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AGE AND SEX RELATED CHANGES IN THE AMOUNT OF CORTEX OF NORMAL HUMAN RIBS[1]

By

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The group of diseases designated by the term "the osteoporoses" is becoming increasingly important as the average age of our population rises. Present methods of treating these diseases leave much to be desired, since it is only rarely possible to demonstrate an increase in bone mass even after years of faithful adherence to one of the commonly used therapeutic regimes. As *Sedlin* noted (1964a, 1964b), this failure of treatment has suggested to many that our present concepts of the physiologic mechanisms causing osteoporosis may benefit from reexamination. In this respect it is axiomatic that it is difficult to understand diseased tissues unless one has a good knowledge of the normal.

These facts have stimulated a number of investigators to perform longitudinal studies (with respect to age) of normal bone, hoping thereby to learn how to define what the normal is and to provide a rational basis for comparing abnormal skeletal tissue with normal. These studies include the ash and volumetric studies of *Trotter, Broman & Peterson* (1960) and of *Merz, Trotter & Peterson* (1956), the physical densities of *Wray, Sugarman & Schneider* (1963), the roentgen densities of *Lindahl & Lindgren* (1962), the highly accurate densities of *Arnold* (1960); and the osteoid seam counts of *Jee et al.* (1964). Almost all authors who have worked on these problems have

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tried to devise or/and refine some basis for quantitative and accurate measurement or one or more properties of bone.

This study was influenced by the following truism: In a very general frame of reference, and in adults, bone may be gained or lost at one or any combination of four locations: the periosteal surfaces, the surfaces of the vascular channels within cortical bone, the cortical endosteal-surface and the trabecular-endosteal surface. In defining normal, it seems reasonable to measure the age-related changes at these surfaces, and then to compare diseased skeletons with these data. The precise definition of the so-called "physiologic" age related changes in quantity, density and composition *within* cortical bone at a standard sampling site has been undertaken by others (*B. N. Epker & H. M. Frost* in Detroit, *W. S. S. Jee* in Salt City and *J. S. Arnold* in San Diego), as has the measurement of trabecular bone changes with age (by *W. S. Jee & coworkers* in Salt City and *J. S. Arnold & R. Murray* in San Diego). In this article we report a study of the age-associated changes in the transverse sizes of the periosteal and endosteal envelopes of standard rib samples, taken from metabolically normal people of all ages, supplementing thereby earlier reports by *Sedlin* (1964a), *Sedlin et al.* (1963) and *Epker & Frost* (1964).

MATERIALS AND METHODS

Materials

The mid-diaphysis of the 5th, 6th or 7th rib from 326 cases (117 females and 209 males) was available for this study through systematic sampling extending over an 8 year period. Ages ranged from one week to 90 years, and the age distribution is shown in Tables 1 and 2. Approximately one-quarter of the ribs were obtained from the operating theatre where thoracotomy was performed. Indication for the thoracotomies included repairs of lesions such as coarctation of the aorta, hiatus hernia, esopheageal diverticulum and trauma, and biopsy of the lung or the mediastinum for previously undiagnosed but nondebilitating solid lesions. The remaining cases were collected from the medical examiner's office and a general hospital autopsy room. Causes of death in this group included automobile accidents, homicides, suicides, vascular incidents, unknown cause and asphyxiation. These subjects were thought to be healthy, were functioning normally, and were not receiving medical attention, until their unexpected death. Generalized, serious metabolic diseases were believed to be absent in these people, on the basis of both the clinical history and the findings of the autopsies. No cases which were diagnosed during life as having osteoporosis or other metabolic bone disease were included in this series, and no cases were accepted if their records were inadequate to substantiate these matters. We are greatly indebted to the generosity of Drs. E. S. Zawadski, R. H. Horn and G. Fine for this material and for access to all relevant records.

Table 1. 209 Male Ribs: Cross Section Area Measurements.

Age range	Mean Age	Number of Subjects	Cortical Area (S.E.)	Marrow Area (S.E.)	Total Area (S.E.)
0–4	1.2	19	11.6 (0.9)	6.7 (.8)	18.3 (1.5)
0–10	2.9	25	13.6 (1.1)	8.9 (2.5)	22.4 (2.3)
11–20	15.3	14	26.6 (1.5)	26.7 (3.1)	55.0 (3.1)
21–30	24.5	29	26.3 (1.8)	36.1 (1.3)	62.2 (1.7)
31–40	35.7	29	22.5 (2.0)	43.4 (1.6)	66.1 (2.4)
41–50	44.2	31	21.7 (3.2)	40.3 (1.9)	62.5 (3.5)
51–60	54.5	33	21.7 (0.9)	40.9 (1.1)	62.0 (0.9)
61–70	64.3	23	19.3 (1.6)	44.5 (2.1)	64.0 (2.2)
71 +	73.8	23	20.1 (1.2)	53.7 (1.8)	73.7 (2.6)

Table 2. 117 Female Ribs: Cross Section Area Measurements.

Age range	Mean Age	Number of Subjects	Cortical Area (S.E.)	Marrow Area (S.E.)	Total Area (S.E.)
0–4	1.3	14	10.0 (1.6)	6.2 (2.1)	16.3 (2.8)
0–10	2.8	18	11.8 (2.6)	7.6 (1.7)	19.2 (3.0)
11–20	17	6	22.3 (2.9)	15.8 (2.3)	38.1 (3.4)
21–30	25.0	20	20.0 (1.7)	21.1 (1.4)	41.5 (2.5)
31–40	34.0	23	19.5 (2.2)	21.1 (1.9)	40.8 (2.5)
41–50	44.1	22	19.6 (.8)	23.3 (1.5)	42.9 (1.7)
51 +	58.9	30	16.1 (1.8)	26.7 (1.4)	42.9 (2.1)
61 +	71	14	17.9 (3.0)	33.9 (2.6)	52.6 (2.9)

(S.E.): The standard error of the mean.

METHODS

Sections

Fresh, mineralized, cross sections averaging 50–70 micra in thickness were made by hand grinding of the ribs that were examined (*Frost* 1958). The sections were cut within 5 degrees of perpendicularity to the longitudinal axis of the rib. They were stained 48 hours with a 50 per cent ethanolic, 1 per cent basic fuchsin stain, air dried and mounted in resin. There were three complete cross sections per case, and a total of 978.

Measurements of Cortical and Total Cross-sectional Area

A point count method employing a calibrated grid and described elsewhere (*Sedlin, Frost & Villanueva* 1963), was used to measure the areas of the cortex and of the marrow space as observed in the complete cross-section. (See Figure 1). The results are shown in mm^2. Each area in each section was measured with a precision of ± .8 mm. Values for each of the three cross-sections per case were thus obtained and the mean for each case calculated. The cases were arrayed in 10 year age groups and means for each group were calculated.

Figures of Merit

The C/T ratio of each group was obtained as described by *Sedlin* (1964 a), by division of the cortical area (A_c) by the total area (A_t). This may be written:

$$C/T = \frac{A_c}{A_t} \quad (1)$$

This number is the decimal part of the volume of the periosteal envelope that is filled with cortical bone.

The parabolic index of each group was also calculated. It has an optimum numerical value of 0.25 (*Epker & Frost* 1964) which is obtained by substituting in this formula:

$$Y = X\ (1 - X) \quad (2)$$

where Y is the parabolic index, X is the cortical area expressed as a decimal fraction of the total area, and unity represents the normalized total area. In terms of the parameters which were actually measured, this equation can be written, where A_m is the marrow cross section area:

$$Y = \frac{A_c \times A_m}{(A_t)^2} \quad (3)$$

This number (*i.e.*, Y) indicates the relative resistance of a rib to buckling when under longitudinal compression, and the farther below 0.25 the number is, the weaker is the bone.

RESULTS

The cortical, marrow and total cross section areas are summarized in Table 1 for men and 2 for women. The figures of merit are shown in Table 3.

The amount of cortical bone in ribs is definitely different between male and female, women having less. This difference is highly significant ($p < .001$) as was also found by *Sedlin et al.* (1963). The maximum amount of cortical bone occurs between ages 15 and 25 in both sexes, and declines afterwards. The decline by age 60 is about 25 per cent of the value at age 20. It is again demonstrated that the ratio of the cortical to the total cross section constantly decreases throughout life in both sexes. Women consistently show a larger ratio than men, with the exceptions of the youngest and oldest groups. After skeletal maturity, the parabolic index of the male ribs shows a steady decrease, but that of the females tends to stay near the maximum level up until age 60, when it begins to decrease rapidly.

Table 3. Figures of Merit: 326 Human Ribs.

Age range	A_c/A_t ratio*		Parabolic Index		Mean Age	
	Male	Female	Male	Female	Male	Female
0–4	0.633	0.615	0.232	0.237	1.2	1.3
5–9	0.594	0.609	0.241	0.238	6.9	7.9
10–14	0.489	–	0.250	–	12.8	–
15–19	0.482	0.584	0.250	0.243	16.8	17.2
20–24	0.413	0.512	0.242	0.249	21.9	22.5
25–29	0.435	0.463	0.246	0.249	27.0	28.1
30–34	0.349	0.506	0.227	0.250	31.0	31.3
35–39	0.338	0.446	0.224	0.247	37.4	37.0
40–44	0.355	0.444	0.229	0.247	41.8	42.1
45–49	0.339	0.470	0.224	0.249	47.0	47.0
50–54	0.338	0.438	0.224	0.246	51.5	52.9
55–59	0.311	0.411	0.214	0.242	56.8	57.3
60–64	0.321	0.430	0.218	0.245	61.4	62.0
65–69	0.283	0.360	0.203	0.230	67.3	66.8
70 +	0.272	0.267	0.198	0.196	73.8	79.8

* Cortical area/total area ratio.

DISCUSSION

1. *The Menopause.* The changes in total and cortical cross section areas do not correlate with the onset of either puberty or the menopause[1]. This is interesting since it has been widely believed (*i.e., Albright & Reifenstein* 1948, *Snapper* 1957) that ovarian function bears some causal relationship to postmenopausal osteoporosis.

A similar lack of evidence for a change in amount of bone especially at menopause has been found by others (for example, *Lindahl & Lindgren* 1962, *Merz et al.* 1956, *Trotter et al.* 1960). These facts suggest that (i) in healthy women there is no increase in the rate of loss of bone at or immediately following cessation of cyclic ovarian function and (ii) if the menopause is causally related to postmenopausal osteoporosis, it may be through an extraovarian mechanism. It does not seem likely that ribs provide a false picture of the age-related changes in the skeleton in general, because it has been shown that ribs do reflect the general trends throughout the skeleton, and in fact do so sooner than most other bones. For example, this is shown by an elegant study done by *Amprino & Marotti* (1964), and was noted also by *Johnson* (1964a, 1964b).

[1] Unless otherwise noted the .05 level was tested for significance.

2. *The Total Cross Section Area.* There is a significant increase in the total cross-sectional areas of both male and female ribs after age 60. This increase is proportionately larger in women than men. When it is realized that the 65 and 70 year old patients in this study grew up in a public health and nutritional environment that was more than 35 years behind that of the subjects aged 20–35, and were therefore of generally smaller stature, it can be seen that one would have been led to predict, as more likely, *a smaller* total area in the older groups rather than a larger one. This kind of age-related increase in size of a bone was first reported by *Sedlin et al.* (1963), on the basis of fewer rib samples than are reported here. Since then, *Smith & Walker* (1964) have reported a highly significant age-related increase in the transverse diameters of femurs in more than 2000 women. The increase approximated 5 per cent between ages 40 and 80. These findings suggest that periosteal new bone apposition does not stop at skeletal maturity, but rather subsides to some basal level.

One meaning of the age-associated changes in total area in both men and women is that the periosteal surfaces of ribs are *never in negative balance* during life. That is, in sum they never lose bone, so the volume of space inside the periosteum never shrinks.

3. *The Cortical Area.* In both men and women the amount of cortical bone peaks at age 15–30, and thereafter declines. The loss is on the order of 25–30 per cent for both sexes. This parallels previous similar findings by many, for example, *Trotter, Broman & Peterson* (1960), *Lindahl & Lindgren* (1962). It appears that the aging process normally carries with it an associated loss of skeletal material, which has been called the "physiologic" osteoporosis.

4. *The Marrow Area.* The cross section area of the marrow cavity continually enlarges during life, the rate of enlargement leveling off temporarily during the age span 20–40 years. The shape of this curve is similar in both men and women. Since the cortical areas decline after age 30, while the total areas increase, the enlargement of the marrow cavity must be the direct cause of the decrease in cortical area, and it must be larger than the increase in the total area. It follows that after age 30, the cortices of these ribs should become thinner, and this is the case.

One meaning of the changes in marrow area is that when regarded as a whole, *the endosteal surface of the cortex is never in positive* *balance.* In other words, the marrow cavity never normally shrinks in size. This suggests that in osteoporosis, this negative endosteal balance probably is the mechanism directly responsible for the associated cortical thinning.

5. *The C/T Ratio. Sedlin* (1964 a) reported a study of the age-associated changes in the proportion of the periosteal envelope that is filled with bone, in ribs. His findings are essentially confirmed in this study, which contains well over twice as many subjects as his. This study does show that there is more tendency to retain bone in aging women than in men, until age 50. Thereafter women lose bone quickly, especially when compared to men. It has been stated, on the basis of histological findings, that estrogen suppresses both bone resorption and formation (*Frost* 1963). If this were true, one could predict that women would retain bone better than men before the menopause, and lose it faster afterwards. It is important that this change, which does correlate with the menopause, is the result of a change in the proportions of bone resorption and formation at two surfaces: periosteal and cortical endosteal. The changes at either surface alone fail to show statistically significant menopause-associated change.

6. *The Parabolic Index.* In mechanics this relationship (which is usually given in different but equivalent form) is known as the *parabolic index for nominally concentrically loaded columns* (*Popov* 1962). The closer the figure of merit approaches to the ideal value of 0.25, the more efficiently is the available structural material being used to withstand longitudinal compression loads. While the figure of merit may assume any lesser value than 0.25, it cannot exceed this number.

Again a significant difference emerges between men and women. The men's index falls off steadily after age 35, while the women's remains high until age 50, after which it then shows a rapid decline. Values at the end of the life span are similar in both groups. Again this parameter seems to show a change associated with the menopause. This would be expected because of the similar finding concerning the C/T ratio, and because of the close mathematical relationship between these two figures of merit.

SUMMARY

Cross section areas were measured on the middle third of the 5th, 6th or 7th rib from 326 metabolically normal people. In this sample the amount of bone in the cortex peaks between ages 15–25 in both sexes, and thereafter declines, reaching values 25 per cent less by age 65. The space inside the periosteal envelope increases during childhood, levels off at age 20, and begins to increase again after age 55. The periosteal bone surface seemed never to be in net negative balance (between resorptive and formative activity), while the cortical endosteal surface seemed never to be in a positive one. The observed changes did not associate clearly with puberty or the menopause.

RESUME

Des sections transversales ont été mesurées dans le tiers du milieu des 5ème, 6ème et 7ème côtes chez 326 sujets normaux métaboliquement. Dans ces échantillons la quantité d'os dans le tissu compact culmine entre l'âge de 15 et 25 ans chez les deux sexes pour décliner ensuite en atteignant des valeurs inférieures de 25 pour cent à l'âge de 65 ans. L'espace à l'intérieur du périoste augmente durant l'enfance, atteint son niveau à 20 ans et recommence à augmenter après 55 ans. La surface du péroste ne semble jamais avoir un équilibre négatif (entre la résorption et l'activité de formation) tandis que la surface corticale endostale ne semble jamais avoir un équilibre positif. Les modifications constatées ne sont pas clairement liées à la puberté ou à la ménopause.

ZUSAMMENFASSUNG

Querschnittsschnitte am mittleren Drittel der 5., 6. oder 7. Rippe von 326 Personen mit normalen Grundumsatz wurden gemessen. In diesen Präparaten erreichte die Knochenmenge in der Cortex die höchsten Werte zwischen 15–25 Jahren bei beiden Geschlechtern, und sinkt hernach indem sie im Alter von 65 Jahren Werte erreicht, die 25 pro Zent niedriger liegen. Der Raum innerhalb der periostalen Hülle nimmt während der Kindheit zu, hält sich unverändert von 20 Jahren ab und beginnt nach dem Alter von 55 Jahren wieder zuzunehmen. Die periostalen Knochenoberflächen schienen sich niemals in einer negativen Balanz (zwischen resorbierender und aufbauender Tätigkeit) zu befinden, während die kortikale endostale Oberfläche niemals eine positive aufzuweisenschien. Die beobachteten Veränderungen standen nicht in deutlicher Verbindung mit der Pubertät oder der Menopause.

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