_{mn}}$$

$$-e^{-kT_{mn}} = \frac{Vn - 2V}{2V}$$

$$e^{-kT_{mn}} = -\frac{Vn\text{-}2V}{2V}$$

$$-kT_{mn} = -\ln(2v\text{-}Vn)\text{-}\ln(2V)$$

$$T_{mn} = \frac{\ln(2v\text{-}Vn)\text{-}\ln(2V)}{-k} \tag{18}$$

In figure 2 the change in mean age with the same four-decade spread in bone formation rates as in figure 1 is outlined. In Table II the individual values obtained from equations (16,18) are listed. The solution of equation (18) is greatly simplified if V and V_n are used in their normalized form. (V) will then disappear since its value is one; this number must be substituted in its place. (V_n) is given as a decimal part of (V).

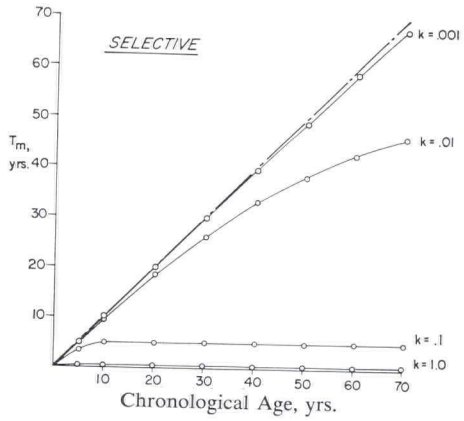

Figure 1

A chart of the mean ages plotted against chronological age of the person for the case of linear remodelling distribution. A four decade range in bone formation rates is covered. The rates are noted beside the curve of mean age produced by each. The change in mean skeletal age caused by changing from the lowest rate plotted to zero remodelling, or from the highest rate plotted to infinitely fast remodelling, is insignificant.

Table II

	Age	5	10	20	30	40	50	60	70
k									
	Tm	0.685	0.693	0.693	0.693	0.693	0.693	0.693	0.693
	Tmn	0.689	0.693	0.693	0.693	0.693	0.693	0.693	0.693
1.0									
	Vo	0.005	0	0	0	0	0	0	0
	Vn	0.995	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	Tm	4.33	6.1	6.59	6.6	7.38	6.87	6.89	6.92
	Tmn	2.2	3.8	5.6	6.4	6.7	6.9	6.9	6.93
0.1									
	Vo	0.6	0.37	0.14	0.05	0.02	0.006	0.002	0.001
	Vn	0.59	0.63	0.86	0.95	0.98	0.99	0.99	0.999
	Tm	4.8	9.5	18.1	25.8	32.7	38.9	44.5	49.3
	Tmn	2.8	5.0	9.6	13.9	18.1	21.9	25.6	28.9
0.01									
	Vo	0.95	0.9	0.82	0.74	0.67	0.61	0.55	0.49
	Vn	0.049	0.096	0.18	0.26	0.33	0.39	0.45	0.50
	Tm	4.9	9.0	19.8	29.5	39.3	48.8	58.3	67.6
	Tmn	3.0	5.0	10.0	15.0	20.0	25.0	30.0	35.0
0.001									
	Vo	0.995	0.99	0.98	0.97	0.96	0.95	0.94	0.93
	Vn	0.005	0.01	0.02	0.03	0.04	0.05	0.06	0.07

Mean skeletal age calculated according to equation (16) for the probabilistic model. The mean age is Tm; the other symbols have the meaning given in the list of rotation and described in the text. Note the difference between Tmn in Table I and here, aspecially in the decade 0.1 — 1.0 for (k).

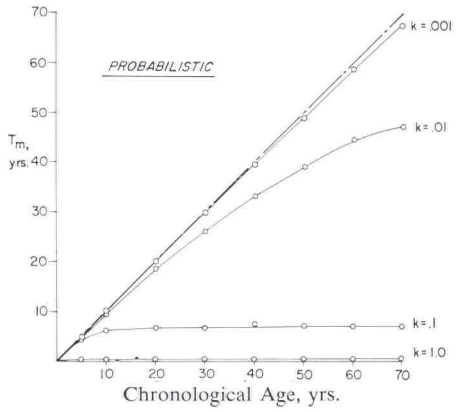

Figure 2

A chart of mean age calculated according to probabilistic distribution of remodelling foci, using the same four decade spread of bone formation rates as in figure 1.

Mathematical Notation

e: Base of Naperian logarithms.

k: Bone formation rate, defined as the decimal part of an original amount of bone duplicated as newly formed bone per year.

ln: Logarithm to the base (e).

t: Time in years.

T: Age of some part of a bone.

T_m: Mean age of the whole bone.

T_{mo}: Mean age of the original bone remaining.

T_{mn}: Mean age of newly formed bone.

V: Volume of the whole amount of bone.

V_o: Volume of the original bone remaining.

V_n: Volume of newly formed bone.

Discussion

Several features and applications of the foregoing material warrant some comment.

LAG IN MEAN AGE RESPONSE TO BONE FORMATION RATE CHANGE

The mean age of a skeleton will change slowly in response to sharp changes in the bone formation rate. The chief reason for this is the overwhelming bulk of the stable skeleton compared to the amount of it that is being remodelled at any moment. Doubling the bone formation rate changes the absolute value of the proportion of the skeleton undergoing remodelling by a small fraction of a per cent per day.

Accordingly the observed mean skeletal age is a time-averaged value dependent on the bone formation rate over some months prior to the day of observation, and

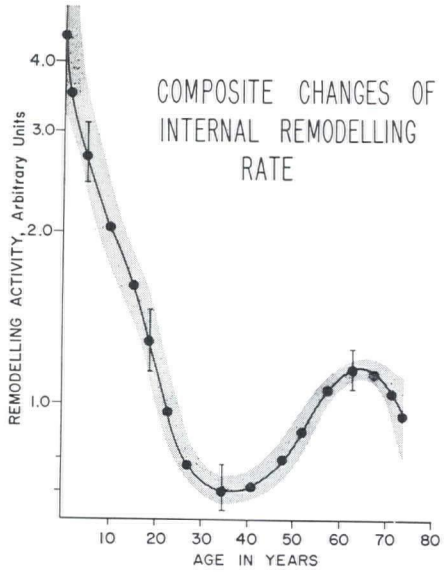

Figure 3

A chart of the changes in bone remodelling rate with age in normal human ribs. This is a composite of a number of different indices of remodelling activity. The changes shown are statistically highly significant ($p<.02$). Note that remodelling activity is at a minimum at about age 35, and that it increases thereafter. Note also that the (Y) axis is logarithmic so that the increase in remodelling after age 35 is magnified thereby.

relatively independent of the bone formation rate on the day of observation. Tracer transfers in in vivo studies would be similarly dependent on the bone formation rate over previous months, and little affected by the bone formation rate on the day of observation. Bone formation rate is used here in its most literal sense. This stand represents a sharp disagreement with the orthodox interpretations of skeletal tracer studies in many respects. We have other, factual as opposed to theoretical, grounds for this disagreement.[9,10]

It may be pointed out that the problem created by the lag in response of mean age to changes in bone formation rate is solved simply by delaying tracer studies until the treatment or pharmacologic agent being tested has had several months in which to do its work.

NONLINEARITY OF RESPONSE OF MEAN AGE TO CHANGE IN BONE FORMATION RATE

The curves in figures 1, 2 and 4 indicate that in the median range of values plotted a given increment in bone formation rate causes a much larger change in mean skeletal age than the same increment does at the extreme rate ranges. Significantly, an approximate, normal bone formation rate for a 40 year old adult is 0.02, based on measurements of tetracycline labelled bone by one of us.[9] As figure 4 suggests, this places the normal bone formation rate in the range where any change

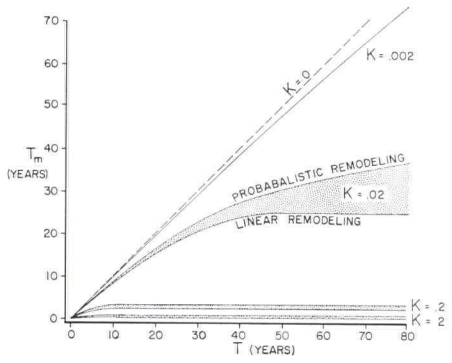

Figure 4

In this chart a different four decade spread of mean ages is plotted, ranging from 2.0 - 0.002. Both linear and probabilistic distributions are plotted, and the shaded areas between curves show the difference in mean age caused solely by the difference in the method of distributing the remodelling activity. This difference is maximal in the central area when the bone formation rate is 0.02. This coincidentally happens to be the approximate bone formation rate for 40 year old adults. Note that there is little difference between the mean ages calculated according to either model for bone formation rates smaller than 0.002 and larger than 0.2.

would cause proportionately the largest possible change in mean skeletal age. Any characteristic change in tracer physiology and in the physical characteristics of bone accompanying a change in mean skeletal age should therefore exhibit a similar sensitivity to changes in the bone formation rate.

This nonlinearity of response of mean skeletal age to changes in bone formation rate is probably the reason for the fact that the observed change in bone formation rate between the ages of 2 and 35, which is on the order of 75 - 1,[10,13] is accompanied by changes in tracer physiology and physical characteristics of much smaller magnitude.[16] The location of normal bone formation rates in the part of the mean age "spectrum" which is most sensitively responsive to change in rate probably partly explains the effects of Cushing's syndrome and thyrotoxicosis on tracer physiology,[5,22,32,40] on the physical characteristics of bone[6] and on the fatigue susceptibility of bone.[6,18]

DEPENDENCE OF MEAN AGE ON DISTRIBUTION OF REMODELLING FOCI

Figure 4 particularly indicates that there is a significant difference in the mean skeletal age depending on whether the remodelling foci are distributed according to the linear or the probabilistic model. This difference exists in the face of identical bone formation rates. We know very little about these differences in distribution of remodelling foci, other than that they exist, chiefly because it had not occurred to us that they merited study until we began the preparation of this report.

It is notable that the maximum sensitivity of mean age to change dependent on linear or probabilistic distribution exists near the median range where real bone formation rates lie. At the extreme ranges of bone formation rates there is little effect of change between linear and probabilistic models on mean age. Mean ages

are younger for the linear model than for the probabilistic one; some of the remodelling in the latter is "wasted" on young bone.

There is a third mode of distribution of remodelling activity which we have observed occasionally. In this mode the remodelling activity centers around fixed foci in the cortex, so that while reasonably normal amounts of new bone may be formed, it is formed in physically small, frequently remodelled regions. As a result the bulk of the bone largely escapes remodelling and becomes more highly mineralized than normal, simultaneously exhibiting typical aging features such as large numbers of empty lacunae, of mineral-plugged canaliculae and lacunae,[12] and of microcracks.[18] More will be said of this phenomenon later.

RELATIONSHIP OF BONE FORMATION RATE TO TRACER PHYSIOLOGY

An increase in mean skeletal age is accompanied by poorer diffusion of tracer through bone and thus less rapid mixing between blood and bone. Even were there no accompanying change in the number of crystallites per unit amount of bone with an increase in mean skeletal age (there probably is an actual increase in numbers of crystallites), the resulting impairment of diffusion should lead to poorer skeletal uptake of tracer, and slower back exchange of fixed tracer back to the blood. The converse is also true. Whether these concepts represent the correct explanation or not, this is the behavior that is observed in practice by numerous investigators working with numerous techniques.

The change in *numbers* of crystallites accompanying changes in mean mineralization density are such as to oppose the effects of the density changes on diffusion. This suggests that our concepts of the roles of diffusion impedance, mean mineralization density and mean age are correct, being of sufficient magnitude to overcompensate for the accompanying but opposing changes in numbers of crystallites.

For the above reasons plus those previously adduced it is reasonable to conclude that increased mixing between bone and blood of a bone seeking tracer is the ultimate result of an increase in the bone formation rate, and conversely. It must be remembered that this increase must have existed for some months (exact number not specified) before the moment of observation. Since new lamellar matrix requires about 14 days to become ready to mineralize,[10,25] it may be stated with some confidence that the bone formation rate in the 14 day period preceding a tracer study cannot affect the tracer study. Any changes seen in this period of time must be almost if not wholly due to effects of the experimental or therapeutic situation on diffusion impedance, on resorption or on accretion, but not on new bone formation. Accretion designates the progressive increase in mineralization of already partly mineralized bone. If the mineral deposited *only* in the first day of mineralization of new matrix is considered apart (as being a cell-mediated transfer) then the remainder of the mineral this matrix will accept is deposited as part of the accretion process. Accretion is for the most part independent of the existence and metabolic activity of active osteoblasts.

While an increase in mixing may be interpreted as being the result of an increase in new bone formation over previous time, the exact amount of the increase cannot be deduced from available published data.

There is an important exception to this interpretation which is in itself strong evidence of our belief that diffusion impedance effects on isoionic exchange, and not accretion or bone formation, is a major direct determinant of tracer mixing and uptake in the skeleton. This exception is the osteomalacic skeleton. Most (but not all) osteomalacic skeletons have increased amounts of low density bone as the result of a mineralization defect whose origin at the moment is unimportant. We know from study of a considerable amount of tetracycline labelled human osteomalacics that the bone formation rate in these cases is usually pronouncedly depressed.[15] It is also known that tracer mixing and uptake in these cases is considerably increased. This increase must be the result of improved diffusion through large amounts of low density bone, the tracer ions fixing in the stable mineral mass by several or all of the possible mechanims known or postulated to account for this fixation.

Interpretation of tracer based studies of skeletal physiology must therefore be done after the presence or absence of an osteomalacic state has ben established. Serum chemical studies are not an adequate basis for such a decision, since osteomalacic states may exist without detectable changes in the usual serum chemical values of calcium, ionized calcium, phosphorus and alkaline phosphatase.[7,13] The only currently available conclusive method of ruling out an osteomalacia known to us is examination of iliac crest biopsy by means of undecalcified sections prepared and stained by special methods. (9,10) Decalcified sections will not suffice.[13]

MEAN SKELETAL AGE AND THE PHYSICAL CHARACTERISTICS OF BONE

It is known that the bone of children is more elastic and weaker in compression and in shear than that of adults.[4,6] It is also known that children's bone is less highly mineralized than adults, whether the basis of measurement be the ratio of ash to mass at constant weight at constant temperature, or the ratio of nitrogen to ash.[6] One of us has presented elsewhere measurements of the bone formation rates of children and adults.[9,13] It has already been mentioned that at age 2, bone formation is about 75 times more active than it is at age 35.

It is reasonable to deduce that a major determinant of the change in physical quality of bone betwen childhood and adult life is the change in mean skeletal age and its occompanying change in mean mineralization density. When quality is discussed here it is done so in terms of unit quality rather than the quality of the whole bone, since the latter is also determined by the absolute amount of bone present.[6]

It is observed fact that adult bone is more brittle, more susceptible to notch effects and more fatigue susceptible than is children's bone.[3,4,6] We believe that these qualities too are determined to a major degree by the mean skeletal age and the subsidiary properties of bone determined in turn by it.

Even the mode of distribution of remodelling foci should theoretically lead to corresponding changes in the physical properties of bone. For example in the linear remodelling case the bone as a whole is relatively homogeneous; only small parts of it escape remodelling and so have the opportunity to become unusually old, brittle and fatigue sensitive. Such bone should be relatively strong in tension, compression and shear.

In the probabilistic remodelling mode some of the remodelling activity is wasted on new bone, so that a given amount of remodelling activity is less effective as an agent removing very old bone and replacing it with young, new bone.

It is known that bone formation rates may vary widely in different parts of the same bone.[19,21] This suggests that different parts of the same bone might have differing mean ages and physical characteristics where such are determined partly or mostly by mean age. It is possible that some of the known variability in physical characteristics of test specimens taken from different parts of the same bone[6] arises from differences in mean age. Mean age differences would be difficult to recognize by any currently available and practicable technique so that to most methods of examination there would seem to be no significant explanatory differences between the various test specimens to explain their differences in behavior under physical load.

In the occasional person in whom remodelling is centered around fixed foci the bone becomes a two-phase solid at the histological level, with the older part being continuous as well as unusually brittle, notch sensitive and fatigue sensitive.[15] The younger part is discontinuous in phase, although highly elastic, notch resistant and fatigue resistant. Such a two-phase solid is unusually fragile, in contrast to the case when the most elastic phase is the continuous one and the brittle phase the discontinuous one.[3]

Summary

Mean skeletal age is the weighted mean of the ages of all of the moieties of bone in a skeleton. The man mineralization density (in grams of inorganic solids per ml. of absolute bone volume) is partly determined by the mean skeletal age. The resistance to diffusion experienced by tracers being transferred into or out of bone is determined in part by the mean mineralization density. The amount of tracer transferred between bone and blood is determined to a major degree (the authors hypothesize) by the diffusion resistance, termed diffusion impedance.

Therefore the mean skeletal age is a determinant of the physiology of bone seeking tracers. Increasing mean skeletal age decreases tracer transfer between bone and blood.

Methods of calculating mean skeletal age are outlined. By chance the greatest sensitivity of mean skeletal age to change in the bone formation rate (which ultimately determines the mean skeletal age) lies in the range of normal 40 year old human bone formation rates.

Differences in the method of distributing sites of new bone formation lead to significant differences in mean skeletal age. Some known differences in physical characteristics of bone appear to be attributable largely or partly to differences in mean skeletal age.

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