

## Occasional Survey

# Bone and ageing

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That regular decay of nature which is called old age, is attended with changes which are easily detected in the dead body, and one of the principal of these is found in the bones, for they become thin in their shell and spongy in their texture.

SIR ASTLEY COOPER, 1824

Bone involution has become an important clinical problem and is of primary importance for the differentiation between bone loss with age and pathological bone loss. In order to eliminate this problem it is necessary to define bone loss (osteoporosis). The classical definition of osteoporosis by Albright and Reifstein (1948), 'Too little bone, but what bone there is, is normal', has been widely accepted (Nordin, 1960; Saville, 1965; Dent and Watson, 1966; Harris and Heaney, 1969a). This fundamental definition has never been seriously challenged and a clear distinction made between osteoporosis and osteomalacia. Albright's definition does not define 'too little bone'. If this means too little by the standards for adults in the prime of life, many persons who have no symptoms have osteoporosis simply because physiological changes of ageing have affected their bone. In order to determine the decline in skeletal mass some standard of normal is necessary.

### **Skeletal mass and ageing**

With increasing age there is a decrease in bone mass as measured in various ways. The radiographic density of finger bones and spinal column measured *in vivo* becomes less (Balz, Birkner, and Smith-Rohde, 1957; Lindahl and Lindgren, 1967), as does the monochromatic gamma source density of the radius (Johnston, Smith, Yu, and Deiss, 1968; Goldsmith, Johnston, Ury, Vose, and Colbert, 1971; Dequeker, Roh, Van Dessel, Gautama, and Burssens, 1973b). The weight of the skeleton decreases as does the physical density (weight/volume) of individual bones (Trotter and Peterson, 1955; Trotter, Broman, and Peterson, 1960).

The amount of cortical bone, measured by mor-

phological methods, diminishes in rib cross-sections (Sedlin, 1963), in the second metacarpal (Nordin, McGregor, and Smith, 1966; Garn, Rohmann, and Wagner, 1967a; Morgan, Spiers, Pulvertaft, and Fourman, 1967; Dequeker, 1972a), in the radius (Meema, Bunker, and Meema, 1965), and in the femur (Smith and Walker, 1964). Density of iliac plugs similarly diminishes with age (Saville, 1965; Dequeker, Remans, Franssen, and Waes, 1971b) as does the mineral content of femoral fragments removed in the treatment of hip fractures (Wray, Sugarman, and Schneider, 1963). Trabecular bone loss with age has been documented by quantitative histology (Beck and Nordin, 1960; Sissons, 1964; Coupron, Meunier, Vignon, Edouard, Bernard, and Thomas, 1971). The microradiographic appearance of ageing compact bone is one of porosity, of great variation in mineral density, and of plugged canals (Jowsey, 1960; Sissons, 1962; Lacroix and Dhem, 1967). Bone loss with age is not confined to modern population samples. Similar decreases in bone mass have been reported for prehistoric populations (Van Gerven, Armelagos, and Bartley, 1969; Dewey, Armelagos, and Bartley, 1969; Perzigian, 1973).

The uniformly reported cross-sectional data on bone loss with age were confirmed by longitudinal data, precluding differential sampling and selective mortality (Garn and others, 1967a; Adams, Davies, and Sweetnam, 1970; Dequeker, 1972a). Thus the decline in bone mass is a real ageing phenomenon not solely due to a secular or sampling error. It is a general phenomenon in man, affecting men as well as women of all races. In both sexes there is a period of growth of cortical bone up to the fourth decade, which is then followed by a decrease of cortical

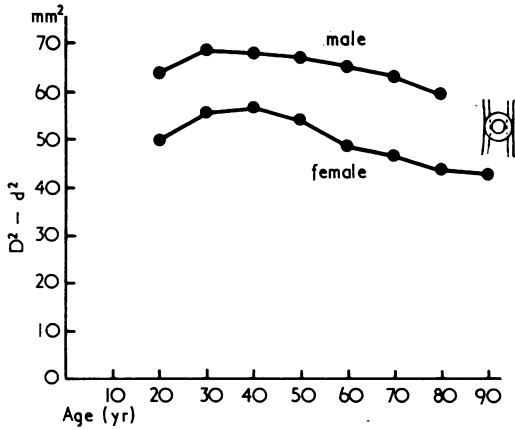


FIG. 1 Age-associated changes in cortical area ( $D^2 - d^2$ ) calculated from measurements made at midpoint of the second metacarpal in 643 women and 194 men

bone. The decrease is faster in women than in men.

Fig. 1 shows the age pattern of cortical bone at midpoint of the second metacarpal, expressed as cortical area. The average loss in women is about 5.7% and in men 3.1% per decade. For trabecular bone at the iliac crest the loss amounts to 5.5% per decade in women and 1.6% in men, age range 40–80 years. According to Doyle (1972), the 'average man' can expect to lose one-eighth of the cortical bone and approximately one-quarter of the trabecular bone in his left ulna between the fifth and ninth decades. The 'average woman' can expect to lose just over one-quarter of the cortical bone and more than half of the trabecular bone.

Fig. 2 illustrates the author's findings with respect to the age changes in iliac crest trabecular bone as determined by Archimedes principle (Dequeker and

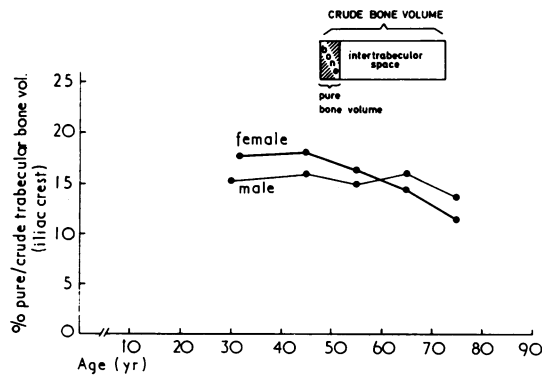


FIG. 2 Age-associated changes in percentage pure/crude trabecular bone volume at the iliac crest in 91 women and 121 men

others, 1971b). Women had a higher mean relative amount of trabecular bone than men in early adulthood, and a lower mean relative amount in old age. These sex differences did not reach formal significance, but Coupron and others (1971), using the larger sample, found a significantly larger bone density in females than males aged less than 50 years. Fig. 2 shows a fall in the amount of trabecular bone in elderly females, but not in males. Other workers (Garner and Ball, 1966; Sissons, 1967), using morphometric methods and smaller samples, found a significant fall in iliac trabecular bone in elderly males and females and no sex difference at any age level. Arnold (1964), studying vertebral trabecular bone by Archimedes method, found a fall in bone density in elderly males and females. The explanation for these observer differences is not clear. It is important to realize that in any age-sex category, there is a large variability in bone density which makes differentiation between sexes and between physiological and pathological bone loss difficult.

There is a good statistical relationship between changes in the peripheral and axial skeleton (Fig. 3); between metacarpal cortical bone and stature (Dequeker, Baeyens, and Claessens, 1969); between cortical thickness and spinal porosity grades (Meema, 1963; Saville, 1967; Dequeker, Franssen, and Borremans, 1971a); between cortical thickness and fat-free dry bone weight per unit volume of iliac crest biopsies (Saville and Nilsson, 1966; Dequeker and others, 1971b); between ulnar density and vertebral strength, or iliac biopsy ash weight (Chalmers and Weaver, 1966); between metacarpal

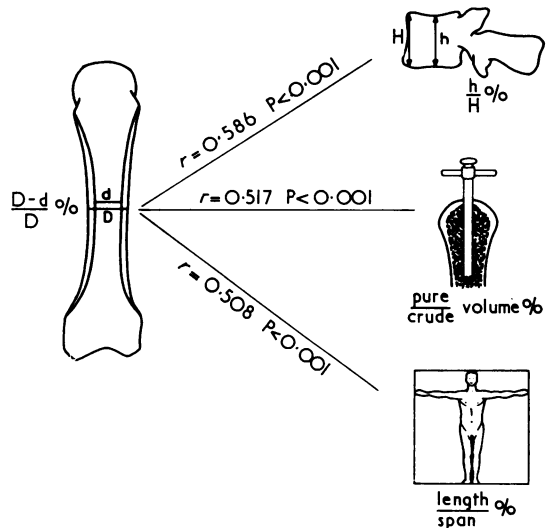


FIG. 3 Correlation of % metacarpal cortical thickness with, respectively, lumbar biconcavity index, % pure/crude bone volume iliac crest, and length/span ratio in women

density and vertebral density (Nordin, Young, Bentley, and Sykes, 1968); between mineral concentration of the distal 8 cm of the left ulna and ash weight per unit volume of the third lumbar vertebra (Doyle, 1972).

Although the correlations between peripheral and axial skeletons are significant, less than 40% of the variation is accounted for in the regression. This observation indicates that a knowledge of the amount of bone in one particular bone is of no help in predicting fractures in other parts of the skeleton. Adams and others (1970) have shown that measurements of metacarpal cortical thickness in surveys 11 years apart, or of change in thickness between the surveys, were of no value in selecting the people who sustained peripheral or vertebral fractures.

### Fracture epidemiology and ageing

Bones of the elderly appear to be more fragile than those of younger people. This fragility appears to be selective and tends to be mainly localized to the proximal femur, the proximal humerus, the distal radius, and the vertebral bodies—areas where the main bone structure is cancellous. Fractures of the proximal end of the femur are particularly common among the elderly and it has been considered that the incidence of such proximal fractures may be taken as an index of general osteoporosis.

Increasing attention has been paid to the epidemiology of the 'fractures themselves' not only to assess the size of the medical problem now and in the future, but also in the hope that some light might be shed on their aetiology (Stewart, 1955; Buhr and Cooke, 1959; Alffram and Bauer, 1962; Knowelden, Buhr, and Dunbar, 1964; Alffram, 1964; Wong, 1966; Solomon, 1968; Chalmers and Ho, 1970). Although these studies have provided valuable information to the aetiology of fractures and their relation to bone loss with age, they have provided more questions than answers (Doyle, 1972). Chalmers and Ho (1970) compared the frequency of hip fractures (the annual age-specific incidence of hip fractures per 100000 population) quoted for several different populations (Chinese in Hong Kong, Swedes in Malmö, Britons in Dundee and Oxford, South African Bantu in Johannesburg, and a mixed south-east Asian community in Singapore). In all communities, the incidence of hip fractures increases with age after 45. The rate of increase varies greatly, being greatest in the Swedes and least in the Bantu.

After the age of 45, the incidence of hip fractures in Sweden and Britain is twice as high in women as in men. In Hong Kong the incidence in men and women is almost equal, while in Singapore men with hip fractures significantly outnumber women. The higher incidence of fractures in women of 'advanced' societies seems to be to some degree an

undesirable consequence of the easier work-load which the western societies appear to regard as a major objective and desirable attainment. The age at menopause is the same in all the populations studied.

The relationship between the incidence of hip fractures and the dietary intake of calcium and protein, both widely quoted as factors relevant to the problem of osteoporosis, is inverse in the populations considered. The relationship between hip fractures and osteomalacia as a contributing factor is of considerable interest since the latter can be corrected. Aaron, Gallagher, Anderson, Stasiak, Longton, Nordin, and Nicholson (1974) found some evidence in Leeds of osteomalacia in iliac crest biopsy specimens obtained from 125 cases of fracture of the proximal femur in 45% of the women and 47% of the men. Using more rigid criteria, 20% out of the total 125 cases had osteomalacia. Partial gastrectomy was the most important predisposing factor.

### Relation of bone mass or bone density to bone strength

Although a lower mean value of bone mass or bone density in women with idiopathic vertebral fractures or with femoral neck fractures compared to the mean value in controls matched for age and sex has been found, only a few patients have a value below the lowest value recorded in the controls (Fig. 4) (Doyle, 1972; Dequeker, 1972a; Dequeker, Van Wallegghem,

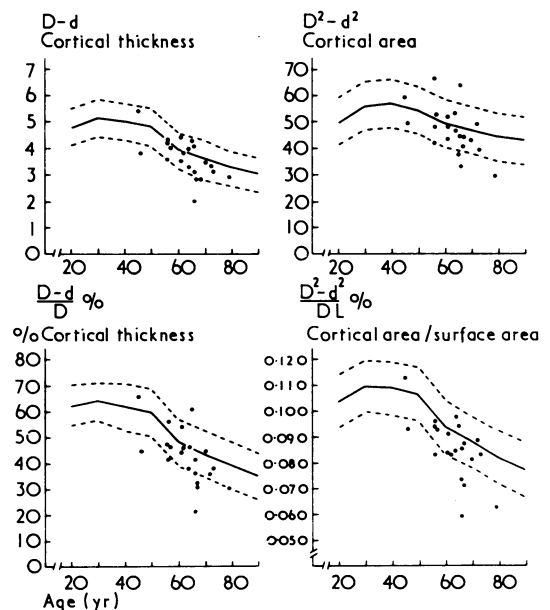


FIG. 4 Radiography of second metacarpal. Distribution of metacarpal bone mass indices in 21 female vertebral collapse patients. The normal mean values are indicated by — and the range by ----.

De Schepper, Roh, Gautama, Van Dessel, and Burssens, 1973a; Dequeker and others, 1973b; Alhava and Karjalainen, 1973; Aaron and others 1974). Thus, measurements at the peripheral skeleton are unable to distinguish between 'normal' women and women with vertebral fractures.

These observations provoked some speculations, formulated by Doyle (1972), as follows.

*First speculation* Women with vertebral fractures are different from 'normal' women of the same age only in respect of the amount of bone in their vertebrae. Either: at the time of fracture the vertebrae had too little bone because they never had much to begin with, and some relatively trivial loss of bone was enough to tip the scale and convert a bone which was just strong enough to support the mechanical demands placed on it into a bone just weak enough to be fractured by the ordinary demands of living. Or: at the time of fracture, the vertebrae had too little bone because large amounts of bone had been selectively lost from the axial skeleton, the appendicular skeleton being relatively unaffected.

*Second speculation* Women with vertebral fractures are different from 'normal' women of the same age only in respect of their vertebral fractures. The amount of bone in their vertebrae does not distinguish them from women without vertebral fractures. The mass of bone in a vertebra or the bone mass per unit volume of a vertebral body does not accurately reflect the 'strength' or the 'fragility' of the vertebra.

Since a sufficiently accurate method of measuring the amount of bone in a vertebral body *in vivo* has yet to be devised, there are no studies which confirm, refute, or modify one of these speculations. Studies on mechanical properties of vertebral bodies of patients diagnosed in life as having spontaneous vertebral fractures are not available. A few studies, however, on the relationship between vertebral bone mass and bone strength showed that the ash weight per unit volume is significantly correlated with the compressive strength (Weaver and Chalmers, 1966) and with breaking stress (Bell, Dunbar, and Beck, 1967). Rockoff, Sweet, and Bleustein (1969) assessed the relative contribution of trabecular and cortical bone to the strength of lumbar vertebra. They concluded that the cortex of a lumbar vertebral body generally contributes 45 to 75% to the peak strength regardless of the ash weight per unit volume of trabecular bone. Rockoff (1970) further suggested that bone 'strength' (measure of compliance) and bone 'brittleness' (a measure of breakability) may be different things and that old people might have 'bad bone' in terms of brittleness.

Perhaps the simplest way to assess and to follow the failure of vertebral bone 'strength-brittleness' is the measurement of loss of stature as compared to armspan length. Dent (1955) pointed out that loss of stature due to shortening of the trunk is the most important early sign of pathological bone loss at the

vertebral column. With normal ageing a decrease in stature of 1.3 cm per decade from the fifth decade onwards has been reported (Dequeker and others, 1969; Kalliomäki, Siltravuori, and Virtama, 1973). The majority of patients with vertebral collapse have a loss of stature greater than the expected normal loss with age (Saville and Nillson, 1966; Dequeker, 1972b). It should, however, be realized that disc degeneration may influence body height.

### Bone composition and ageing

So far the first part of Albright's definition, 'too little bone', and age have been defined; the second part concerning the composition of bone and age will now be discussed. With increasing age no significant changes in bone composition has been found. The percentage ash weight is not affected by age (Trotter and Peterson, 1962; Dequeker, 1972a). The calcium and phosphorus content and Ca/P ratio of human trabecular bone remains unchanged with normal ageing (Follis, 1952; Dequeker, 1972a). Vogt and Tønsager (1949), however, found a significant increase with age in calcium content.

Although collagen, the principal structural component of bone matrix, has received more attention than any of the other constituents, publications are not in agreement on changes in collagen content with age or with disease. Casuccio (1962) found an increasing content of collagen in human dry spongy bone (lumbar vertebra) with age; Rogers, Weidmann, and Parkinson (1952) a decreasing collagen content with age in human femora; and Birkenhäger-Frenkel (1966) reported a lower collagen content in iliac crest bone in osteoporotics. Dequeker and Merlevede (1971) found no quantitative changes with ageing in collagen per fat-free dry bone weight or per unit pure bone volume, in contrast to the finding of Eastoe (1956) who noted a definite fall with increasing age in femora.

In Table I the results on human bone composition according to age are reported (Dequeker and Merlevede, 1971). An average of 13% fat-free dry bone weight is not accounted for, as the sum of the weights of ash (59%) and organic matter after demineralization (28%) amounted to 87%. As pointed out by Robinson and Elliott (1957), in the process of ashing bone, in addition to oxidizing and driving off the organic material a variable amount of chloride, potassium, intracrystalline water, and carbon dioxide (CO<sub>2</sub>) is lost, and some soluble organic matter is lost during decalcification.

Since no significant quantitative differences with age or sex have been reported for the mineral or collagen content of human bone, a concomitant osteomalacic phenomenon with ageing is not established. Bone collagen, however, shows qualitative changes with age. The results of sequential

**Table I** Collagen, ash, calcium, and phosphorus content of fat-free dry trabecular bone according to age in both sexes

Age groups (yrs)	Collagen (g/kg) fat-free dry bone			Ash (g/kg) fat-free dry bone			Calcium (mol/kg) fat-free dry bone			Phosphorus (mol/kg) fat-free dry bone		
	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
20-29	18	229.7	2.66	9	593.9	1.83	9	6.29	0.79	9	3.65	0.45
30-39												
40-49												
50-59												
60-69	20	223.2	2.86	21	594.0	1.35	21	6.28	0.49	21	3.59	0.23
70-79												
80-89												
Total 20-89	73	228.5	2.84	49	593.1	1.55	49	6.28	0.66	49	3.57	0.33

collagen extraction in various salt solutions reported by Dequeker and Merlevede (1971) indicate that the extractability of bone collagen decreases progressively after maturity, probably due to increasing cross-links (Fig. 5).

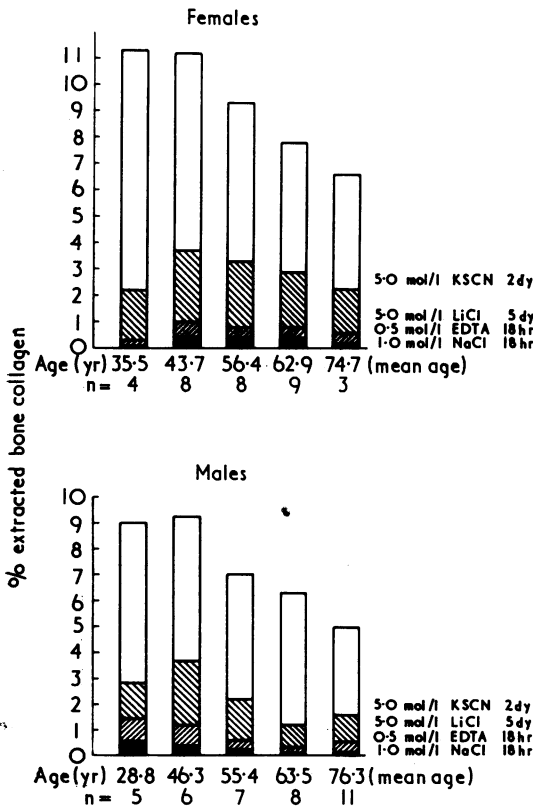
Bone collagen behaves after maturity in the same way as rat skin collagen (Nimni, Deshmukh, and Bavetta, 1967), human skin collagen (Bornstein and Piez, 1964), human tendon collagen (Steven, 1966), and human costal cartilage collagen (Miller, Van der Korst, and Sokoloff, 1969). Although the quantitative estimation of collagen in bone is unaltered during ageing, a significant qualitative change does occur.

**Biochemical parameters of skeletal metabolism, and ageing**

Biochemical data obtained from body fluids are a great clinical tool for diagnosis and therapeutic effectiveness. Normal biochemical values are usually standardized for a young adult population. Information on variations with age in the adult population is limited.

**URINARY PARAMETERS**

In Fig. 6 negative correlation between age and the urinary excretion of calcium, phosphorus, and total hydroxyproline in women is shown (Dequeker, 1972a). Saleh and Coenegracht (1969), Davis, Morgan, and Rivlin (1970), and Bulusu, Hodgkinson, Nordin, and Peacock (1970) found the same decrease in excretion of calcium, phosphorus, or total hydroxyproline with age also in men. The decrease of calcium excretion with advancing age can be explained by a reduced intestinal absorption of calcium since it occurs in spite of the same calcium intake (Caniggia, Gennari, Bianchi, and Guideri, 1963; Avioli, McDonald, and Lee, 1965; Bullamore, Gallagher, Wilkinson, Nordin, and Marshall, 1970). The reduced excretion of phosphorus in the older age groups is probably also due to reduced absorption from the intestine. Assuming that the skeletal collagen determines the amount of total hydroxyproline excretion is correct, then the fall of total



**FIG. 5** Distribution of collagen between the different fractions extracted in the cold from trabecular bone according to age and sex (results are expressed in % of total collagen content)

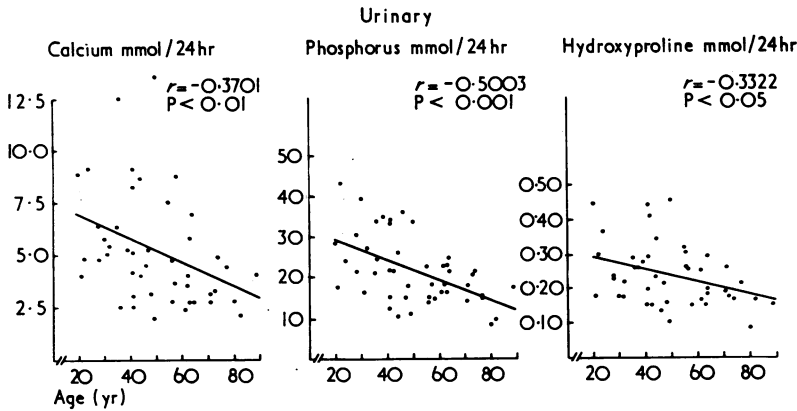


FIG. 6 Regression of urinary calcium, phosphorus, and total hydroxyproline on age in 59 women

hydroxyproline excretion with age, especially after the age of 50, can be explained by the age-associated decrease of skeletal mass. Under normal circumstances the excretion of urinary constituents varies from day to day in any one person but there is a greater variation from one person to the next, especially among young individuals (Fourman and Royer, 1968). The urinary calcium excretion expressed in mmol/kg body weight is better than the expression mmol/24 h, as it reduces individual variations, and according to Bulusu and others (1970) also sex differences. It is also preferable to express urinary total hydroxyproline excretion as mmol/24h per m<sup>2</sup> of body surface area as suggested by Jasani, Nordin, Smith, and Swanson (1965). Results expressed in this form are equal for both sexes and have a smaller variation around the mean (Mautalen, 1970). Taking body size differences into account, a significant decrease in calcium, phosphorus, and total hydroxyproline excretion with increasing age remains (Dequeker, 1972a).

A diurnal rhythm in the urinary excretion of various constituents including calcium has been reported by several workers in young adults (Stanbury and Thomson, 1951; Heaton and Hodgkinson, 1963; Loutit, 1965; Min, Jones, and Flink, 1966; Buchsbaum and Harris, 1971). The influence of age on the diurnal pattern of excretion of urinary constituents is shown in Fig. 7 (Dequeker, 1972a). This study confirms the day-night difference in the excretion of urinary constituents reported in young adults and reveals an inversion of the pattern in the elderly.

The change in diurnal rhythm with the advancement of age is progressive for all constituents and does not occur abruptly at the menopause as reported by Nordin (1971) for calcium excretion. At the age of 50 the night excretion equals the day excretion and thereafter night excretion, except for potassium, exceeds day excretion. The inversion of the diurnal

pattern with increasing age is the result of diminished output during the daytime without a concomitant change during the night. The reduced output during the day is probably related to the reduced gastrointestinal absorption or to reduced intake and/or to reduced renal excretion. As the kidney does not seem to have a retaining effect at night, this may lead to negative balances especially for calcium.

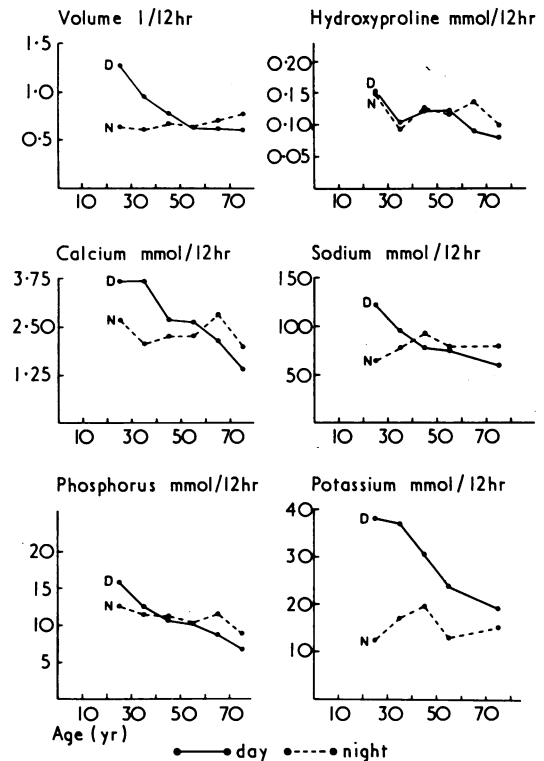


FIG. 7 Age-associated changes in day and night excretion of urinary constituents in 59 women

## SERUM PARAMETERS

Although changes in serum calcium, phosphorus, and alkaline phosphatase have been studied extensively in connexion with bone and parathyroid diseases, little information is available on the age and sex differences of these parameters in a normal adult population. In Fig. 8 are shown the age-associated changes in mean serum calcium and alkaline phosphatase in 729 women and 1374 men (J. V. Joossens, J. Willems, J. Claessens, J. Claes, and W. Lissens, personal communication, 1972). There is not only a sex difference, but also a change with age in serum calcium and alkaline phosphatase. Women up to the age of 50 have a lower calcium and alkaline phosphatase level than men, and in the older age groups the sex differences are reversed. A similar significant sex difference for serum calcium has been reported in young adults by Frank and Carr (1957) and by Roberts (1967); for alkaline phosphatase activity by Dent and Harper (1962), Klaassen and Siertsema (1964), and Roberts (1967). Since the latter author found a significant sex difference in serum protein levels, men having a higher mean value than women (age range 20–50 yrs), the sex difference in serum calcium might be explained by the difference in serum protein.

The reason for the sex difference in serum alkaline phosphatase in young adults is unknown, but may be related to skeletal size difference. Dent and Watson (1966), however, could not find a correlation

within one sex group between alkaline phosphatase activity and body weight or height. They suggested that the difference could be due to a difference in physical activity.

The age-associated increase in serum calcium and alkaline phosphatase after the age of 55 reported is most clear-cut in women. In agreement with the reported changes in serum calcium is the observation of a significantly higher mean serum calcium level in post-menopausal women made by Young and Nordin (1967). A rise in serum alkaline activity with increasing age has been observed previously by several workers who also found a more marked change in women than in men (Clark, Beck, and Shock, 1951; Hobson and Jordan, 1959; Klaassen and Siertsema, 1964; Roberts, 1967). Klaassen and Siertsema (1964) attributed the age-associated increase in alkaline phosphatase activity to a change in liver function, and Roberts (1967) suggested that the increase with age is due to an unrecognized increased incidence of Paget's disease. However, the concomitant increase in serum calcium and serum alkaline phosphatase in women and not in men at the age of 55 suggests the possibility of a hormone-induced change.

If the menopause is responsible for the rise in serum calcium and alkaline phosphatase activity, oestrogenic hormones might be expected to reverse the process. This is in fact the case. Oestrogen treatment in post-menopausal women lowered significantly the serum calcium (Jasani and others, 1965; Parfitt, 1965; Aitken, Hart, and Smith, 1971) and alkaline phosphatase activity (Lafferty, Spencer, and Pearson, 1964). Riggs, Jowsey, Kelly, Jones and Maher (1969) found that oestrogen significantly reduced serum calcium, phosphorus, and alkaline phosphatase levels and the urinary excretion of calcium and total hydroxyproline. At the same time an inhibition of bone resorption, measured by microradiographic studies, was observed. Since oestrogenic hormones have been shown to inhibit bone resorption in animals (Lindquist, Budy, McLean, and Howard, 1960) and in men (Eisenberg, 1966; Riggs, and others, 1969), their effect on serum calcium and alkaline phosphatase can be attributed to this action. It is not impossible that alkaline phosphatase activity, which is supposed to reflect osteoblastic activity, is reduced with a decreased resorption, since calcium kinetic studies have shown that bone resorption and formation are coupled (Harris and Heaney, 1969a).

The inhibitory action of oestrogenic hormones on bone resorption is possibly due to a reduction of the effect of parathyroid hormone on bone. In tissue culture experiments with 5-day mouse calvaria, Nordin, Young, Bulusu, and Horsman (1970) found that stilboestrol diphosphate inhibits the bone-resorbing action of parathyroid hormone.

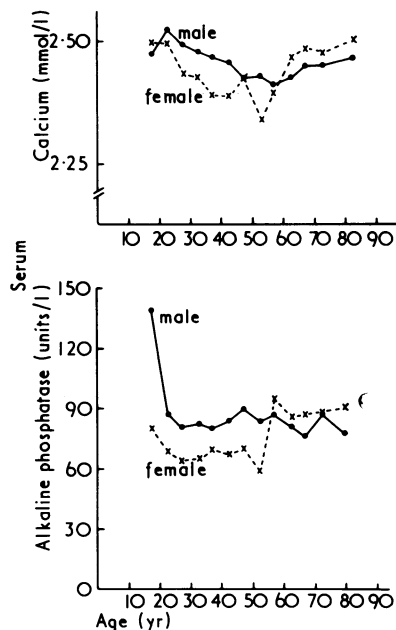


FIG. 8 Age-associated changes in mean serum calcium and alkaline phosphatase in 729 women and 1374 men

Thus the post-menopausal increase in serum calcium and alkaline phosphatase activity would then be related to a lack of oestrogenic protection against the resorbing action of parathyroid hormone. The rise in serum calcium in men after the age of 65 might be explained on the same basis.

### Bone remodelling and ageing

Throughout life, even after cessation of longitudinal growth, cancellous and cortical bone are constantly being replaced by resorption of existing areas and by production of new deposits in microscopical amounts at many sites heterogeneously distributed throughout the skeleton. Changes in this balance between formation and resorption have a critical role in calcium homeostasis and underlie every disease with a notable influence on the adult skeleton (Harris and Heaney, 1969a). X-ray determination of periosteal and endosteal surface changes in long bones in different populations or in the same population over a period of time provides information on skeletal dynamics. Skeletal renewal at the second metacarpal during ageing is shown in Fig. 9 (Dequeker, 1972a). The periosteal and endosteal diameters increase significantly with age in both sexes. The observed increase in periosteal diameter confirms the large scale cross-sectional findings reported by Bugyi (1965), Virtama and Helelä (1969), Garn and others (1967a), and Adams and others (1970). The latter authors were able to exclude selective survival or a secular trend on the basis of longitudinal data on older adults followed over a 15-year and an 11-year period, respectively. Smith and Frame (1965), however, did not observe a significant increase in metacarpal periosteal diameter in 2063

women, age range 45 to 90 years. Increases in periosteal diameter have been reported for the femur in women aged 45–90 (Smith and Walker, 1964), for rib cross-sections of subjects of both sexes aged 0–69 years (Epker, Kelin, and Frost, 1965), and for the skull of subjects of both sexes aged 25–84 years (Israel, 1973; Garn and others, 1967b).

Continuing bone growth is thus a general phenomenon not necessarily related to weight bearing or flexion stress as suggested by Smith and Walker (1964). It is also unlikely that periosteal bone growth is a compensatory response to endosteal bone loss, as the rate of periosteal growth is not necessarily in proportion to the rate of endosteal loss (Garn and Poznanski, 1970). As both processes may represent responses to different mechanical and hormonal stimuli, they have to be considered separately in studies of osteoporosis and osteoporotic bone loss.

Medullary cavity expansion due to endosteal bone loss is characteristic of advancing age in both sexes. Though medullary expansion rates and the endosteal bone losses are relatively low in the fourth and the fifth decade, expansion in both sexes increases after the age of 50, more so in women than in men. The endosteal surface enlarges throughout life faster than the periosteal surface, causing a net loss of cortical bone. Thus bone loss with age is not the result of decreased bone formation but the result of a lack of balance between formation and resorption.

### Bone remodelling in pathological conditions versus bone remodelling in ageing

Is osteoporosis a single disease entity, the end result of a normal ageing phenomenon, or a nonspecific reaction of the skeleton to a wide variety of stimuli? Bone involution seems to be a general phenomenon and a normal manifestation of the atrophy of tissues in the process of ageing. The rarer occurrence of osteoporosis in other diseases, particularly those involving hormonal disturbances, and also in younger people for no apparent reason, is of great interest. Since these conditions cannot be attributed to normal ageing, they may provide clues to the nature of the osteopenia in older people. Since the major metacarpal bone dimensions—total subperiosteal width, medullary cavity width, and cortical area—can be measured on x-ray films, it is possible to base skeletal remodelling distinctions on these dimensions and compare them with the norms and standards for an individual of that age, sex, and race.

Table II compares the bone remodelling processes in pathological conditions with those in normal ageing (Dequeker, 1971, 1972a; Roh, Dequeker, and Mulier, 1973). Bone remodelling and bone mass in female patients suffering from idiopathic vertebral collapse did not differ significantly from controls

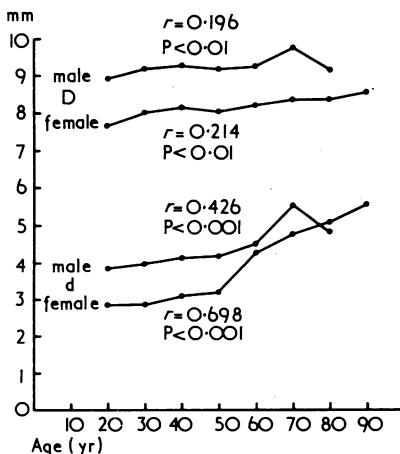


FIG. 9 Age-associated changes in periosteal (D) and endosteal (d) diameter of the second metacarpal at midpoint in 643 women and 194 men



**Table II** *Remodelling processes at the periosteal and endosteal surface of the second metacarpal in different conditions*

<i>Condition</i>	<i>Periosteal surface</i>	<i>Endosteal surface</i>	<i>Cortical area</i>
Ageing	Bone gain	Bone loss	Decrease
Femoral neck fracture	Bone gain	Bone loss +	Decrease +
Vertebral collapse	Bone gain	Bone loss	Decrease
Idiopathic osteoporosis	Bone loss ++	Bone loss	Decrease +++
Hemiplegia	Bone gain +	Bone loss +	Decrease
Rheumatoid arthritis (RA)			
Stage III-IV*	Bone gain	Bone loss +++	Decrease ++
RA + corticosteroid	Bone gain 0	Bone loss ++	Decrease ++
Amputation	Bone loss	Bone loss	Decrease ++
Hyperparathyroidism	Bone gain +	Bone loss +	Normal or decrease
Turner's syndrome	Bone gain	Bone loss ++	Decrease ++
Acromegaly	Bone gain +	Bone loss or gain	Increase
Osteoarthritis	Bone gain +	Bone loss	Increase

+ Indicates the difference with the remodelling process in normal ageing.  
\*Steinbrocker, Traeger, and Batterman (1949).

matched for age and sex. A significant increase in endosteal bone loss was seen in cases with femoral neck fracture, with disuse osteoporosis of hemiplegia, with rheumatoid arthritis anatomical stage III-IV, with corticosteroid-treated rheumatoid arthritis, stage II, with primary hyperparathyroidism, and with Turner's syndrome. A significant difference between bone formation and resorption was seen in pre- and post-menopausal hyperparathyroid women. In the latter an imbalance between bone formation and resorption with cortical bone loss was observed (Dequeker, 1972b). Periosteal bone loss has been noted in a case with idiopathic osteoporosis and in a case with amputated fingers. A significant increase in periosteal bone gain occurred in cases with primary hyperparathyroidism, acromegaly, and primary osteoarthritis.

The observation of increased bone mass measured by radiography (Foss and Byers, 1972; Roh and others, 1973) and confirmed by photon absorptiometry (Roh, Dequeker, and Mulier, 1974) at the forearm is of particular interest since osteoarthritis is a common affection occurring in the older age group. Thus in old people there seems to be a range of cases. At one end are light-boned osteoporotic women without osteoarthritis who suffer fractures. At the other are individuals with strong bones without fractures who suffer from osteoarthritis.

#### **Pathophysiology of bone loss**

Bone loss is not a single disease entity but the end result of different physiopathological processes. Bone loss is a disorder characterized by an imbalance between bone formation and resorption in favour of the latter. Both formation and resorption are regulated by the local environment as well as by the

activities of several hormones. The key problem in bone loss is thus increased resorption rather than decreased bone formation, as Albright (1947) suggested. There is evidence supporting the hypothesis of Heaney (1965, 1970) that the parathyroid hormone plays a major role in this enhanced bone resorption. In order to summarize the various pathological processes which may produce bone resorption with parathyroid hormone as a mediator, a possible sequence of events in the development of increased bone resorption is traced in Fig. 10.

In most instances the role of parathyroid hormone is probably indirect by a change in end organ sensitivity, due to hormonal changes (oestrogen-androgen), immobilization, and ageing collagen. The latter factor, however, is purely hypothetical. The calcium deficiency theory, mainly advocated by Nordin (1960), can also be incorporated into the parathyroid hypothesis of Heaney as in the absence of parathyroid glands no calcium deficiency osteoporosis could be produced in animals (Jowsey and Raisz, 1968). Although dietary calcium deficiency produces bone loss in animals (Scott, Greaves, and Scott, 1961; Campbell and Douglas, 1965), in humans dietary calcium deficiency is no longer considered to be a major cause of bone loss (Wills, 1973). The human organism indeed seems to adapt to low calcium diets. There is no consistent difference in calcium intake between patients with symptomatic osteoporosis and controls (Saville, 1970) and calcium intake is unrelated to bone density (Smith and Frame, 1965).

Although patients with deficiency of intestinal lactase who tend to avoid milk are reported to have osteoporosis (Birge, Keutmann, Cuatrecasas, and Whedon, 1967), lactase deficiency is said to be common in the Negro, in whom osteoporosis is rare (Bayless and Rosensweig, 1966).

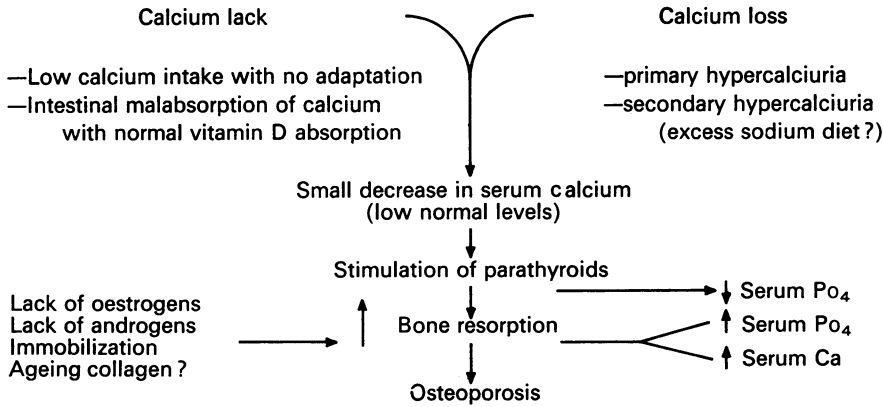


FIG. 10 Sequence of events in the development of increased bone resorption

Calcium deficiency can also be due to calcium loss in the urine: primary or secondary hypercalciuria. Dietary factors such as increased salt intake or carbohydrate may cause a secondary hypercalciuria. Such a possible cause of calcium deficiency resulting in lowered serum calcium, increased parathyroid excretion, and enhanced bone resorption has never received much attention. This mechanism might prove to be more important than calcium lack in the diet. In support of this hypothesis is the observation that Negro populations, who consume less salt, have a low incidence of symptomatic osteoporosis, and that in alcoholics an increased rate of osteoporosis has been found (Saville, 1965; Dent and Watson, 1966).

**Treatment of bone loss**

If the above discussed pathophysiological mechanism of bone resorption through the mediation of parathyroid hormone is true, treatment with the aim of reducing parathyroid activity should be found beneficial. Repeated calcium infusions as advocated by Pak, Zisman, Evens, Jowsey, Delea, and Bartter (1969) suppress parathyroid activity as manifested by a rise in serum phosphorus, decreased urinary phosphorus excretion, and a long-term decrease of total hydroxyproline excretion over a period of at least a year (Fig. 11) (Dequeker, 1972a; Hioco, Denis, Brodaty, and de Sèze, 1973). This treatment, however, does not result in increased bone mass. Increased bone mass has only been observed in cases suffering from acromegaly where bone apposition exceeds bone resorption (Dequeker, 1971). This finding indicates the potential therapeutic usefulness of growth hormone in the treatment of human bone loss. In dogs the beneficial effect of growth hormone on bone mass has already been shown (Harris and Heaney, 1969b; Harris, Heaney, Weinberg, Cockin, Akins, and Graham, 1973).

Although fluoride is known to increase the amount of bone and to decrease the solubility of bone by altering the size and nature of the bone crystals, the usefulness of fluoride as a therapeutic or preventive agent against bone loss remains a very controversial subject. Protagonists claim that fluoride may limit adult bone loss (Bernstein, Sadowsky, Hegsted, Guri, and Stare, 1966), may relieve bone pain (Rich and Ivanovich, 1965), and promote mineral retention in major bone-losing disorders (Purves, 1962). Antagonists claim that fluoride may produce mechanically different bone (Evans, 1957), spinal stenosis, osteosclerosis with vascular and neurological complica-

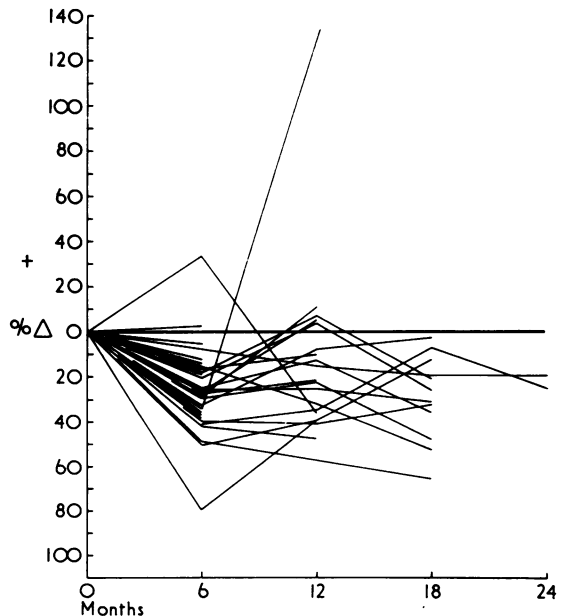


FIG. 11 Long-term effect of calcium infusions on urinary total hydroxyproline excretion

tions (Singh, Dass, Hayreh, and Jolly, 1962), and osteomalacia (Baylink and Bernstein, 1967). Fluoridation has been in effect for 20 years in selected cities. Do the young adults so reared have more cortical bone in their tubular bone and more trabeculae and more formed bone elements in their vertebrae? Present techniques, radiography and direct-photon absorptiometry, are certainly adequate to measure a 5% gain, on a group basis, using matched-pair techniques. It may be expected that in the near future an unbiased answer to this important and potentially useful preventive aspect will be given. A positive report has recently been published in the Netherlands, where the population of two towns, one with a low fluoride content in drinking water of 0.1 mg/l and one with a fluoride content of 1.0 mg/l since 1953, were compared using a photon absorptiometry method. In females aged 25–29 a significant difference was found with a higher bone mass (6%) ( $P < 0.02$ ) in the town with fluoridated drinking water (Melman, Houwink, Pot, Kwant, and Groeneveld, 1973). Conclusions from limited and variable therapeutic regimens, as in the recently published report by Jowsey, Riggs, Kelly, and Hoffman (1972) on the effects of fluoride administration combined with vitamin D and calcium supplementation in 11 'osteoporotic' subjects, have to be handled with great caution (Dequeker and Bursens, 1973). As for fluoride, the same problems concerning the therapeutic usefulness of diphosphonates may be raised. At present it is too early to give a valid answer, although these compounds are studied in many different centres. With the purpose of increasing gastrointestinal calcium absorption, which is frequently reduced in the older age group, vitamin D treatment with or without calcium supplements is used more often (Gallagher, Aaron, Horsman, Marshall, Wilkinson, and Nordin, 1973). Of great concern, however, is the ultimate fate of the absorbed calcium and whether it will be incorporated in the bone or in the soft tissue, e.g. blood vessels.

Although calcitonin does reduce bone resorption in young people and in high turnover bone diseases (for example Paget's disease), prolonged administration of porcine calcitonin in post-menopausal osteoporosis did not improve or made worse the bone loss (Jowsey, Riggs, Goldsmith, Kelly, and Armand, 1971; Cohn, Dombrowski, Hawser, Klopfer, and Atkins, 1971; Riggs, Jowsey, Kelly, Hoffman, and Armand, 1973). The absence of the expected decrease of bone resorption in the calcitonin-treated patients is probably due to increased endogenous parathyroid hormone secretion as a result of the hypocalcaemic effect of porcine calcitonin. Another approach to the treatment of bone loss in post-menopausal women is oestrogen replacement. This treatment has, as shown above, a pathophysiological basis in view of the possibly increased end-organ

sensitivity for parathyroid hormone in the absence of oestrogen. The value of oestrogen therapy in the prevention of bone loss after oophorectomy has been shown in the retrospective studies of Henneman and Wallach (1957), Davis, Strandjord, and Lanzl (1966), and Meema and Meema (1968) and in a double-blind controlled trial (Aitken, Hart, and Lindsay, 1973). When treatment was delayed for 6 years after oophorectomy oestrogen (mestranol) failed to prevent subsequent bone mineral loss with age.

The possible skeletal benefits of prolonged low-dose oestrogen therapy must, however, be assessed in relation to the long-term safety of such measures. Gow and MacGillivray (1971) described a 15% incidence of venous thromboembolism within 4 months of starting treatment. Other authors (Drill, 1972; Aitken and others, 1973), however, failed to show a significant thrombogenic effect of oestrogen-containing oral contraceptives. The extrapolation of the results in oophorectomized women to women with intact uteri is not justified, since in the latter instance treatment would probably have to be intermittent in order to ensure regular shedding of the endometrium.

It is hoped that when the mode of action of the *in vivo* osteotropic properties of oestrogens, growth hormone, calcitonin, vitamin D and its metabolites, calcium, fluoride, and diphosphonates have been elucidated, it may be possible to make a more scientific approach towards the rational treatment of post-menopausal bone loss and osteoporosis. Despite the fact that a number of the above-mentioned agents decrease resorption and hence ought to favour positive bone balance, almost without exception they have failed to increase bone mass in osteoporotic patients. They routinely produce positive calcium balance in acute studies, but months or years later they have produced no *x*-ray evidence of increased bone mass. This failure has usually been explained by the claim that *x*-ray examination and even photon absorptiometry are too insensitive to detect the real changes, or by allusion to a large systematic error in the balance technique to the effect that the patients were not really in positive balance in the first place. Neither explanation is satisfying. One of the most striking, and probably unexpected, results of longitudinal kinetic and morphological studies has been the observation that bone formation and resorption tend to change in the same direction with a variable time lapse in between (Frost, 1973). In other words, treatment will reduce resorption, and the organism will respond by reducing formation to match! Further research on uncoupling this mechanism will probably provide the long expected ideal drug for suppressing bone resorption or for increasing bone formation resulting in increased bone mass.

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#### Correction

With reference to the paper 'Liver disease in patients with joint symptoms' by Angela M. Hilton, B. E. Boyes, Patricia J. Smith, J. Sharp, and I. W. Dymock, which appeared in the November 1974 edition of *Annals of the Rheumatic Diseases* (*Ann. rheum. Dis.*, **33**, 540); we regret that the figures for this paper were incorrectly placed against their legends. Figure 2a should replace figure 1; figure 1 should replace figure 2b; and figure 2b should replace figure 2a.