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RELATION BETWEEN AGE AND SIZE OF OSTEONS IN MAN*

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INTRODUCTION*****

IT HAS BEEN REPORTED that the *rate* of individual osteon formation varies considerably in an age-dependent manner in normal people,[18] as well as between metabolically normal and diabetic people.[21] But in the same cases and bones the above authors reported that the *quantity* of bone in a finished osteon tended to remain at least approximately constant. The range of change in rate observed by these authors was as 7 is to 1 while the range of change in quantity was as .9 is to 1. It was proposed that this might mean that some modes of cellular behavior are age independent, and are in effect constants.

But when it is proposed that within a single cell system (such as that which makes a new osteon) there are (1) separate mechanisms for controlling the *rate* and *total quantity* of useful metabolic work done by the cells in a system, and (2) that the total quantity made when the process finishes is invariant in the face of both aging and widely varying rates, the proposition must be considered radical. It merits the most careful evaluation before being accepted, because if it were true it could seriously affect our concepts of the regulatory mechanism(s) that control the metabolism and aging of mammalian tissues. Partly, the reason for this is that such a phenomenon suggests strongly that a digital, either-or, device† is controlling some of the dynamic aspects of the behavior of a *group* of cells. This is quite a different thing from having a digital device control the structure of a protein (which, in the context used here, DNA is, and does).

With respect to the osteon transverse sizes discussed by Hattner et al,[18] a moment's microscopic inspection of a cross section of the cortex of any long bone

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*****This paper was read to the Biological Sciences Division of the Gerontological Society at its 17th annual meeting in Minneapolis, October, 1964.
†By which is meant that the device functions like an electrical switch: it is either on, or it is off, but there are no gradations in between.

will show that there are large variations in the sizes of individual osteons. Hattner et al[18] circumvented this problem by determining the *mean* size of these osteons in any given cross section of a rib. This size *is* relatively constant even though the individual osteon sizes do vary widely. But these facts raise the possibilities that (1) there may be major age-related changes in the frequency distribution which were concealed by the methods used in the studies alluded to, and (2) that therefore the interpretation of these authors was unjustified. And in fact, they did observe an approximately 15 per cent age-dependent change in size.

In this report the size-frequency distribution of osteons in ribs from normal people of various ages is defined. In part this is done by using previously published data but some new data are added.

Materials and Methods

MATERIALS: We obtained the middle third of the 5th, 6th or 7th rib from 130 metabolically normal people. Their ages ranged from 10 to 70 years. The cases were obtained, some at autopsy at the county medical examiner's office, some at autopsy at this hospital, and some at thoracotomy for the repair or biopsy of anatomical, nondebilitating lesions. All of the cases were felt to be metabolically normal up to the time of skeletal sampling,* and records were sufficient in all cases to substantiate this claim.

METHODS: Fresh, mineralized, unembedded, 50-75 micron thick cross sections of the ribs were made by methods previously reported.[14,15] They were oriented within 5 degrees of perpendicularity to the long axes of the bones. While the sections were stained by 1 per cent basic fuchsin in a 50 per cent ethanol solution, the staining method is not critical in this work. An average of three sections per case were available for this study.

MEASUREMENTS: The cross section areas of secondary osteons were measured by a previously described point count method, utilizing the Zeiss integrating eyepiece I.[19,27] Measuring precision was arbitrarily set at $\pm$ .005 mm^2. In the *first series* of measurements, we measured the total area inside the cement line, using as the criterion of an osteon that was selected for measurement, that it be any unremodeled secondary osteon† in the section. There were 1,155 such structures. In the *second series,* we made this same measurement, but changed the selection criterion so that only actively forming osteons were measured. An osteoid seam was taken as the criterion of the state of being in active formation.[22,23,20] There were 604 such structures. The data were then arrayed by age decades, the total frequencies normalized and the size increments standardized.

The data are shown in tabular form in Table I and Table II. Figures 1 and 2 are representative histograms, constructed from columns 2-6, Table I, and columns 2-6, Table II.

Results

Within the limit of precision of the measuring method, no significant change was found in the distribution of the various sizes of total osteon cross section areas across the 60 year span of life that was studied, as long as the selection criterion was an actively forming osteon. There is a systematic, age related change in the size distribution when the selection criterion was any unremodeled secondary osteon.

*We wish to thank Drs. E. S. Zawadski, R. H. Horn and G. Fine for their generosity in donating this material and for making the records and autopsy reports available to us.

†A secondary osteon is any osteon formed *after* the formation of the cortical bone in which it is deposited.

Table I

THE SIZE-FREQUENCY DISTRIBUTION OF CROSS-SECTION AREAS OF OSTEONS WITH OSTEOID SEAM

Range of Normalized Size of Osteons (%)	*Normalized Frequencies*				
	10s	20s	30s	40s	50s
0- 10.3	2.4	3.9	12.7	6.9	6.3
10.4- 21.5	15.6	16.4	10.1	20.7	23.6
21.6- 32.7	24.1	18.0	21.5	16.3	27.5
32.8- 43.9	20.5	27.3	26.6	21.6	13.7
44.0- 55.1	21.8	14.9	12.7	13.8	16.3
55.2- 66.4	12.0	11.7	8.9	6.9	7.4
66.5- 77.6	3.6	7.0	2.5	3.5	4.7
77.7- 88.8	0	0.8	5.0	6.0	0.5
88.9-100.0	0	0	0	4.3	0
Over 100.0%	0	1.6	0	3.4	1.1
Total osteons	83	130	79	120	192

A selection of the cross section areas within the cement line of 604 actively forming osteons in 90 subjects, arranged by age decades. Their differences are not felt to be significant. Both the sizes, and the frequencies, are given as per cents of the maximum or total, respectively. In the first column, 100 per cent corresponds to .107 mm² in both this Table and in Table II.

Table II

THE SIZE-FREQUENCY DISTRIBUTION OF CROSS-SECTION AREAS OF UNREMODELED SECONDARY OSTEONS

Range of Normalized Size of Osteons (%)	*Normalized Frequencies*				
	10s	20s	30s	40s	60s
0- 10.3	6.8	15.0	12.8	13.0	17.6
10.4- 21.5	15.8	19.8	29.2	31.0	20.7
21.6- 32.7	22.3	19.0	27.3	20.6	25.0
32.8- 43.9	21.0	22.6	16.2	17.6	18.7
44.0- 55.1	17.2	11.6	8.1	7.4	7.7
55.2- 66.4	7.1	6.4	4.6	3.0	5.6
66.5- 77.6	5.8	4.0	1.5	4.4	3.0
77.7- 88.8	2.7	0.8	0	2.7	1.0
88.9-100.0	1.3	0.8	0.3	0.3	0.7
Over 100.0%	2.4	0.8	0.3	0.7	0
Total osteons	303	250	400	302	300

Similar to Table I, but constructed from measurements of any unremodeled secondary osteon. The accumulated excess of small, unremodeled osteons described in the text can be seen by comparing the tops of columns 2 and 6.

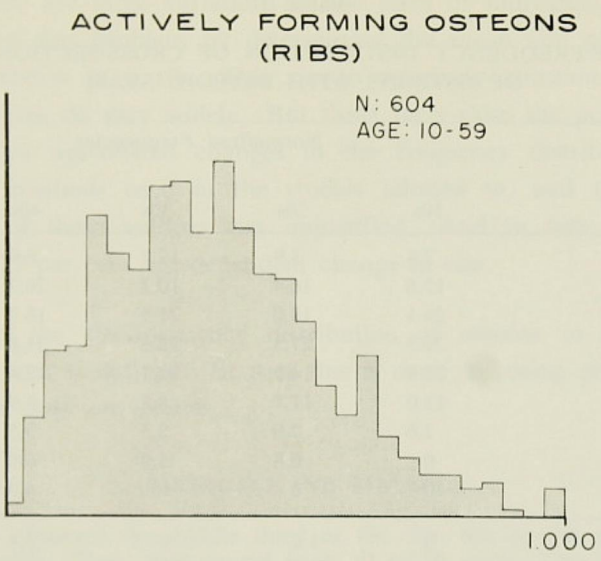

Figure 1

A histogram of the cross section areas of actively forming osteons. There is no significant difference in their distribution according to age.

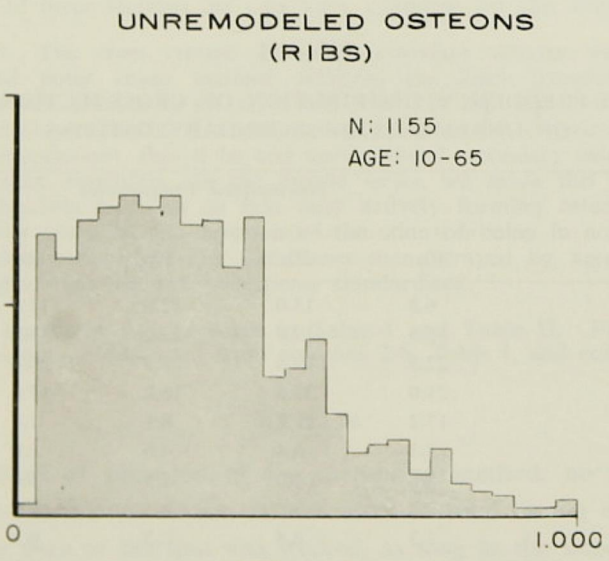

Figure 2

A histogram made from all secondary osteons, whether they were actively forming or not. Whereas the average age of the structures in Figure 1 is 45 days, for those in this figure it is on the order of 10 years. There is a definite relative increase in the smaller size osteons in this figure. Both the X and Y axes in these figures have been normalized so that the total frequency is 1.00, and the maximum size is 1.00; this device makes different sized groups of data comparable.

Discussion

Effect of Size on Remodeling of Osteons: The distribution of sizes in actively forming osteons remained unchanged by any amount that could be detected by our methods, i.e., it was less than ± .01 mm². Because these structures are actively forming, they are relatively young, and it can be shown that their average age is 42 days.* This means that these measurements indicate the *relative incidence* of formation (as distinguished from *relative prevalence*) of the various sizes of osteons.

Then what was the origin of the small, age related changes in mean osteon cross section area (± .006 mm²) that were found by Hattner et al,[18] as well as by Landeros and Frost,[21] and as well as of the changes in osteon diameters found independently by Currey[5] and Frost?[13] These changes proved to be an illustration of the difference in meaning of incidence and prevalence, and were created by the criteria for selecting osteons for measurement. None of the authors mentioned above measured an osteon if it had been partially remodeled, and there seemed to be sound reasons for this procedure. But large osteons are more likely to be partially remodeled by newer remodeling processes than are small ones, given equal periods of time after their completion. Thus, with increasing time, there is an accumulated excess of unremodeled smaller osteons that is out of proportion to that of unremodeled large ones. For this reason the *arithemetic means,* both of diameters and of cross section areas, of all secondary osteons, (i.e., both completed and actively forming) tend to decline with advancing age. This effect can be very convincingly shown by comparing Figure 1 to Figure 2. The first is the histogram obtained from the cases in the age 10-59 decade, the selection criterion being that the osteons were actively forming, i.e., had an osteoid seam lining their central canal. This portrays the *relative incidence* of the formation of the various osteon sizes*. The second figure is a histogram of the same sections, but using the selection criterion that any unremodeled secondary osteon was measured. This portrays the *relative prevalence* of the various osteon sizes†.

Invariance in Osteon Size: A Markov Property: The meaning of this study then is that, whenever a new osteon is about to be made in human ribs, there is a definite probability that it will have a given cross section area, and this probability is invariant (i.e., changes less than ± 10 per cent) over the span of life, and in the bone, we studied. This is true in spite of independent evidence that during this same span of life the rate at which this amount of bone is made declines to some 40 per cent of its original value.[9]

At the macroscopic level, the amount of proteinaceous matrix in a cubic millimeter of bone (absolute bone volume)[9] changes less than 7 per cent across the span of life that was studied.[2]

*By substituting in equation 6.09, p. 53, (Frost)[12] the data in the cited references ([9,32]) and dividing by two. The assumption of linear radial rate of osteon closure involved in this procedure has been shown to be approximately true by Epker, Hattner and Frost.[8]

†Incidence means how often something happens in unit time. Relative incidence is how often it happens compared to other happenings. For example, the statement that male births are 52 per cent of all births is a statement of relative incidence. Prevalence is the composition of a population or sample at any instant. For example, the prevalence of males in the nurses residence is around .03, although the relative incidence of male births (outside of this residence!) is around .52.

The Basic Metabolizing Cellular Unit: Thus, a special kind of invariance has been shown to be present in a system of cells (i.e., that making new osteons). This is an invariance in the *distribution of transition probabilities* in a matrix of available choices of action. This embraces the fact that the distribution of sizes of osteons made this year seems to be unaffected by what happened last year or earlier, a situation which has the properties of the probability chain described by Markov,[6] and can be represented as an ergodic probability matrix.[3]

The property we have unearthed in this study could not be seen in cell-free homogenate systems, nor in studies of macroscopic portions of any organ such as the femur, lung or kidney. The reason is that this appears as a property of the basic, bone-forming unit inside of cortical bone, the secondary osteon.* This structure is made by a collection of cells of different kinds, and involves several different kinds of cell behavior and function which have varying degrees of synchrony with respect to their generation, and metabolic activity. The collection of cells and their functions appear to merit recognition as being a *system,* which is the smallest anatomical unit displaying the full range of behavior which is required to produce the phenomena known to occur in all cortical bone remodeling. (Elsewhere this system will be called a Basic Metabolic Unit, or BMU.) When intact organs or slices of them are studied that are made up of such units, the dynamic idiosyncrasies of individual BMU tend to be "drowned out" by the similar but asynchronous contributions of thousands of others in all different (i.e., asynchronous) stages of function. The idiosyncrasies of the individual units may thus appear as "noise", and tend to be ignored by observers.

Effect of this Invariance on Metabolic Regulation: It is natural to suspect that the biodynamic controls of some soft tissue systems may possess properties analogous to those we have shown here in bone. If so, this knowledge would be of crucial importance in learning how to regulate their metabolic activities on an *a priori* basis.† One reason for this is quite simple: Given: a tissue system whose total work load is divided up into a number of physically, temporally and functionally discrete units. The amount of "work" that each of these units had produced when finished would be invariant in the sense just described. Given further: that the function of these units can be turned on by some suitable stimulus. *There is only one way of producing a permanent change in the rate of metabolic output of such a system, and that is by changing the number of units that are functionally activated, or "turned on", in a unit period of time.* (In bone we have called this the mesenchymal cell activation function.)[12] *Changing the rate at which individual units function can*

*Which, as we will show later, *provides us with a synchronously generated culture or system of cells* (osteoclasts and osteoblasts), provided the system is studied in cross section. Moreover this culture can be observed as it functions in its *in vivo* state, completely unaffected by the observing act, because the cells leave a record of what they do. The record is permanent, and it is read after its transcription. This may be the only human situation in which synchronous cell culture can be studied *in vivo!*

†By a priori is meant that a system is well enough understood to manipulate its functions intelligently and with a high degree of confidence that a given manipulation or change will produce exactly the effect desired. The opposite of this would be "cut-and-try", or shooting in the dark, or purely empirical.

only cause temporary changes in the rate at which metabolic work is produced (i.e., system transients), which must always return to normal levels, given time enough and when the output of the entire tissue or organ is considered. The theoretical rate at which systems of cells can produce metabolic work is a function of the maximum, limiting amount of work per unit, the rate at which this work is produced by the unit, and the number of units that are active at any moment. One degree of freedom is removed from this system when the limiting amount is set constant. When the time parameters of such a system are known, the duration of the transient (or temporary change) caused by disturbing the rate of evolution of individual units can easily be calculated.

SUMMARY

The distribution of osteon cross section sizes in human rib is constant over the age span of 10-70 years, in spite of a more than two-fold change in the rates at which they are made over this same time. It is suggested (1) that similar dynamic invariants occur in other tissues, (2) and that analytical accuracy and comprehension of metabolic and aging processes would be improved in the future by recognizing and separating invariant from variable dynamic properties of experimental biological systems. This is a new concept in the study of the dynamics of multicellular systems.

References for this and the following two papers will be found on pages 49-50.