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NORMAL HISTOLOGICAL, TETRACYCLINE AND DYNAMIC PARAMETERS IN HUMAN, MINERALIZED BONE SECTIONS*

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I: Introduction

Bone is a living, dynamic and durable record, whose past events are recorded in a unique symbology. It is formed and destroyed in characteristic ways by specific cells responding to control factors of diverse intracellular, local extracellular and systemic origin.[3] Major departures from the normal imprint and leave behind evidence of their occurrence, their time and their magnitude.[40] This record can be translated with the aid of mineralized sections, a tissue time marker and dynamic concepts that were developed with the aid of cybernetic analysis.[13,17,18]

This report summarizes the major normal histological and histodynamic parameters that are part of the human bone record, which help to translate it, and which let diseased bone be compared to healthy bone in meaningful numerical terms. The material is divided into studies of the bone tissue's envelopes, remodeling, and cell population dynamics. The specific studies made to define these parameters are discussed only briefly. Before giving the results, the sampling problem posed by bone, and the composition of our "library" of normal bone will be discussed.

II: The Standard Bone Approach

The variances encountered in bone make it necessary to study it by what we term the *standard bone approach*.[13,15,25] The middle thirds of the 5th, 6th, 7th, or the anterior 5 cm of the 11th rib, are the standard bones used in this laboratory since 1955. The approach involves these steps: (*i*) the subject is of known health and age; (*ii*) his skeleton is sampled at a standard site; (*iii*) his measurements are pooled with those of other patients of the same health and age and similarly sampled, to obtain a group mean; (*iv*) comparisons are made with norms similarly obtained (*v*) so that their disease is studied primarily.

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Normal dynamic parameters of bone must be defined on three different bone surfaces. These surfaces are most naturally conceived as *envelopes.*[15] With minor exceptions, this report concerns studies of only one of them — the haversian envelope. Remodeling on this bone surface has variously been called internal remodeling,[13] osteonal remodeling, haversian remodeling and intracortical remodeling.

III. Case Material

A) *Patients:* Standard rib samples have been collected from 209 males and 117 females, whose ages span from birth to 98 years. These 326 people were considered *metabolically normal.** They yielded bone either because they died suddenly and unexpectedly, or because they had thoracotomies for problems that did not involve systemic or metabolic illness. It was intended that 20 males and 20 females be obtained in each age decade up to age 70. As Table I** shows, we were not able to do this in all decades.

Table I

Age Range	Mean Age for Males	Number of Male Subjects	Mean Age for Females	Number of Female Subjects
0-4	1.2	19	1.3	14
0-10	2.9	25	2.8	18
11-20	15.3	14	17.0	6
21-30	24.5	29	25.0	20
31-40	35.7	29	34.0	23
41-50	44.2	31	44.1	22
51-60	54.5	33	58.9	30
61-70	64.3	23	71.0	14
71+	73.8	23		

Sex and ages for the 326 Normal subjects in the laboratory's "library" of normal rib.

One hundred fifty of these patients had received tetracycline one or more times before death[54] (found by examining their bone sections with the fluorescence microscope), 26 of them at known times and for known durations so that the critical factor of new bone added to surfaces of osteogenetic sites per year could be measured.

The results obtained in this normal material have been compared with results found in bones from more than 1,000 persons with a wide assortment of diseases, both treated and untreated.

B) Biopsy: Our preferred biopsy site is the anterior 5 cm of the 11th rib.[62] The biopsy is done under local anesthesia (78 have been done at present), and there is surprisingly little morbidity. Eight patients have readily assented to a second biopsy after a period of prescribed treatments. This is in contrast to the considerable

*In the sense that autopsies did not show changes that would be unexpected in at least 50% of the cases of accidental death in the same age group in any county medical examiner's office.

**We are greatly in debt for this material to Drs. R. Horn, G. Fine, R. Tabor, C. Lam, E. S. Lam, E. S. Zawadski and M. Raven.

discomfort after iliac crest biopsy. Five small pneumothoraces have been encountered. Since the visceral pleura is not damaged, the wound is closed promptly without other treatment. Chest tubes were unnecessary, and in 4 patients the other side was successfully biopsied five days later.

C) Autopsy: In autopsied subjects, the sampling site has been the middle third of the 6th rib. While remodeling parameters are similar in the 6th and 11th rib, their cortical, total and marrow cross section areas cannot be directly compared. Such norms have yet to be established for the 11th rib. We no longer do iliac crest biopsies because of its large variances, which require a prohibitive number of samples to achieve useful levels of statistical significance. This site has no other major disadvantage, and good work has been done with it.[56,61,80]

D) In Vivo Labeling Technique: A dual label is recommended that is called locally the 3106 (thirty-one-O-six).[60,72] This consists of a three-day course of tetracycline, followed by 10 days without it, followed by six more days on it. Biopsy should then be done more than one, but less than three weeks after the second label. This procedure lets mineralizing matrix completely incorporate the second band without disappearance of the osteoid seams, which would make it hard to distinguish the new from any old, previously labeled osteons. Demethylchlortetracycline is preferred, 900 mg/day orally in divided doses for adults. Gram for gram, it gives brighter labels than the other tetracycline antibiotics we have evaluated.[30] If the patient is known to be osteomalacic, it is better to have the two labels separated by 20 to 60 days. Such long interband intervals should not otherwise be employed because they create a sampling problem that cannot readily be corrected,[72] but it is too complex to discuss here.

E) Sections: Sections for tetracycline work should be fresh and undecalcified, without embedding or fixation.[19,20] If osteomalacia is present and the label is too recent, prolonged staining or embedding in certain plastics removes the tetracycline. This could create the false impression that it was not deposited.[48] Sections should be stained, for only then, and only with the resolution of the light microscope, can the observer be certain that all seams and Howship's lacunae will be identifiable.[23,25,75,76] The principles underlying both light microscopy and optical sectioning should be understood for the best results.[1,12,55]

IV: The Three Bone Envelopes, of Triple Surface System[15]

A) Periosteal Envelope: The periosteal surfaces of the skeleton enclose a volume of tissue space that can be called an envelope, here the *periosteal envelope*.[15] The *length* of this envelope is set by enchondral ossification, and will not be considered here.[68] The *transverse* shape and size of this envelope are determined by groups of 'clasts and 'blasts which act on its bony surface, chiefly transverse to the direction of the bone's long axis.[8,9] Figure 1 shows how the cross section area of the 5th, 6th, or 7th rib changes with age in normal people. See curve A_t (cross section *A*rea, *t*otal).[8,63,64,67] Mathematically the curves in this figure are the integral of all past resorption and formation rates, summed over each envelope. The dip at age 40 might

be due to the '29 - '32 depression, since these subjects were growing rapidly then and could have lost some of their growth potential due to restricted dietary intake. Other explanations are also possible and further study will be needed to settle the matter.

B) Endosteal Envelope: The walls of the marrow cavity are the cortical endosteal surface,[11] and define another envelope entirely within the first, the *endosteal envelope*. The changes in this envelope are shown in Fig. 1, curve A_m (*A*rea, *m*arrow cavity), for the same standard bone.[8,63,64,67]

The amount of cortical bone in the body is the volume of the periosteal envelope less that of the endosteal envelope,[35] and its changes with age shown in Fig. 1, curve A_c (*A*rea, *c*ortical).[8,63,64,67]

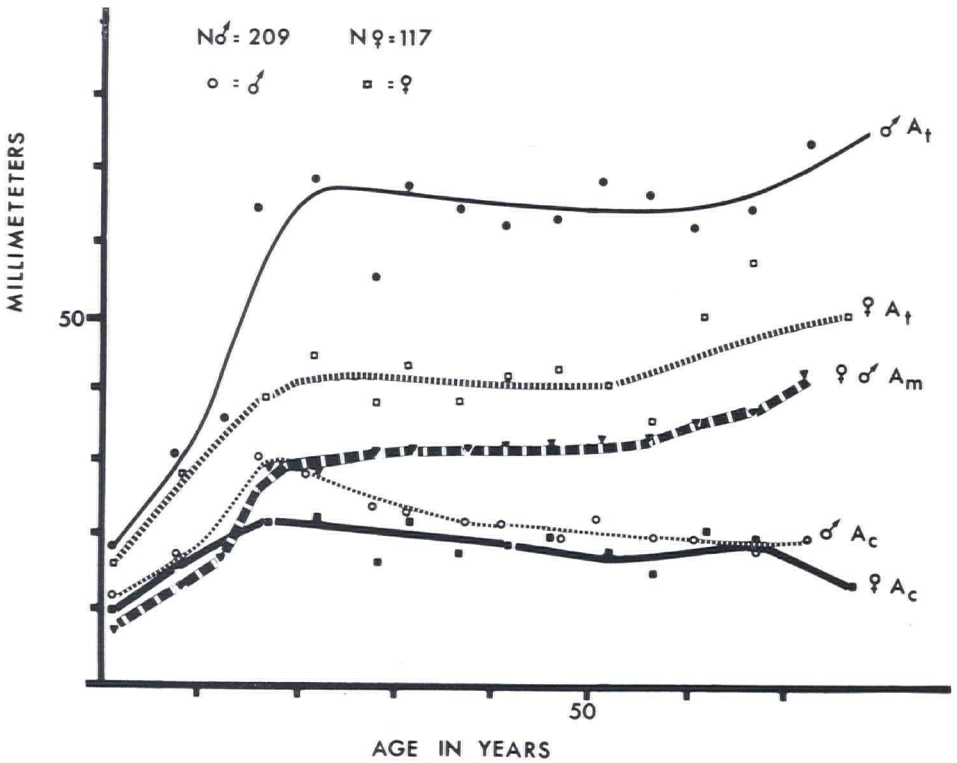

Figure 1

Curves for the cross section areas of various rib parameters, taken from normal 5th, 6th or 7th ribs by Epker,[8] Sedlin,[63,64] and Takahashi.[67] N = 326 people, and throughout this report capital letter N will mean the number of people (usually) or structures (occasionally) which were measured to obtain the values.

A_t: Total cross section area, which is the transverse size of the periosteal envelope, i.e., the volume of space it encompasses.

A_c: Cortical cross section area, or transverse size of A_t minus A_m.

A_m: Marrow cavity cross section area, or transverse size of the marrow cavity and the endosteal envelope.

The areas are given in mm^2; precision of measurement per section was better than $0.5mm.^2$ Unless otherwise stated, all norms in this article are for the middle third of the 6th rib.

C) Haversian Envelope: The walls of the haversian canals define a third distinct volume of space which is called the *haversian envelope*. Topologically it is harder to visualize, but it is real and easily measured.[15,39] It changes as shown in Fig. 2, top curve,[8,37,49] and it lies sandwiched between the other two envelopes.

These age-related changes in a standard bone are the same in *kind* as those found by others in different standard sampling sites,[5,51,61,73] and probably affect the whole skeleton.

V: Bone Remodeling

The growth-related, age-related and disease-related changes in the size and shape of the three bone envelopes are caused by "packages" of bone remodeling activity.[65] These packages are cellularly, temporally and physically distinct and separate bone

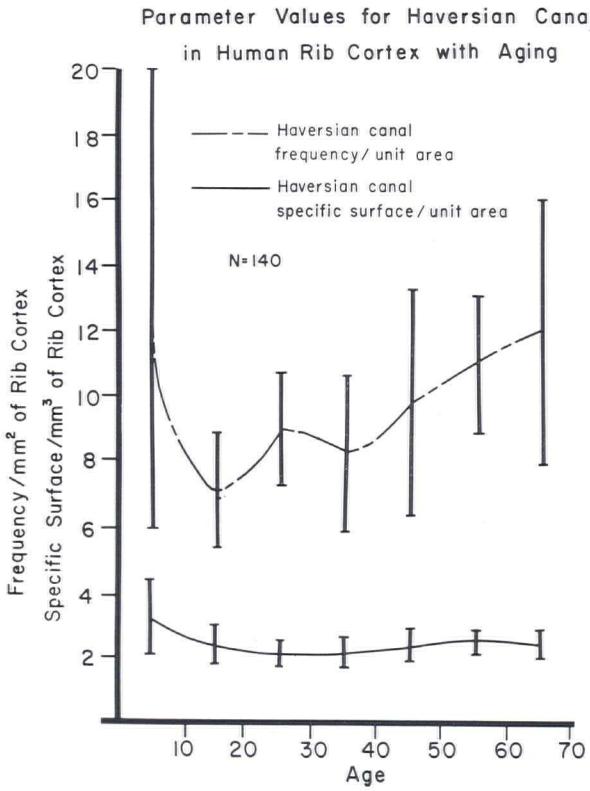

Figure 2

Top curve: The mean number of haversian canals per mm² cortical cross section area. Bottom curve: the total area in mm² of the walls of haversian canals in the representative cubic millimeter of rib cortex; this is the amount of haversian envelope surface per unit amount of compacta — taken from B. N. Epker.[8,11] The volume of space encompassed by the envelope's surface, per cubic millimeter of compacta, can be found at any age by multiplying the appropriate value in the top curve by the haversian canal cross section area. The latter is obtained from Table III by subtracting the value in the second row from that in the first. N = 70 people.

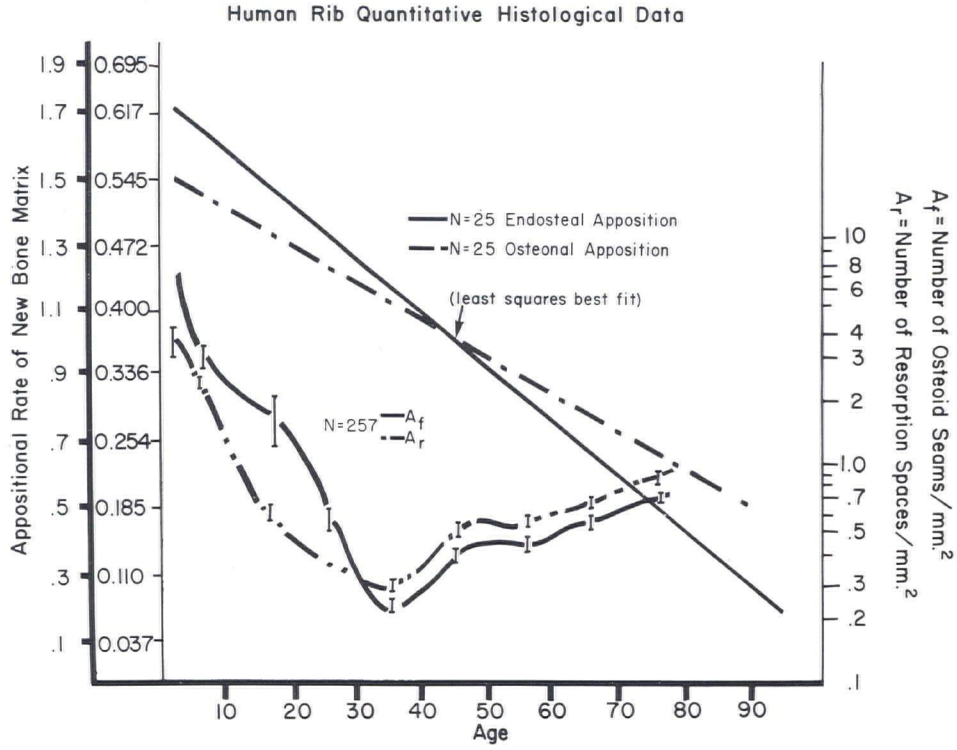

Figure 3

Solid curved line: the number of osteoid seams per square millimeter (A_f) of cortical cross section area in ribs (N = 257 people) from metabolically normal cases plotted against age. Dashed curved line: the number of resorption foci/mm² compacta (A_r) in the same sample; read against the right hand vertical axis (N = 257) measured by E. Sedlin, A. R. Villanueva and Mary J. Frost. The short vertical bars are one standard error.

Straight solid line: The appositional rate on cortical endosteal surfaces in 26 of these ribs. Dashed straight line: this rate in actively forming osteons in the same 26 ribs. Read both lines against the left vertical axis, which gives both microns per day (furthest left) and millimeters per year (next furthest left).

resorbing and bone forming centers or foci.[15,17,18,25,27,28,29,53] These activities can be measured histologically in mineralized (i.e., undecalcified) cross sections of ribs.[18] This requires that (*i*) the number of bone forming and resorbing foci be counted, (*ii*) that they be reduced to the mean number in a unit amount of tissue, which in this laboratory is the cubic millimeter, (*iii*) that the surface area of the average focus be measured, (*iv*) and that the thickness of material either formed or resorbed per time unit be measured. When the number of bone forming foci is divided by the amount of bone (cortical cross section area) in which they reside, this is A_f (*A*ctivated focus, *f*ormation); and for resorption the symbol is A_r (*A*ctivated focus, *r*esorption). Normal values are shown in Fig. 3, and scattergrams showing the normal spread are shown in Fig. 3, 4.[34,66,74,75] When the sections are stained with the Villanueva tetrachrome (available as a single powder to be dissolved in 70% ethanol from Harleco, Philadelphia),[76] about 20% more seams (i.e., A_f) will be apparent than if they are stained with Frost's fuchsin.[20] When counts are done with the high dry objective

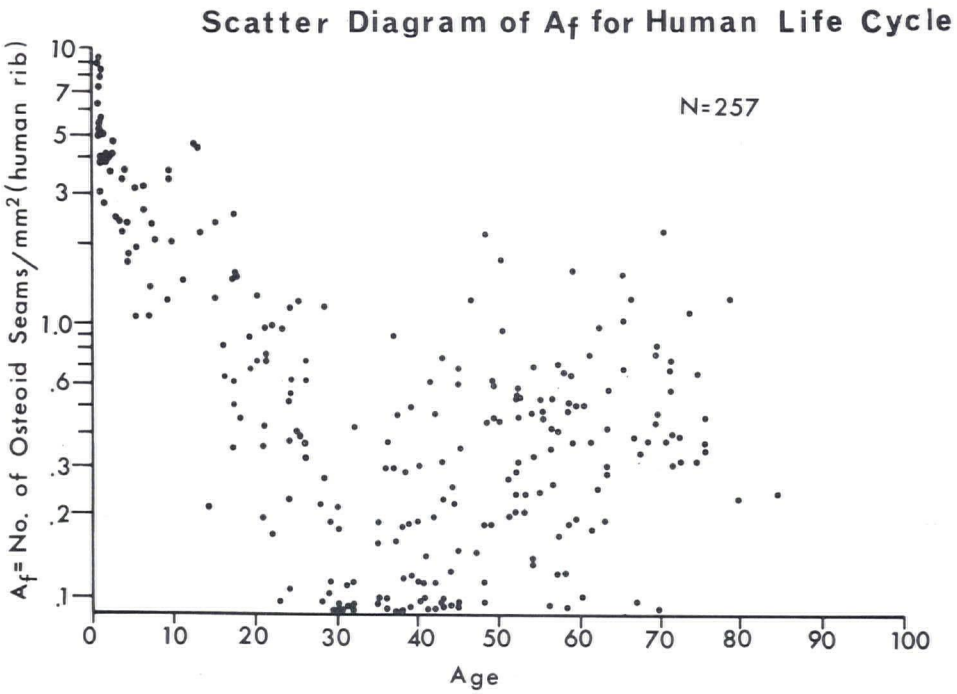

Figure 4

Scattergram of the seam measurements (A_f) in Fig. 3. Vertical axis is logarithmic. This and Fig. 5 show the necessity for the standard bone approach if valid inferences are to be drawn concerning the changes that characterize a disease process. The means we report here are about 40% higher than those originally published, for technical reasons which are mentioned in the text. N = 257 people. Relative precision of values better than 2%.

(45X, N.A. 0.65) about 20% more seams will be resolved than with the low power (10X, 0.25 N.A.), because some very thin seams exist in nearly completed osteons which cannot be resolved with the 10X objective.[7,59] Such seams probably cannot be recognized in microradiographs.[45] The curves shown in Fig. 3 are for high dry measured, tetrachrome stained material.

The most imprecisely measured parameter in this work is the number of resorption cavities. Mean precision* here is about 15%. While published studies provide useful comparisons of normal with diseased material,[78] it is likely that the *absolute* number of resorption cavities given in previous reports and shown in Fig. 3 is too high by a factor of at least two, as has been properly pointed out in different discussions by L. C. Johnson,[42] W. S. S. Jee,[41] and J. S. Arnold.[4] This reflects a defect in interpretation of what we see, not an inaccuracy of the method. This problem can be minimized by decreasing the resolution of the method of observation, for example, by using numerical apertures of 0.25 or less in the light microscope, or by using only the microradiograph. The curve in Fig. 3 was obtained with a high dry achromat of N.A. 0.65.

*Precision is used in the sense of reproducibility. It is not the same as accuracy, as the next sentence shows.

The circumferences of osteoid seams and resorption cavities are a measure of the mean surface area on the inner wall of these structures in cross sections exactly one mm thick. Normal values are shown in Fig. 6 and Table V.[46,47]

The rate at which thickness of new bone is added to bone forming surfaces (i.e., osteoid seams) has been measured in human tetracycline labeled bone by Taylor et al;[72] Frost;[14,22,24] Manson and Waters,[52] and Lee.[50] The human data is summarized in Fig. 3 and Table V. This is a critical parameter without which meaningful *rates* cannot be measured in bone by microscopy or radiography; this is substantiated by errors in interpretation[21,44,45,48] that were recently corrected.[60,77] The implication that equal areas of formation surface in bone must mean equal amounts of bone tissue formed is clearly in error.[48]

BONE FORMATION RATE: This can be calculated from the histological measurements by solving equation (*5.06*) in reference.[18] Normal values for the standard rib are shown in Fig. 7.[58] Since the steady state assumption applies to this material, this is also the *bone resorption rate*.[69,70,71] The bone formation rate can also be measured directly, at a sacrifice of all other information, however. This was done first in man by Frost[22,32] and later (in animals, however) by Amprino and Marotti,[2] Lee,[50] and Marotti.[53]

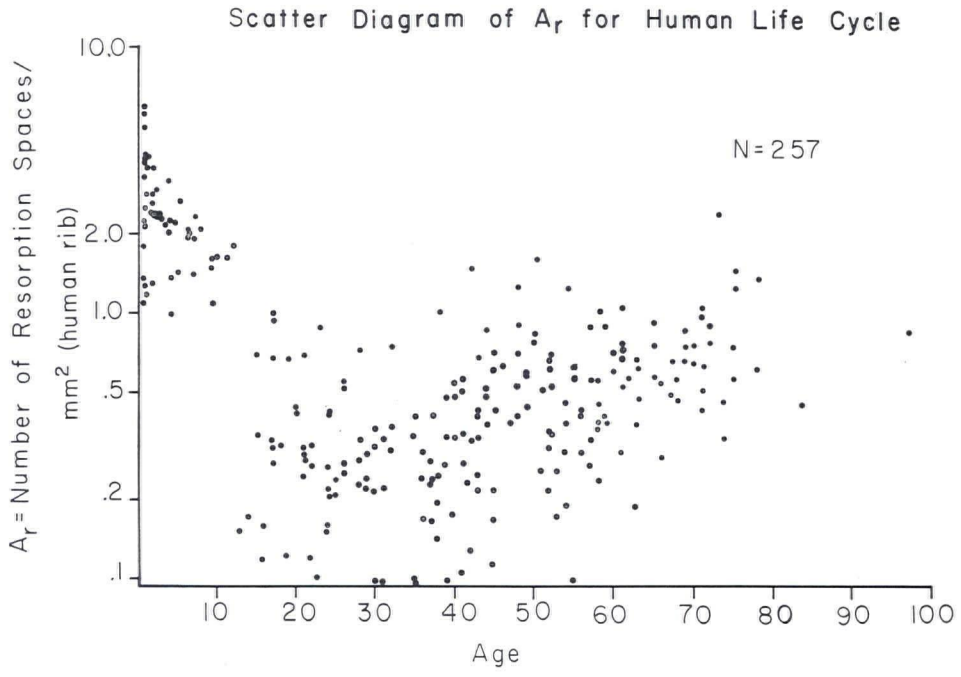

Figure 5

Scattergram of the resorption space measurements (A_r) in Fig. 3. This laboratory was the first to report the age — 35 minima, and the subsequent increase in remodeling foci,[33] a finding initially met with open disbelief, but which has now been confirmed by others.[45] N = 257 people. Relative precision of values better than 15%.

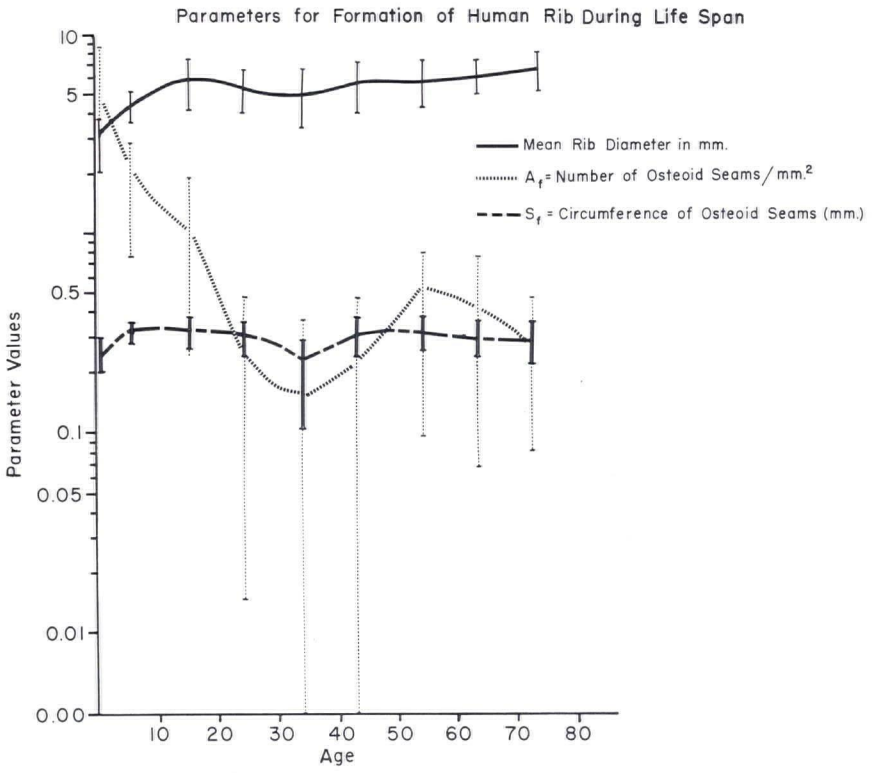

Figure 6

The mean osteonal seam circumference (S_f)[46] in mm is graphed with the medial — lateral outside diameter of the standard rib,[63] and the mean number of seams/mm² (A_f). S_f involved measuring over 5,200 seams in 139 normal ribs by M. Klein; the rib diameters were measured on the same sample by E. Sedlin; the A_f curve is reproduced from Fig. 3. Precision of the diameters: 0.1mm; of the mean circumferences: 10^{-3}mm. The vertical bars represent one standard error except in the A_f curve, where they are one standard deviation.

To recapitulate briefly, the *tissue dynamic parameters* of bone are the formation rate (V_f) (equation *5.03*); *the resorption rate* (V_r) (equation *5.04*); and the *remodeling rate* (V_t) (equation *5.12*), equations taken from reference.[18]

VI: Cell Population Parameters

The cell population parameters are the numerical size of the population (symbol: A), the "birth rate" (symbol: mu) of packages of new remodeling activity, and their average "life span" (symbol: sigma). Both can be computed from simple measurements.[18,60,77] Analysis of these parameters depends on the fact that in the steady state the numerical size of *any* population is the *birth rate* of new subjects multiplied by their average *life span*.[25] The steady state exists when the "birth rate" equals the "death rate." (Here, the "death rate" is the number of bone remodeling sites or foci that finish per unit time, and subside into histological inactivity.) The average life span of the osteoid seam (i.e., the length of time it takes to make its new osteon or

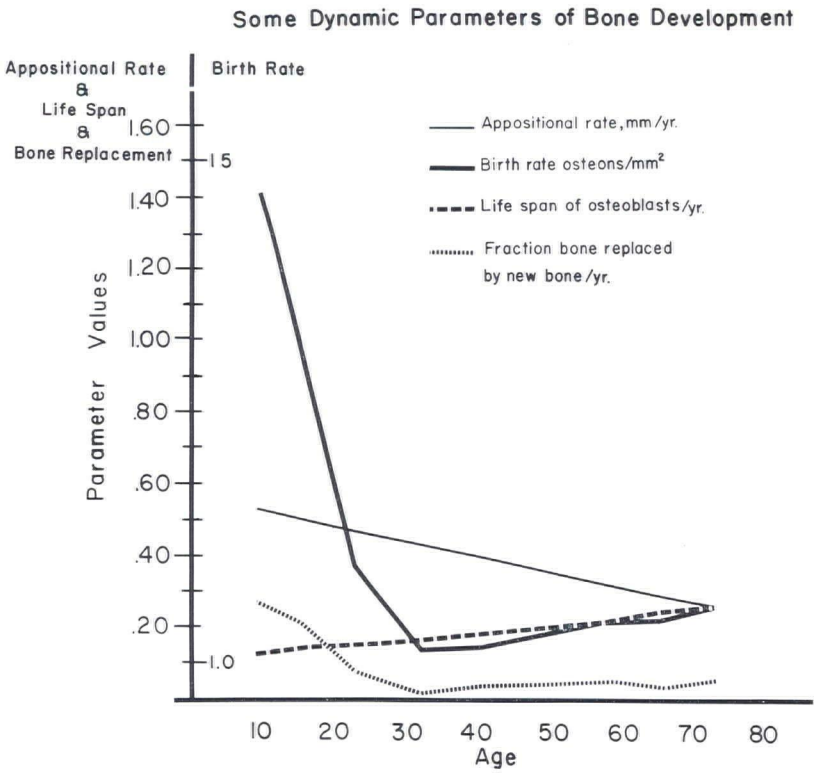

Figure 7

Light dashed line: the bone formation rate in normal rib compacta, given as the per cent of the compacta replaced by new bone per year, and to be read against the left vertical axis. Computed with the equations in *Mathematical Elements,* from the normal values for A_r, and S_r and M_r.

Heavy solid line: mu, the birth rate, or number of new osteons and resorption spaces introduced into a cubic millimeter of rib compacta per year, in the steady state. Computed with the equations in *Mathematical Elements,* with data given in this report. This parameter is taken to be a measure of mesenchymal cell (i.e., osteoprogenitor cell) activity.[15,18] Read against the right vertical scale.

Heavy dashed line: the time in years taken to make the representative new osteon in rib compacta. This may be as much as 30% too small, see below. Read against the left vertical scale.

Thin solid line: the appositional rate in mm/year in 26 ribs.[72] This was obtained primarily from singly banded normals. Because of an effect called the TISZ,[24] this is probably too large by about 30%. When sufficient doubly banded metabolically normal subjects are available it will be possible to be sure about the magnitude of this error.

other "package" of bone) is found by dividing the mean thickness of bone in finished foci by the rate at which it is built up (*radial closure rate*).[10] Curves for normal mu (birth rate) and sigma (osteon formation period) are shown in Fig. 7. These parameters are needed because bone formation over the whole cortex is a function of both the speed of bone formation at the level of the actively forming osteon, and the total number of actively forming osteons. Given an osteon formation "speed," the total number of forming osteons will be determined both by this, and the frequency with which new osteons are introduced into the bone. This frequency is the "birth rate" mentioned above. This relationship is given exactly in equations (*6.03, 6.04*) of reference.[18]

V: Special Studies

A) Per cent Labeled Seams:

Not all of the calcification fronts in bone (i.e., zones of demarcation) incorporate a tetracycline label at any one time,[7,10,13,15,60,77] although the contrary has been suggested recently.[45,48]

Preliminary figures on the per cent of osteoid seams labeled in some normal human ribs are shown in Table II.*[58]

Table II

Preliminary Comparison of Tetracycline Bands/mm² Vs. A_f (Osteoid Seams/mm²).

Age	Tetracycline Band /mm²	Osteoid Seams/mm² (A_f)	N+	Percentage of Seams Labeled
1 yr.	3.7 (±4.1)*	4.44 (±2.68)	4	83%
1-10 yr.	1.50 (±1.16)	1.87 (±1.09)	9	80%
61-70 yrs.	0.49 (±0.28)	0.60 (±0.52)	6	81%
71-80 yrs.	0.62 (±0.46)	.70 (±0.63)	12	88%
Mean All Cases				83%

+N number cases

*One standard deviation

The normal values for tetracycline bands per mm², A_f, and per cent of seams becoming labeled with tetracycline are shown for several age groups as studied by the first author. This is a preliminary report, but should be considered as indicative. Note a definite incidence of nonlabeling seams, which seems to have been missed so far by other observers. These data are not corrected for the "age" of the label, or for remodeling, and give values of per cent labeled that are too low by an as yet undetermined factor.

B) Osteon Wall Thickness:

When the mean thickness of the osteon wall is divided by the mean rate at which this wall increases in thickness, the result is the osteon formation period. This value must be found in order to obtain another parameter, the osteon "birth rate" or mesenchymal cell activation frequency.

Normal values for osteon wall thickness in rib are shown in Table III[6,24] and IV. In this parameter, the coefficient of variation in one case is 0.3; that of the means of different cases of the same age is only 0.1.

*Tetracycline deposits in zones of demarcation, and a zone of demarcation exists wherever there is an osteoid seam, so that while it is semantically inaccurate, a seam will be said to "take" a label.

Table III

The Relation between Age and Size of Osteons in Man

Age Group	5-15	16-25	26-35	36-45	46-55	56-65	N
Total Cross Section Area Resorption Space (mm^2)	0.042 (0.005*)	0.046 (0.007)	0.043 (0.007)	0.040 (0.008)	0.034 (0.008)	0.035 (0.003)	12,000
Cross Section Area Bone in Osteon (mm^2)	0.040 (0.004)	0.045 (0.007)	0.041 (0.006)	0.037 (0.005)	0.033 (0.007)	0.034 (0.003)	12,000
Osteon Wall Thickness, mean (microns)	68 (±25)	69 (±25)	72 (±30)	68 (±25)	64 (±30)	65 (±25)	630
Osteon Formation Period Transverse (days)	37.7	57.5	72.0	75.5	85.3	108	
C.V.	.3	.3	.3	.3	.3	.3	
Osteoid Seam Thickness, microns		7.5 (±7)		7.0 (±7)		6.8 (±6)	

*Numbers in parentheses are one Standard Deviation. C.V.: Coefficient of variation.

The values shown here are from studies by R. Hattner et al. Values for osteon wall thickness are averaged measurements of width from the cement line to the Haversian canal wall.

Osteoid seam thicknesses were measured by H. Frost and R. Wilson; the latter's study is the most recent and accurate, and is probably definitive. The S.D. in the first two rows are of the case means with respect to the group means in the age decade. The S.D. in the third row are of wall thickness within single cases.

C) Distribution of Osteon Cross Section Areas:

The modal value of osteon diameters and cross section areas changes during life as shown in Fig. 8A. This change is largely due to the fact that big osteons are more likely to be subsequently remodeled than small ones, as is shown by the histogram in Fig. 8B,[37,49,71] constructed from studies by R. Hattner and H. Takahashi.

D) Osteoid Seam Thickness:

This is shown in microns in the bottom row of Table III. It was found by R. Wilson, who measured each seam at four points equispaced on its circumference, and took the mean as the value for the seam and took the mean of all seams in a case as the case mean.[79] The values are about two microns less than previously reported,[31] but are more accurate.

E) Interlamellar Separation:

This is shown in microns in Table IV. It was found by measuring under the polarizing microscope the distance between adjacent anisotropic lamellae as seen in cross section.[26,58] Regions where these lamellae were not well defined were not measured; there can be many such regions in some bones.

Table IV

Mean Dimension of Human Osteons

Age	N (Femur)	Diameter in Microns	Haversian Canal Diameter in Microns	Mean Lamellar Width in Microns
35	1	270 ± 46	36 ± 13	7.6 ± 3
47	1	320 ± 37	111 ± 39	7.2 ± 3
47	1	250 ± 31	47 ± 22	7.8 ± 3
57	1	270 ± 35	45 ± 09	7.3 ± 3
All Cases	4	270 ± 35	60 ± 34	7.5
18.6	Rib - 15	197 ± 56.0	42 ± 8.0	
33.0	Rib - 15	194 ± 34.5	51 ± 19.3	7.2 ± 4
41.2	Rib - 16	187 ± 57.8	43 ± 14.5	
55.0	Rib - 17	189 ± 29.6	47 ± 8.1	
Total	Rib - 63	192	46	
Clavicle	15	255 ± 52	64 ± 12	
Humerus	4	282 ± 70	72 ± 23	
Femur	4	297 ± 98	76 ± 29	
Radius	2	259	63	
Ulna	1	248	59	

Osteon and haversian canal diameters in selected human bones. The values shown in the top four rows for femurs were compiled by the first author. Measurements of rib and other human bones were made by Frost. Currey has published the largest available study of diameters in femurs.[6] Normal interlamellar separations are shown in the right hand colum, as measured by the first author. The values agree with those reported previously by Frost.

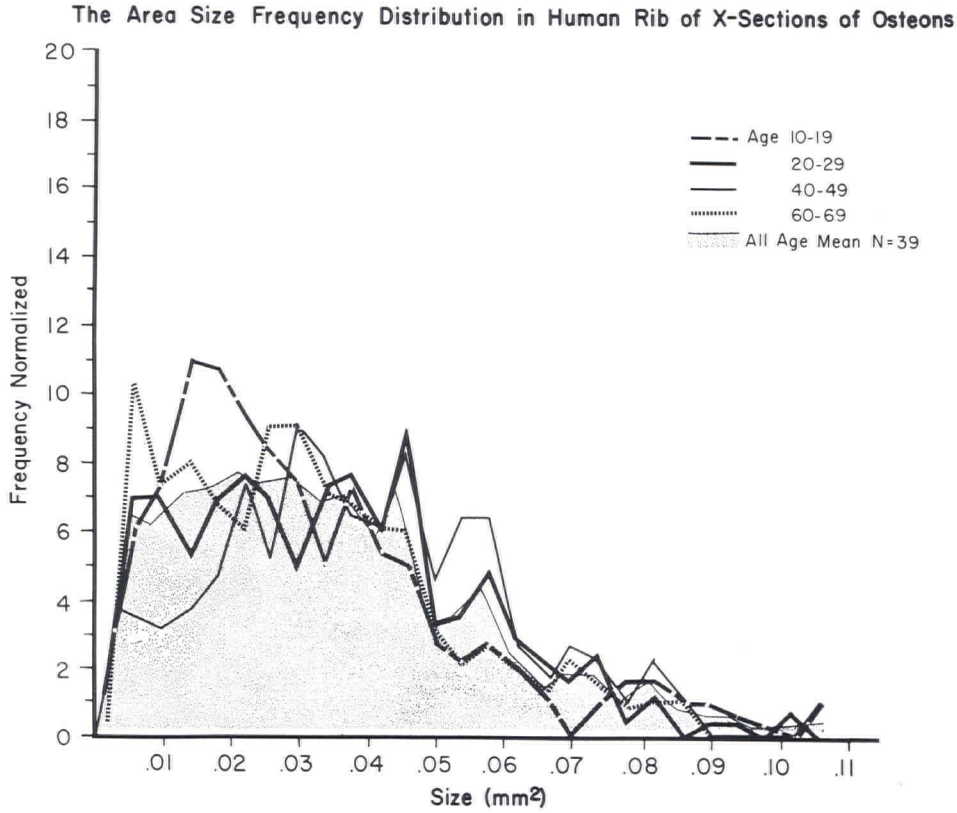

Figure 8A

Histogram of osteon cross section areas (total area within the cement line) in ribs, measured on the basis that they were not partially remodeled out after their formation. The vertical axis is the per cent of the population, the horizontal axis the area in mm². There were 39 patients in this group, in whom more than 600 osteons were measured. Some of these osteons were a few weeks old, some over 20 years old.

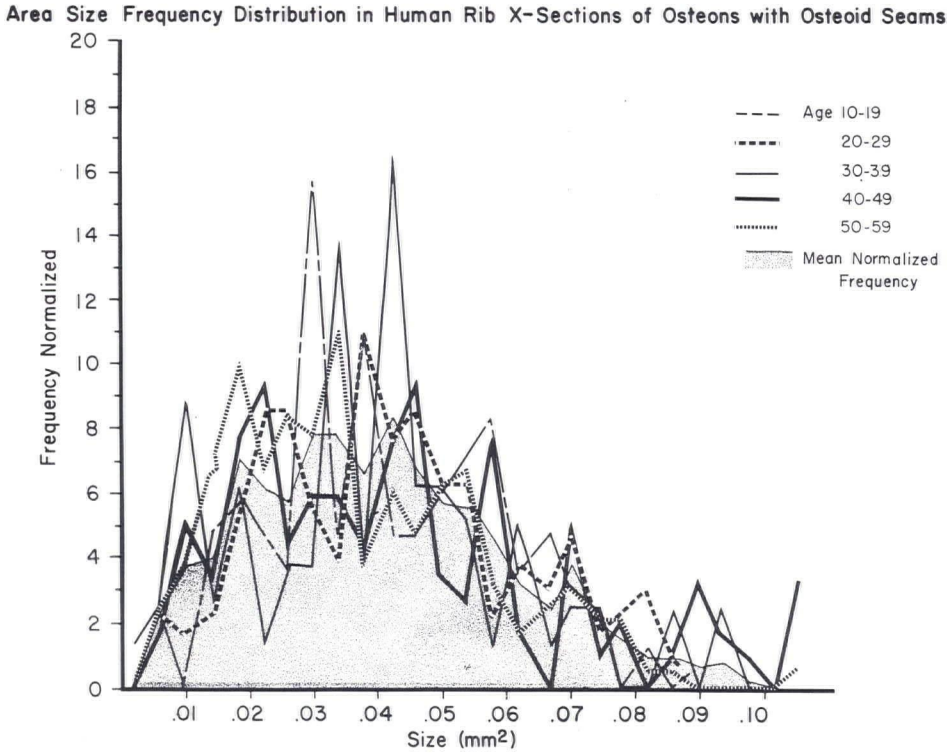

Figure 8B

Like Fig. 8A but only osteons with seams were measured, assuring they were all less than four months old. The modal value is clearly different here than in 8A, showing that small osteons are less apt to be remodeled than large ones. These figures taken from studies by R. Hattner;[37] O. Landeros[49] and H. Takahashi.[71]

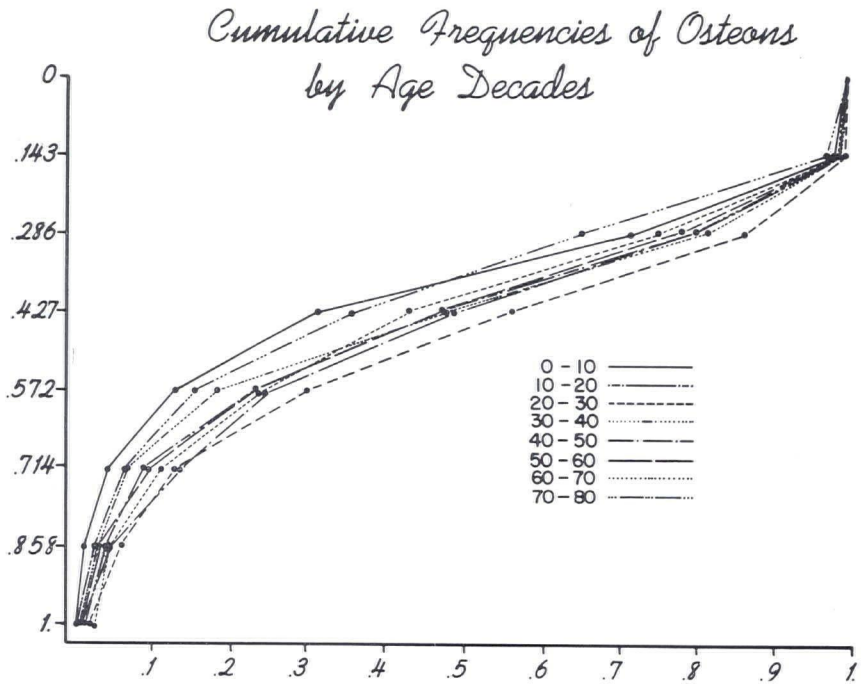

Figure 9A

Frequency-to-time domain transformation of osteonal osteoid seam circumferences, shown for each decade from Kelin's work. N = 5,207 seams, 139 people. The spread is not systematic.

F) Time Domain Transformations:

When the various sizes of osteons are plotted against the relative frequencies with which they occur, and the two axes are then transformed from the frequency to the time domain, a curve is obtained which plots the completion of an osteon against its formation period. The same applies to the resorption space which must be made before an osteon can be made. Representative curves are shown in Fig. 9A, formation, and 9B, resorption. These curves are dimensionless with respect to time, effected by arbitrarily setting the periods equal to unity.[46,69,78]

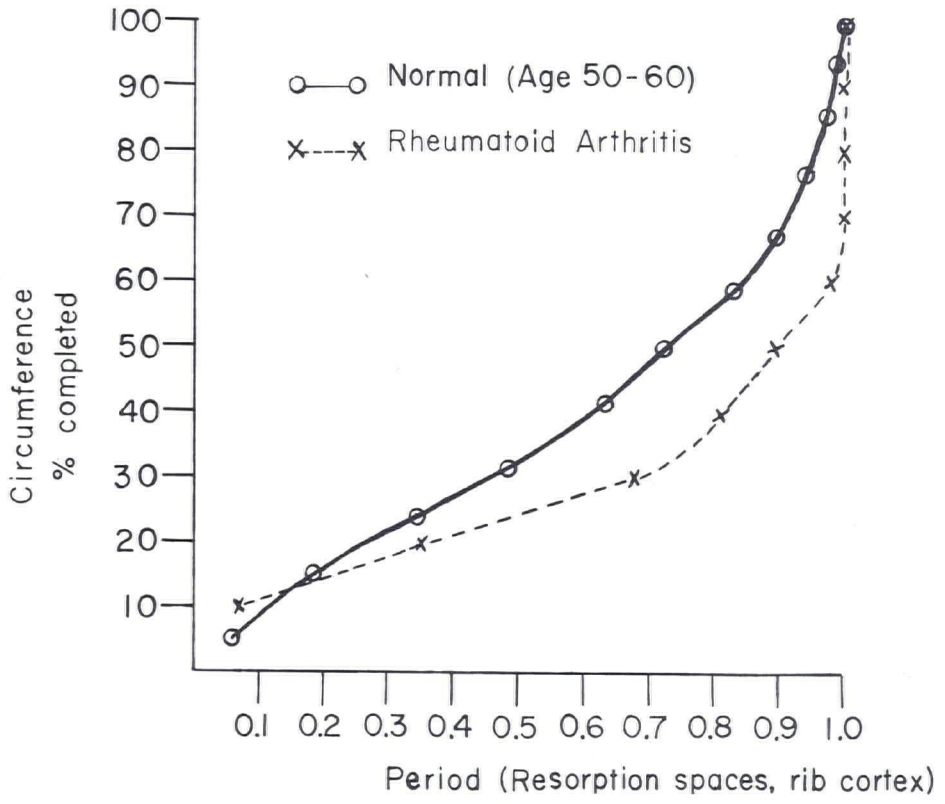

Figure 9B

A frequency-to-time domain transformation of osteonal resorption spaces, taken in part from A. Villanueva's work in normal bone, and in the rheumatoid cases (treated with salicylate only) by O. Landeros and H. Duncan. The curves are different, and significantly so, but the reason is primarily that resorption cavities are somewhat smaller in size in R.A. than in normals.

VIII: Conclusion

The material presents the chief parameters of normal bone dynamics currently in use in this laboratory. Through the bone "window," one can study some of the basic mechanisms of disease,[38] aging,[65] growth,[43] pharmacology and cell dynamics.[16, 28, 29, 40, 81]

A glossary of terms used in the text and in this relatively new field follows. While this is a special jargon, its use saves time and printing space.

The references give sources for the actual data, for methods of measurement, for their present interpretation, and for the basic concepts which are peculiar to but useful in this field.*

*We are much indebted for help in preparing this report to the art department of Henry Ford Hospital, particularly John Gray, John Kroll, and to Mrs. D. Smith and Miss C. Chalmers.

Table V

Dynamic Parameters

Age	Appositional Rate mm/yr.	Wall Thickness mm	Life Span (Sigma) Wall Thickness/ Appositional Rate/ yrs.	A_f Number Seams/ mm^2	Birth Rate (mu) A_f/σ Osteons/ mm^2/yr.	S_f mm	Bone Volume Formed $A_f \times S_f \times$ Appositional Rate (Bone formation rate) decimal fraction/yr.
9	0.53	.068	.128	1.80	14.06	0.28	0.27
15	0.50	.068	.136	1.30	9.56	0.33	0.21
23	0.47	.069	.147	0.55	3.74	0.31	0.08
32	0.44	.072	.164	0.22	1.34	0.24	0.02
40	0.40	.068	.170	0.25	1.47	0.32	0.03
59	0.31	.065	.210	0.45	2.14	0.33	0.05
66	0.27	.065	.241	0.53	2.20	0.31	0.04
73	0.26	.065	.250	0.65	2.60	0.30	0.05
Coef. of Variation (Typical)	0.30	Single case 0.30 Between case 0.10	Single case 0.30 Between case 0.10	0.50	0.30	Single case 0.55 Between cases 0.1	0.30

The cell dynamic parameters listed here were computed by the first author from the normal values shown in Fig. 3, 6, 7, and 8 and in Table III. The bottom row lists the coefficient of variation, which is one S.D. divided by the arithmetic mean. Note that as a rule the relative variance changes much less with age than the absolute variance.

GLOSSARY

ABV: absolute bone volume = the volume of bone remaining after subtraction of all the microscopic and macroscopic holes usually found in bone. These include the lacunae, caniliculae, vascular channels and marrow spaces.

A_c: cortical area of cross section = area inside the periosteum less that of the marrow space, in mm².

A_f: number of sites of bone formation/mm² (population of osteoid seams/unit amount of bone).

A_m: area of marrow canal in cross section, in mm².

Appositional Rate: thickness of a label, in microns, divided by its duration in days.

A_r: number of sites of bone resorption/mm² (population of resorption spaces/unit amount of bone).

A_r/A_f: number of bone resorbing foci divided by number of formation foci.

A_t: total area of cross section inside periosteal envelope in mm².

Balance: the net result of two opposed rates, fluxes or changes. Negative balance means loss with time, positive the converse, and zero means no net change.

Band: a single tetracycline ring deposited in one bone-forming focus.

Birth Rate: see mu.

Bone Formation: the manufacture of new bone matrix, a cell mediated process. Mineralization is distinct from formation.

Bone Formation Rate: the fraction of the bone replaced by new bone per year.

Bone Modeling: the changes in *geometry* and *quantity* due to growth or disease. Different from remodeling.

Bone Remodeling: the sum or combination of bone formation and resorption. Does not change shape or amount.

Bone Resorption: the destruction of bone, a cell mediated process. Both matrix and inorganic material are destroyed together.

Bone Resorption Rate: the decimal fraction of the bone removed by resorption per year.

C/T ratio: $A_c \div A_t$

Cytodynamic: pertaining to the dynamics of cells, including their biochemical function, their motions in space and their generation from other cells.

Cytodynamic Parameters: the functions and symbols designating cytodynamic activity.[18]

Endosteum: the lining of cells on the inner walls of the cortex, and on the surfaces of the trabeculae inside the bones' medullary cavity.

Endosteal Envelope: the surface (walls of marrow cavity) which envelopes the marrow cavity and trabecula but excludes the cortex.

Endosteal Remodeling: remodeling activity occurring on endosteal surfaces.

Extra haversian: all bone that is not intact, functioning haversian system.

Fibrous Bone: a primitive type of bone found in repair, neoplasia, and inflammation. It participates in longitudinal growth. It has distinctive structural features and the osteoblasts that form it have distinctive physiological features.

Frequency: the number of events or other periodic activity that occur in one unit of time.

Haversian Canal: the cylindrical vascular channel lying in the central axis of haversian systems and containing one or two blood vessels which nourish the cells in the system.

Haversian Envelope: the surface of all haversian canals, which encloses a certain volume of space.

Internal Remodeling: that remodeling occurring between the periosteal and endosteal envelopes.

Label: a course of tetracycline (or other labeling drug) given to a living vertebrate. *Labeling:* The deposition of tetracyclines in the zone of demarcation so that they may function as a marker in time in living bone.

Lamellar Bone: containing lamellae. Comprises the bulk of the child's and adult's skeleton, and is the tissue involved in the bulk of bone pathology: analogous to bricks; of it are made cortex, the trabeculae, endosteal lamellae, circumferential lamellae, haversian systems.

Life Span: see sigma.

Medullary Cavity: the visible space in the center of a bone containing the marrow tissue elements.

M_f: see radial closure rate.

M_r: linear rate of resorption, mm/year (must be computed).

$Mu = \mu_f$: "birth rate" of new bone-forming foci = A_f/σ_f = the number of new foci whose formation (or resorption, u_r) is *initiated* per year per mm^2.

Osteoid: also osteoid seam: new, unmineralized bone matrix regardless of whether it lies in normal or abnormal bone.

Osteon: synonymous for haversian system.

Parabolic Index: $(A_c \times A_m) \div A^2_t$ (See[9])

Parameter: an equation term representing a functional constraint(s) between two or more variables. Pool parameters are those properties with which pool physiology and state may be specified; they are not the causes. The geometric remodeling parameters are those geometric features which reflect two or more cytodynamic activities and/or properties. The parameters are not causes, but are effects of the cytodynamic activity.

Percent Labeled: the fraction of foci-containing osteoid seams that accept a tetracycline label.

Periosteal Envelope: the periosteal surface of bone, which encloses all of it.

Radial Closure Rate: the appositional rate multiplied by the fraction systems with seams that take labels. Given in mm/year.

Remodeling: the summation of bone formation and resorption. Ideally does not change the amount, shape or size of a bone.

Seam Thickness: thickness of an osteoid seam in the direction perpendicular to its surface, and parallel to the radius of an osteon.

Sigma (σ_f): life span of bone-forming foci = wall thickness/M_f = osteon formation period = time in years between initiation and completion of a "package" of new bone.

Sigma (σ_r): life span of resorption foci = time in years between its initiation and its disappearance, when new bone begins to cover it over.

S_f: circumference of the representative osteoid seam as seen in cross sections.

S_r: circumference of the representative resorption site in cross section; also its area in one-mm-thick cross sections.

BONE SECTIONS

Standard Bone Approach: limiting study to one part of the length of one bone, collecting this sample from a large number of people of like age, sex and health and obtaining from sections of this sample a mean value for the group which may be compared to other groups that differ in one or more aspects from the original or from the normal. The normal has to be established in the same manner.

Steady State: an arbitrary form of equilibrium, the condition when there is no net change in the system being observed; input equals output; birth equals death; resorption equals formation.

Surface Remodeling: periosteal and endosteal surface.[27]

Turnover: the continual replacement of a pool with new material. Both influx and efflux are implied. Remodeling and turnover are the same thing.

V: volume, the preferred measure of an amount of bone.

V_f: the bone formation rate: volume of bone matrix in mm^3 formed/year/mm^3 of bone; (population of osteoid seam/unit amount of bone) x (mean osteoid seam circumference) x (appositional rate).

V_r: the bone resorption rate: volume bone matrix in mm^3/year/mm^3 of bone; (population of resorption spaces/unit amount of bone) x (mean circumference of resorption space) x (M_r as computed during steady state situation).

V_t: the proportional bone remodeling rate: The proportion of bone tissue turned over/year/mm^3 of bone $= (V_f + V_r)\ /2$.

Wall Thickness: of the osteon; mean distance from cement line to haversian canal.

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