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A Model Of Endocrine Control Of Bone Remodelling

Harold M. Frost

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A MODEL OF ENDOCRINE CONTROL OF BONE REMODELLING

HAROLD M. FROST, M.D.

INTRODUCTION

THIS PAPER outlines a model of the qualitative control of bone remodelling by known endocrine factors. The model has been synthesized from the writer's work and from work of other investigators, contemporary and antecedent. The model system is neither complete nor immune from future revision. It provides a point of reference in a field notorious for its slippery footing.

The key factor characterizing the endocrine control of bone remodelling may be given in one word: complexity.

Nature camouflages secrets behind screens of complex variables which are interrelated and act in unexpected ways.

How is a complex system to be understood in first approximation when all of its operating parameters and functions are not known? This is the problem posed by the present topic.

Consider briefly three progressively complex examples outlined by Roston:[91]

(1) The pituitary anterior lobe secretes TSH[a] which stimulates T_4[a] secretion by the thyroid. T_4 in turn inhibits TSH secretion.

(2) Parathormone stimulates osteoclastic activity which elevates serum calcium. The hormone also increases urinary loss of phosphate and lowers blood phosphate. Hormone secretion is controlled by serum ionized calcium concentration.

(3) Serum Na, aldosterone, vasopressin and osmolarity interact, governing body Na and water balance.

It is immaterial that these three examples are simplifications. It is material that as complexity increases the difficulty in intuitive understanding increases. Beyond a certain point, complexity is not only incomprehensible; it is beyond available computational solution. The nature of the variables and their number determine the point at which problem insolubility occurs. Such problems may be solved, however, by artificially isolating and examining certain parts of the whole fabric.

Endocrine control of bone remodelling is the result of more than eleven simultaneously operating variables.

[a]Term defined in the Glossary, p. 154.
*In addition to the writer, Dr. E. J. Collins and Dr. R. Johnston of Kalamazoo, Michigan.

Solving such a problem is an unusual challenge which this text attempts to meet. The gist of the message in the text is summarized in figure 1. In order to understand this figure, some degree of Gestalt about bone morphology, bone physiology and physiological kinetics must be imparted. Concepts are adapted from other fields for this purpose which will be unfamiliar to many, creating a need to outline them.

The form of this text is unconventional and is as follows:

(1) Orientation: To define the scope and restrictions and establish an initial mind "set".

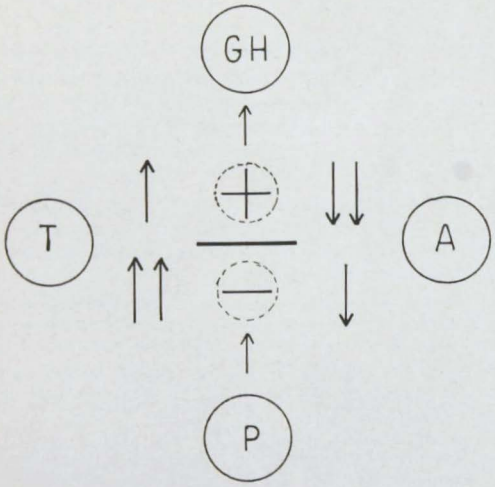

Figure 1

GH: Growth or Somatotrophic Hormone. T: Thyroid Gland Hormones. A: Adrenocortical Hormones. P: Parathormone.

The plus sign indicates bone formation, the negative resorption. Arrows pointing up indicate rate is increased, pointing down — decreased.

Salient features are: Thyroidhormones unequally accelerate both formation and resorption; adrenocortical hormones unequally decelerate both formation and resorption; growth hormone accelerates lamellar bone formation; parathormone accelerates bone resorption. Where there are two effects of the same sign, one arrow designates the lesser, two arrows the major, effect.

Mutual adjustments made by the endocrines in the intact organism to significant changes in the internal milieu are not considered in this diagram, although they are certainly important in accounting for observed phenomena in intact humans. Little is known about these interactions at present, or about the mechanism of the effects illustrated here, or about other osseotrophic effects.

(2) Skeletal Physiological Kinetics: To continue the mind set and present some useful ways of thinking about bone dynamics. Emphasis is on change and rate of change rather than on morphology.

(3) Model Endocrine Control System: Known direct artificially isolated effects of hormones on bone formation and bone resorption are described, followed by a separate section on general endocrine physiology which seems to be pertinent to the theme.

(4) Discussion: Some questions and some implications suggested by the textual material are explored.

(5) Glossary: A glossary in alphabetical order is given so there need be no misunderstanding about the sense of this text, though there may be disagreement about the choice of terms. The liberty has been taken of expanding on some aspects of bone physiology seldom encountered in texts.

Small (a) in the text indicates that the definition in the glossary should be referred to. Abbreviations used in the text are defined in figure 2, as well as in the glossary.

ABBREVIATIONS APPEARING IN TEXT

ACTH:	Adrenocorticotrophic Hormone
ASV:	Absolute Skeletal Volume
B_{sk}:	Skeletal Balance
gm:	Grams
ICSH:	Interstitial cell stimulating Hormone
L:	Liters
mg:	Milligram
ml:	Milliliter
STH:	Somatotrophic Hormone; Growth Hormone
TSH:	Thyroid Stimulating Hormone
T_{r50}:	Bone Formation Half-Time
T_{r50}:	Bone Resorption Half-Time
T_3:	Triiodothyronine
T_4:	Tetraiodothyronine; Thyroxine
V_1:	Internal Remodelling, kinetic sense
V_t:	Total Remodelling, kinetic sense
V_{t1}:	Total Remodelling in one year, kinetic sense

Figure 2

The abbreviations used frequently in the text are defined and may be referred to when necessary.

ORIENTATION

I: Dual Final Path to Bone Pathophysiology

Osteoblasts[a] and osteoclasts[a] may be regarded as dual, final paths to bone health and disease. These cells are the disordered biological tools responsible for such affections as the osteoporoses,[a] osteopetrosis, osteogenesis imperfecta, Paget's disease of bone, fracture nonunion, delayed union and fatigue fractures. The disorder may be qualitative, quantitative or both.

Regarded in this light, it is logical to examine both quality and quantity of osteoblastic and osteoclastic activities if clues to behavioral regulation are sought. Such clues were difficult to acquire until the advent of isotopic methods of labelling bone exemplified by reports of numerous authors[7,8,10,11,14,15,16,17,19,56,58,62,66,68,71,87,107,108] of simple and expedient methods of making undecalcified sections,[32] and of the use of tetracycline bone labelling[a] for measurements of formation rates[44,50,52,78].

These and other methods[13,24,29] yielded valid information on rates of osteoblastic and osteoclastic activities, although this information has not always been properly interpreted. Indeed some of it cannot yet be interpreted.

II: Rates

In this text rate means the absolute bone volume[a] formed or resorbed[a] in a unit of time in a unit reference absolute bone volume. The realization that the presence of many osteoblasts in tissue sections told nothing about the quantities of bone being formed in unit time was the factor leading to the selection of this definition of rate and leading to the search for rate-illuminating methods and facts. Without a direct method of observing rates, interpretation of available balance data

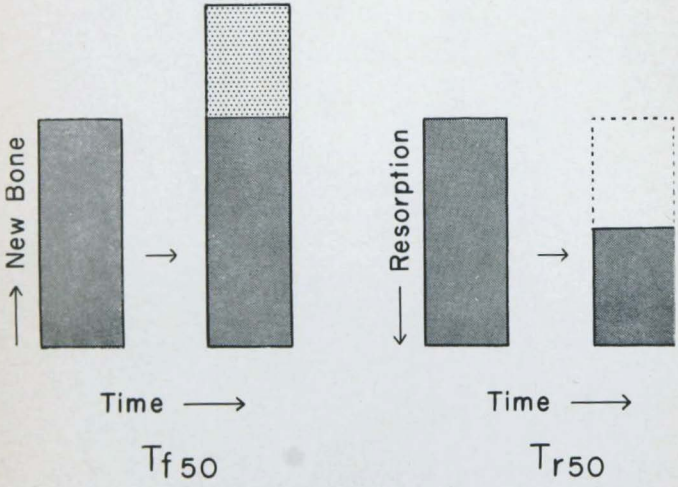

Figure 3

On the left the meaning of bone formation half-time is illustrated. The time is the period required for an amount of new bone equal to half of that originally present to be formed by the tissue elements present in a unit reference volume of bone. The amount of the unit reference volume is unimportant. Resorption is ignored deliberately.

On the right the meaning of bone resorption half-time is illustrated, and it may be seen that it is the opposite of the T_{r50}. Formation is ignored deliberately in its formulation.

is hopeless. It will be shown that positive or negative balance reveals nothing about the absolute change in rate producing the balance.

III Mechanisms:

The model synthesis outlined in figure 1 deals with rate controlling mechanisms. There are several genera of such mechanisms. Some act at the cellular level, such as 0_2 tension and membrane permeability. Some arise locally, others arise at a distance from the site of action. Some are exogenous, some are endegenous. Some act directly on pathways of energy flow, others act indirectly.

This text devotes itself to the effects of hormones upon osteoblasts and osteoclasts. The process of growth is ignored insofar as it concerns enchondral ossification, and *attention is fastened on lamellar bone remodelling only.*

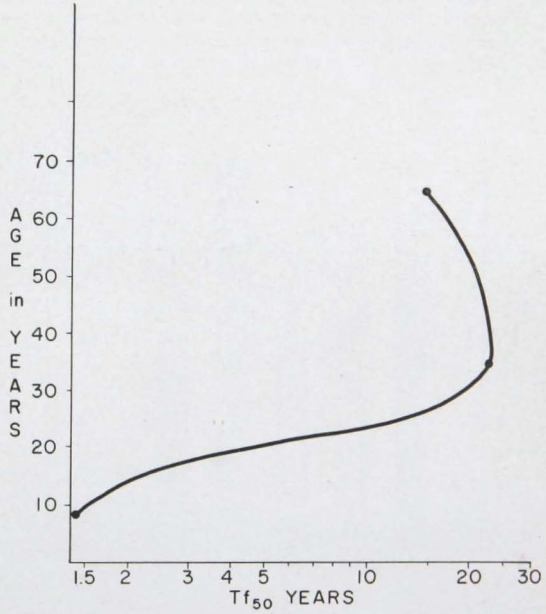

Figure 4

A tentative curve of the bone formation half-times of 40 human bones, determined from measurements of tetracycline labelling. At 3 points means were found and these points are the 3 dots seen on the graph line. The curve was drawn over these 3 points. A number of reasons exist for accepting this curve with caution and it is presented as a tentative representation of the change in bone formation activity with increasing age. It is significant that formative activity appears to increase after age 35. Similar conclusions were made from a different study from which the diagram in figure 11 is reproduced.

IV: Concepts

Unfamiliar ideas will be found in the text. These ideas have no magic and are not facts. They are ways of looking at bone physiological dynamics. Their value lies in their usefulness in explaining and predicting behavior. This usefulness extends beyond mere bone physiology.

V: Gestalt

This German word means grasp of the whole picture. It was a bone Gestalt which led to the present synthesis by three people brought together at the right time.*

To understand the present synthesis sufficiently to use it as a basis for extrapolation, (a device used in designing experimental tests of an hypothesis) the reader must possess a bone physiological Gestalt. This Gestalt has elements of thermodynamics, mathematics, biochemistry, endocrinology, bone histopathology, optical microscopy, pharmacology and clinical orthopedic medicine, among others. These elements are given in English and in translation and abstraction the ideas of the specialized fields naturally suffer somewhat.

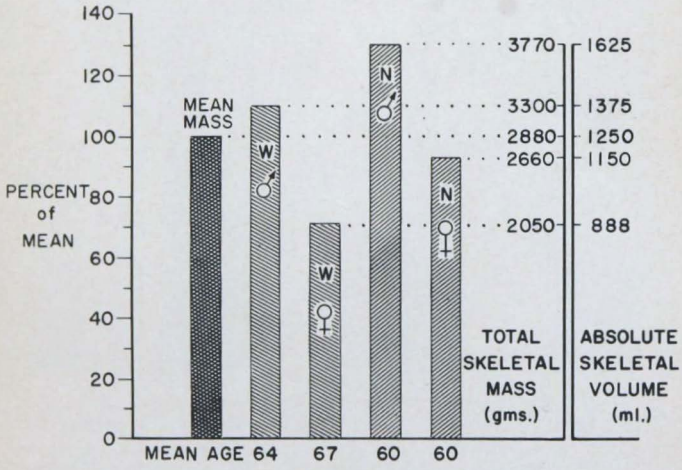

Figure 5

The far right scale is absolute skeletal volume (ASV) in milliliters. The scale to its left is total skeletal mass, dried and degreased, corresponding to the ASV opposite. The ASV was calculated on the basis that normal, dry, degreased human bone has a specific gravity of about 2.3.

The far left scale is the mean in percent, 100 being the norm. The bars between the sets of scales designate the average values for adult negro and white males and females. The leftmost bar is the mean determined by Lowrance and Latimer from a group of Asian skeletons. It is likely that the mean of U. S. skeletons is from 10% to 20% higher.

The diagram was prepared from calculations based on the work listed in references 2, 5, 12, 69, 76, 77, 88, 89, 111, 112.

VI: Fibrous and Lamellar Bone[a]

The existence of two histologically different types of bone in man is well known.[1,20,27,40,76,85,98,117] Several clear physiological differences associated with the histological differences have been pointed out by Cretin[20] and the writer.[41,42] It should be understood that lamellar bone physiology is the present topic and that the physiology of fibrous bone formation and of enchondral ossification[a] is not.

Skeletal Physiological Kinetics

I: Remodelling Kinetics

Remodelling kinetics means the rates at which bone formation and resorption occur in terms of the absolute volume of bone formed or resorbed per unit time per unit reference volume. The purpose of this discussion is to show why absolute changes in rates of formation and resorption bear no fixed relationship to skeletal balance.[a]

(A) The T_{f50} is the time in years required to form half as much bone as originally started with and in words is the formation half-time.[a]

The T_{r50} is the time in years required to absorb half as much bone as originally

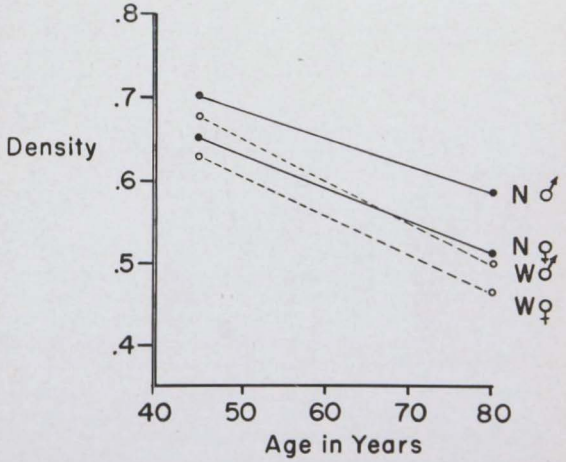

Figure 6

This diagram reveals the rate of loss of ASV (absolute skeletal volume) with increasing age. It is prepared from data in reference (112), and reveals the order of magnitude of the normal loss of bone substance with age. This degree of loss should probably not be considered an osteoporosis. The lines are the result of determinations made upon standard bones from a number of skeletons in each group designated at the right of the regression lines. The density in this case does not mean true physical density but rather the ratio of total mass of the bone that was measured to the volume encompassed by its periosteum. The average loss of bone between age 40 and 80 seems to be about 25%. This regression may be applied in reverse to the data in figure 5 to obtain mean values for younger persons.

present and in words is the resorption half-time.[a] These two parameters are true physical rates (Figure 3).

Working values of T_{f50} in man have been measured by the writer using tetracycline-labelled human bone.[44] A representative curve of the values obtained from a series of 40 bones is illustrated in figure 4. Figures of new bone formation rates can be calculated from data obtained by authors such as Bauer and Ray,[7] Heaney and Whedon,[58] and Bluhm, MacGregor and Nordon.[10,71] Tetracycline-based values are higher (i.e.: yield slower rates of formation) than isotope-based values due probably to the disturbing effect of diffuse exchange[a] on the isotope methods and of sampling selectivity on the tetracycline methods.[44]

(B) Assume consideration of a 20 year old patient with T_{f50} and T_{r50} of five years. The five year figure means that in five years half as much new bone as originally present will have been formed, and half as much bone as originally present will have been resorbed. Because formation and resorption normally balance, the absolute skeletal volume ASV[a] remains relatively constant while this internal remodelling[a] occurs.

One quirk of the half-time method of designating formation and resorption rates is that when the two are equal the T_{f50} is also the time in years for a volume of bone equal to the ASV to be remodelled. This is because total remodelling is defined as that volume of bone formed plus that volume of bone resorbed in a given time.

Referring to ASV in the glossary and to figures 5 and 6, it may be seen that a mean ASV for a 20 year old female is *about* 1250 ml. The actual value of this figure does not affect the validity of the following argument.

(C) Using rounded figures and assuming 5 year T_{f50} and T_{r50} the amount of bone formed and resorbed per day can be calculated. 340 mm^3 are formed, and another 340 mm^3 resorbed per day. Assuming a dry, degreased density[a] of 2.3, and 27 per cent calcium content in dry, degreased bone, it can be calculated that the daily bone deposition fixes 210 mg. of calcium in new bone, while the daily resorption dissolves another 210 mg. into the blood. Thus a total of 420 mg. of calcium is involved in the daily internal calcium turnover due only to bone formation and resorption. The turnover which occurs at the molecular level, independently of formation and resorption, is not considered in these figures.

(D) The bone remodelling and calcium turnover described are not manifested by any external positive or negative calcium balance.

Whether formation and resorption rates are symmetrically accelerated ten times, or reduced to zero, the externally observed balance remains unity, not betraying in any manner the rate of internal events (Figure 7).

In partial summary, there is an internal remodelling rate,[a] designated V_{ll}, which is defined as all bone remodelled in one year without externally manifested net loss or gain in the total volume of bone present. Internal remodelling may be very large or zero.

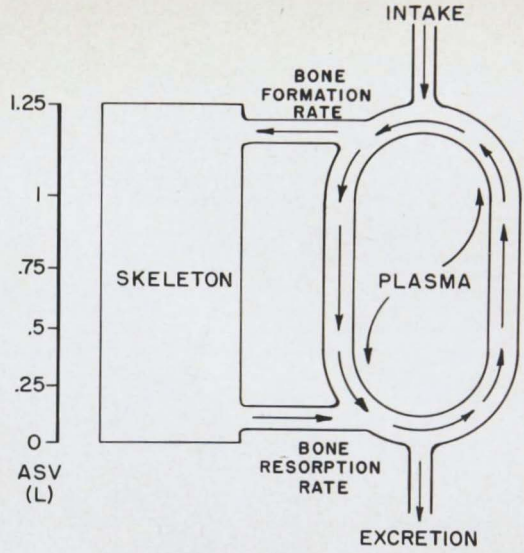

Figure 7

In this diagram the difference between that remodelling which is totally internal and concealed, and the state of skeletal balance or calcium balance is depicted.
The scale at the left represents the ASV in liters.

In the skeletal compartment it may be seen that the rate at which skeletal material flows from skeletal pool to blood back to skeletal pool may be very variable but completely concealed from without, since the building material for new bone may be the dissolved constituents of resorbed bone. The skeletal (or calcium) balance on the other hand is the result only of the proportionality between intake and excretion, and not the result of the absolute rates of formation and resorption. It may also be seen that when an imbalance is present the size of the skeletal pool must gradually change with increasing time. This change in size need not bear any fixed relationship to the speed with which new material enters and old material leaves the skeletal pool.

In particular, as long as skeletal balance is unity, the hidden, internal bone remodelling activity (V_i) may proceed at any rate between zero and very fast without there being any external evidence of what the actual remodelling rate is from study of balances.

(E) Now assume the patient is developing an osteoporosis.[a] How may formation and resorption rates vary yet still permit an osteoporosis to evolve? An osteoporosis is defined as a disease in which there is less ASV than is normally present in a similar, healthy patient.

The following are five ways in which a daily negative calcium balance of 100mg. may occur; figures are rounded off:

1) Formation depressed 48 per cent, resorption normal. Thus 110 mg. calcium per day is deposited in new bone, 210 mg. per day dissolved in the blood by resorption.

The excess 100 mg. appears in urine, stool and sweat as excess calcium over ingested calcium.

2) Formation depressed 75 per cent, resorption depressed 25 per cent. Calcium deposited 53 mg, resorbed 153 mg, net 100 mg. /day negative balance.

3) Formation zero, resorption depressed 52 per cent. No calcium deposition, 100 mg. resorption, net 100 mg. /day negative balance.

4) Formation normal, resorption increased 43 per cent. Calcium deposited 210 mg, resorbed 310 mg, net 100 mg. /day negative calcium balance.

5) Formation increased 50 per cent, resorption increased 98 per cent. Calcium deposited 315 mg, resorbed 415 mg, net 100 mg. /day negative calcium balance.

Positive calcium balance may occur in as many possible variations of opposite nature.

(F) Note Bene: *Skeletal balance, designated B_{sk}, calcium balance and nitrogen balance reveal nothing about the absolute increase or decrease in resorption or about the absolute increase or decrease in formation.* There may be skeletal balance less than unity in the face of increase in both formation and resorption, or in the face of decrease in both formation and resorption. The corollary statement about B_{sk} in excess of unity also holds true.

A drug which causes B_{sk} less than unity, meaning a net daily loss of calcium and bone volume, may do so in the face of a *decrease* in resorption as well as in the face of an *increase*. Failure to realize this has led to unjustified metabolic and biochemical conclusions about the effect of corticoids on absolute resorption rate.

Note that a *rate* designates flow over one, and only one, route. Note that a balance by definition is the *ratio* between at least two opposed routes of flow. *Absolute rates, and ratios between two or more rates, are not identities.*

(G) When a patient loses ASV with increasing time the B_{sk} is less than unity. Refer to figure 8. By definition the B_{sk} is the net remainder in ASV in one year's time. The B_{sk} is expressed as a percentage or as a decimal fraction. In the example considered in (C-F) above, 100 mg. negative calcium balance per day is equivalent to about 37 gm. of calcium per year. Converted to volume this is about 5 per cent of the 1250 ml. ASV assumed. Therefore, the B_{sk} in this hypothetical case would be 95 per cent or 0.95.

The nomogram in figure 8 permits determination of any two of the following four parameters if the other two are known: T_{f50}, T_{r50}, B_{sk}, V_{f1}. Adequate methods of obtaining these values in clinical practice are needed. The x-ray absorption work of Vose[115] offers hope of measurement of total skeletal mass in vivo, a parameter readily converted to ASV. Standard balance studies would then yield a value of B_{sk}. Some clinical method of determining one of the remaining three entities (V_{f1}, T_{f50}, T_{r50}) is needed to permit construction of actual remodelling events. Several possibilities are under investigation in this country.

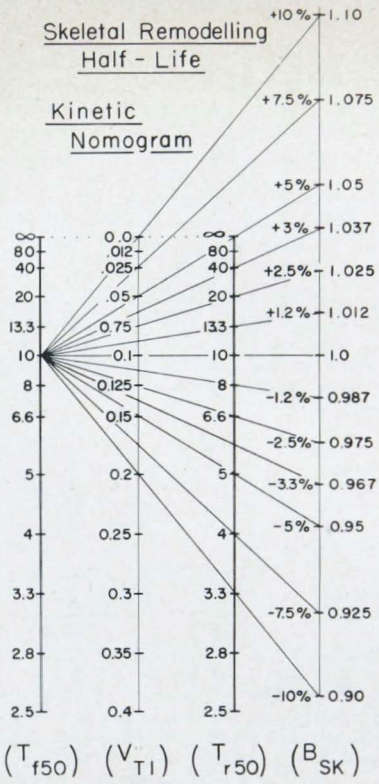

Figure 8

In this nomogram the relationships between the T_{f50}, T_{r50}, V_{t1} and B_{sk} are presented. If any two of these values are known the other two may then be found by connecting the two known values with a straight edge. The intersection of the straight edge on the two unknown scales indicates the respective values.

The scales as drawn are intended to be years, the exception being the rightmost scale which is percent of skeleton lost or gained per year on its left and decimal equivalent on its right.

As long as consistent units are used on the three left hand scales (that is, as long as all values are expressed in years, or in months, or in weeks, or in days) the exact nature of the time interval is immaterial; the nomogram then holds for any arbitrarily chosen time interval. It follows that the V_{t1} in these instances refers to the total bone remodelled in the chosen time interval only, and the B_{sk} predicts the amount of skeleton present at the end of this interval only.

It is important to note that the value on the right hand scale is selected by the *slope* of the line intersecting the three left hand scales, and the origin of the slope-finder rosette lies at 10 on the leftmost scale. If the B_{sk} is known from balance study, only one value is needed on any one of the 3 left-hand scales to define the kinetics completely.

For example, if both T_{r50} and T_{r50} are 2.8 years, V_{t1} is 0.35. The slope of the straight edge joining the formation and resorption half-time scales is horizontal. Starting at the origin of the slope-finding rosette at 10 on the leftmost scale, run the straight edge parallel to the formation and resorption scale intersections; in other words horizontally. The intersection with the B_{sk} scale on the right indicates that at the end of a year there is neither a surplus nor deficit of skeleton.

II: Remodelling Rate and Mean Skeletal Age

In the glossary under lamellar bone[a] it is indicated that all the microscopic moieties of bone in a given skeleton have an age in terms of the years each has been in existence. Therefore, the skeleton as a whole has a mean age which is the mean of the sum of all of the microscopic parts formed at differing times. The skeleton also has an average mineralization density which is related to and varies with the average skeletal age. There is an average diffusion impedence[a] characteristic of a given average age that affects the permeability of the skeletal tissue to inorganic ions in the blood.

The average age of the entire skeleton is dependent on how quickly old bone is resorbed and replaced by new bone. This process has already been defined as the total remodelling or V_{tl}. V_{tl} is the total amount of bone formed plus the total amount of bone resorbed per year in absolute bone volume terms. In other words, the average age of a skeleton depends on the remodelling rate during the time before the moment of observation.

(A) From the foregoing it may be inferred that an agent which retards total remodelling leads to advancing senescence[a] and to increasing average age of the skeleton.

(B) An agent which accelerates total remodelling retards senescence of the skeleton. Note that the functional age of the skeleton is not the chronological age of the personality who uses it but the sum of the lesser chronological ages of the microscopic moieties composing it. Some of these moieties will have been formed within weeks of the moment of obseravtion, others many years before, and the average age is their mean.

(C) An agent that retards total remodelling should cause increasing average diffusion impedence of the skeleton and thus diminishing diffuse uptake of isotopic inorganic ions. This inference has experimental and rational backing in the publications of the writer,[40] McLean,[75] MacGregor and Nordin,[71] and Strandh.[107,108] This backing, plus other backing not quoted, adds considerable weight to the inferences in (A) and (B) immediately precedidng.

III: Biological Push-Pull

The live, multicellular, multiorganed organism makes extensive use of a simple idea: push-pull. If circumstances require that there be a net loss of a given substance from the body, two or more factors often combine to effect the loss. They combine in such a way that the substance is "pushed" out from one place and "pulled" from another (Figure 9).

For example, increase in parathormone secretion increases bone resorption. This "pushes" phosphate, present in the dissolved bone mineral, into the blood. If other things were unaltered, this would lead to increased serum phosphate concentration. But the hormone impairs tubular reabsorption of phosphate, thus depleting the blood phosphate and increasing urinary phosphate excretion — "pull".

Usually the efficiency of the various phases of push-pull mechanisms is such that no significant alteration in serum concentration occurs although large changes

in balance of the substance in question may occur. In the case of parathormone the efficiencies of the phases are not equal with the result that the serum phosphate concentration is lowered; the "pull" is more efficient than the "push".

One effect of push-pull mechanisms is a net increase in the *amount* of a material transported through body systems in unit time without an increase in serum concentration. This is paraphrased by saying that velocity of flow is increased but density or concentration is held nearly constant. The blood is the common transport system.

Push-pull phenomena have to be invoked to explain the large alterations in calcium balance that may occur without alteration in serum calcium concentration. Push-pull phenomena have to be invoked to explain the large alterations in nitrogen balance produced by a number of pharmacologic agents without alteration in

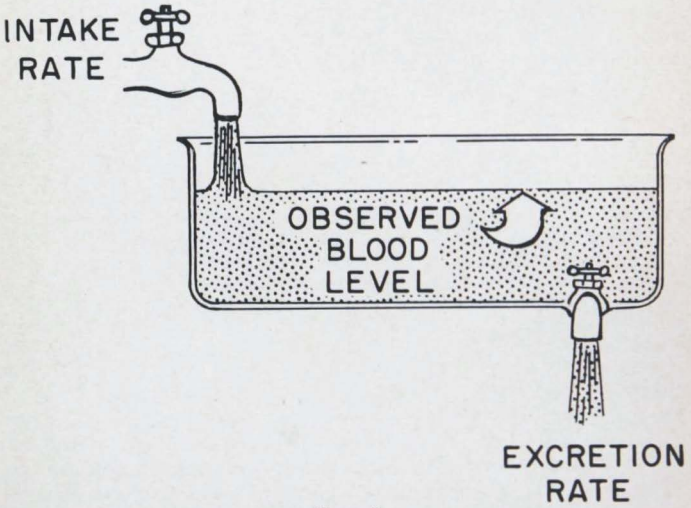

Figure 9

Push-pull: Note in this diagram that as long as the intake and outlet faucets are opened or closed symmetrically and simultaneously a tremendous range of rates of flow of liquid through the container may be achieved without alteration of the level of fluid along the vertical wall of the container. If the level of the fluid is equated to the serum concentration, and if the intake faucet is equated to the mechanism causing entrance of a substance into the blood while the excretion faucet is equated to the loss of the substance from the blood, then the illustration of biological push-pull phenomena is complete.

Note that the actual rate of flow of a substance through the plasma compartment of the body may be determined only by measuring the rate of entrance or the rate of egress, but cannot be estimated from the concentration in the plasma. Certain phenomena occurring in thyroid and adrenal, physiology are due to the presence of push-pull action, as are a group of phenomena occurring in calcium and in phosphate physiology.

Biological push-pull is usually equally efficient at both ends, but occasionally there is an imbalance with the result that alterations in serum concentration occur.

serum NPN. There is solid experimental evidence for the presence of these mechanisms, and for the presence of numerous others of similar nature in biology.

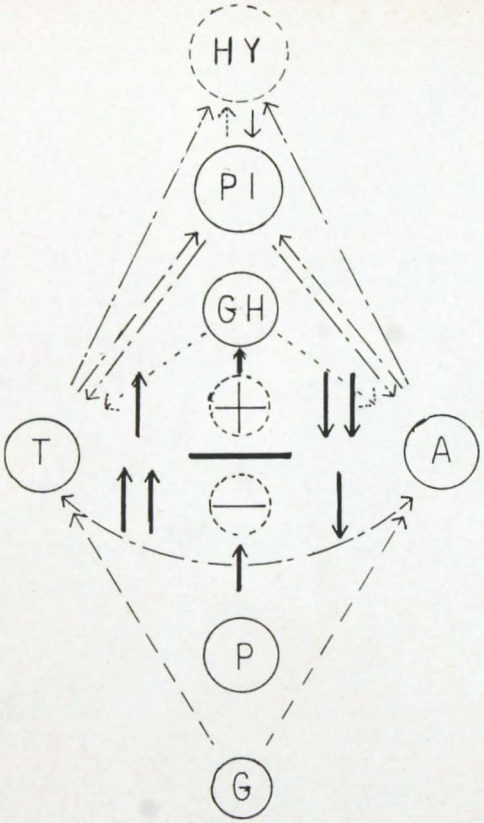

Figure 10

Superimposed on Figure 1 are the major extraosseous endocrine effects. Hy: Hypothalamus. Pi: Pituitary (adenohypophysis). G: Gonad. GH: Growth Hormone. T: Thyroid Hormones. A: Adrenocortical Hormones. P: Parathormone.

Note that the hypothalamus which controls the pituitary, is in turn controleld in part by the thyroid and adrenal. Note the indication that GH exerts some effect on both thyroid and adrenal function without specifying the mechanism. Note that the gonad affects both thyroid and adrenal function, but does not directly affect bone. Note that thyroid and adrenal affect each other in some undefined manner. An effect of the gonad on the pituitary is not shown, but it is possible that the increase in pituitary gonadotrophin which occurs with declining gonadal function diverts some of the pituitary effort from production of GH to production of the gonadotrophin.

Endocrine Control of Bone Remodelling

This part of the text is given in two divisions. First is a brief section on direct effects of hormones on osteoblastic and osteoclastic rates, indicating which effect is dominant. A factor termed the time constant[a] is also given. The time constant is the half-time of the hormone in the blood insofar as known. As better information becomes available, these values will undoubtedly require modification. The time factor is required for computer programming.

Following the direct effects comes a presentation of general endocrine physiology applicable to the present theme. The method of analyzing effects is artificial because in the living system dose-effect relationships are the result of innumerable adjustments and synergistic or opposing actions at the endocrine and cellular level. Separating one hormone from the milieu is unphysiological because separation is unreal. Analytically, however, this separation is essential for comprehension. So, with the understanding that much detail is glossed over, or omitted, or unknown, the first division follows. It must be emphasized that the particular emphasis on certain phenomena in this text may need revision when the phenomena are better understood. The gross structure of the model synthesis is on firm ground (Figure 1).

I: Direct Endocrine Effects on Bone Remodelling

1) *STH (Growth hormone; secreted by adenohypophysis).*[113]

A) Lamellar Osteoblastic Activity: Accelerated.
B) Osteoclastic Activity: No known direct effect.
C) Time Constant: 24 hours (Not well established)
D) B_{sk}: Over Unity.
E) Documentation: Clinically obvious lamellar bone acceleration occurs in growth, in gigantism and in acromegaly.[1,70,101,113,117] Growth is a complex series of events, one of which is rapid lamellar bone formation and resorption in the process of diaphyseal, metaphyseal-cortical and internal cortical remodelling. These involve circumferential lamellar[a] and endosteal lamellar[a] remodelling. In gigantism these processes continue beyond physiological time limits while in acromegaly they reactivate after skeletal maturation. The bones that result are wider than normal and heavier than normal, and these qualities are unrelated to the enchondral ossification process which is disturbed in gigantism. T_4 is probably necessary for the STH action on lamellar osteoblastic rate.

Experimental, STH-induced positive nitrogen and calcium balances in man have been reported by Henneman, Forbes, Moldawer, Dempsey and Carroll.[60] In animals they have been reported by many, Grodzensky's report being an example.[16,17,56,98]

2) T_4*(Thyroxine; secreted by the thyroid)*[113]

A) Lamellar Osteoblastic Activity: Accelerated.
B) Osteoclastic Activity: Accelerated.
C) Dominant Effect: Osteoclastic activity accelerated more than osteoblastic activity.
D) Time Constant: 9 days.
E) B_{sk}: Less than unity.

F) Documentation: Many observers have noted negative nitrogen and calcium balances in human exogenous and endogenous hyperthyroidism.[101,113] Equally well known is the development of osteoporosis[a] in hyperthyroidism. The osteoporosis develops in the face of absolute increases in protein synthesis and protein catalysis.

Decreased lamellar bone formation is well known in hypothyroid states and in cretinism in man. Similar decreases in rate of lamellar bone formation experimentally have been observed and/or illustrated by Ray and co-workers,[87] by the Silberbergs,[99] and by Scow.[97,98] Experimental increase in lamellar bone formation with T_4 has been observed by Scow and by Stanisavljevic and the writer[104] (Figure 9).

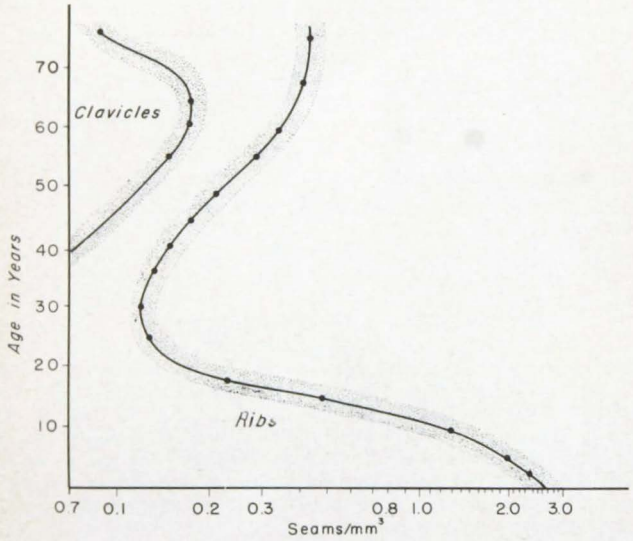

Figure 11

Reproduction of a curve of the incidence of osteoid seams in a series of normal human bones, plotted against age. Attention is devoted to the rib curve.

Maximum bone forming activity occurs as expected during childhood. This activity slows down with increasing age, reaching a minimum thereafter. After age 30-35 the rate of bone formation increases by a respectable amount up to age 65. This curve, from an article by the writer and Villanueva (48), was incomprehensible at the time the data were obtained because it disagreed entirely with the then popular anabolic-hormone theory of bone endocrine control.

In the light of the present model this curve has additional significance. The increase in bone forming activity after age 30-35 would seem to be in part the result of diminished adrenal inhibition of bone remodelling and in part the result of diminished inhibition of thyroid hormone effect on bone remodelling by both adrenal cortical and by gonadal hormones. As indicated in figure 6 the skeleton appears to be in negative balance between the ages of 40-80. This suggests diminished growth hormone effect, and thus an imbalance between the effect on skeletal balance of the pituitary on one hand and the thyroid-adrenal axis on the other.

In man, hypercalcemia occasionally develops in thyrotoxicosis as noted by Kleeman, Tuttle and Bassett,[63] and occasionally new periosteal bone formation occurs as noted by Danforth and Humphrey.[22] The fact that serum calcium concentrations usually are unchanged in the face of thyrotoxic skeletal balances less than unity indicates the action of a push-pull phenomenon, for which there is good evidence in physiology of calcium absorption from the gut and excretion from the kidney.

Separation of T_4 effect on lamellar osteoblastic activity from the synergistic effect of STH is physiologically unreal.

3) *Corticoids (Adrenal cortical hormones, particularly the glucocorticoids, secreted by the adrenal cortex*[113])

A) Lamellar Osteoblastic Activity: Decreased.

B) Osteoclastic Activity: Decreased.

C) Dominant Effect: Osteoblastic activity is depressed more than osteoclastic activity.

D) Time Constant: 25 minutes.

E) B_{sk}: Less than unity.

F) Documentation: Suppression of lamellar bone formation by the adrenal cortical hormones has long been suspected as noted by Sissons.[100] This effect has been measured in man by Villanueva and the writer both by osteoid seam suppression[49] and by decrease in bone formed in tetracycline labelled human material.[44] The effect has been produced experimentally by many observers using varying techniques, among these authors being Grodzensky;[56] Collins, Garrett and Johnson;[17] Clark;[15] Follis;[29] Stanisavljevic, Roth and the writer.[103] As is common in endocrinology, some of these authors have made different interpretations of their data than is made here. Their data is represented in the present comments, not their beliefs. The lamellar bone suppressing effect of the corticoids is not in serious dispute. It should be noted that a similar suppression of fibrous[a] bone formation does not occur in man or in animals, an effect hinted at by Cretin[20] but first remarked by the writer,[42] and of considerable importance in interpretation of human and animal data obtained in the presence of corticoid effect.

That cortisone suppresses resorption may raise eyebrows. The reason is the common misconception that a negative balance produced by an agent has to result from an absolute increase in catabolic activity produced by the agent. The real subtleties of this situation are outlined in skeletal remodelling kinetics, where it is revealed how negative balance may occur in the face of decreased catabolic activity.

Suppression of resorption by corticoids has been observed by numerous authors but not always interpreted correctly. Using isotopically prelabelled skeletons, suppression has been observed by Collins, Garrett and Johnson;[17]by Clark, Geoffrey, and Bowers.[15] Histologically it has been remarked (or illustrated) by Follis,[29] by Storey[105] and by Borle, Nichols and Karnovsky;[11] and by others. It has been observed histologically in man by Sissons,[100] by the writer and Villanueva,[49] and by Mooser[79] and Rutishauser.[96]

A "bounce" or temporary increase in resorption following removal of corticoids has been observed in dogs by Collins, Garrett and Johnson,[16] and in man by at least one observer.

4) *Parathormone (Secreted by the parathyroid glands)*[76]

A) Lamellar Osteoblastic Activity: No known effect.

B) Osteoclastic Activity: Accelerated.

C) Time Constant: 6 hours.

D) B_{ak} Less than unity.

E) The stimulation of resorption by parathormone is well known and is not in dispute. The hormone causes differentiation and proliferation of fibroblasts from primitive mesenchymal cells[110] in the bone spaces. Fibroblasts then in turn differentiate into active osteoclasts with an increased rate of osteoclastic resorption of bone.

5) *Estrogen: No direct effect on bone.*

6) *Testosterone: No direct effect on bone.*

A) Documentation: The idea that sex hormones, especially estrogen, exert an accelerating effect on lamellar bone formation arose by an error in interpretation. This error has been discussed by the writer[41] and by Roth.[92] McLean and Urist[76] in their excellent book refer to the fact that these hormones are ineffective in stimulating the formation of new lamellar bone in human osteoporotics.

The gist of the error referred to is, briefly: estrogen diminishes resorption of the chondroosseous complex[a] under epiphyses and diminishes resorption of intramedullary bone in birds as noted by Budy, Urist and McLean,[13] by Follis,[29] and by Day and Follis.[24] By error this effect was interpreted by others as an acceleration of new bone production. Apparently it was assumed that a positive balance had to result from an absolute increase in synthesis. It has already been shown why this assumption may be invalid. Failure of estrogens to stimulate new bone formation has been observed by many using isotopes, the thorough study of Cordrey, Christie, MacIntyre and Palmer[19] being an excellent example. Failure of estrogen to stimulate human bone formation is now well known. Failure of testosterone similarly to stimulate bone formation is also well known.

IIs First Synthesis

It is now possible to diagram the previously listed events, synthesizing a model system of direct endocrine effects upon bone. This simple model is the gist of this paper. Indirect effects are ignored.

The model is illustrated in figure 1. Note its following characteristics:

A) STH puts the skeleton into positive balance. *STH is the only hormone listed that can put the skeleton into positive balance;* all other hormones put the skeleton into negative balance.

B) T_4 accelerates the rate of renewal of bone by increasing both formation and resorption. Therefore, T_4 should retard senescence of bone.

C) The adrenal corticoids retard the rate of renewal of bone by suppressing both formation and resorption. Therefore the corticoids should accelerate senescence of bone.

D) Increasing T_4 secretion places the skeleton into B_{sk} less than unity.

E) Increasing corticoid secretion places the skeleton into B_{sk} less than unity.

F) Increasing parathormone secretion places the skeleton in B_{sk} less than unity.

G) Simultaneous increases in T_4 and corticoid secretions lead to large under-unity B_{sk}. It has been noted that T_4 induces much more nitrogen loss per day than cortisone; see Fremont-Smith, Iber and Plough.[31]

H) T_4 produces an absolute increase in the amounts of bone formed and resorbed in unit time. Note the clear distinction between relative change (D) and absolute change (H).

I) The corticoids produce an absolute decrease in the amounts of bone formed and resorbed in unit time. Note again the distinction between relative change (E) and absolute change (I).

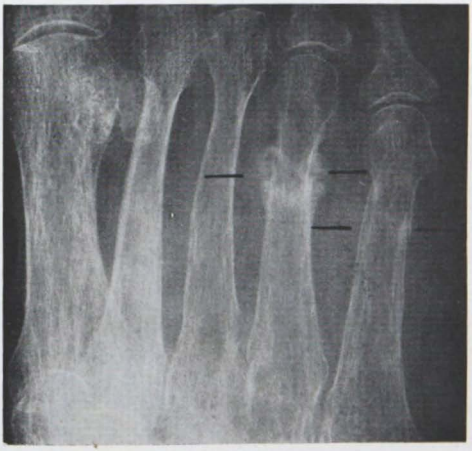

Figure 12

An example of fatigue fracture in exogenous, mild hypercortisonism. There are fatigue failures in the 4th and 5th rays of this foot of a 60 year old woman who had been taking moderate doses of steroid for 5 years for rheumatoid arthritis. There were three such fatigue failures on the other foot. This appears to be the result of the combined effect of depression of remodelling and an inadequate amount of structural material.

J) In the scheme of events outlined, STH secretion assumes prime position in skeletal health. Lack of STH secretion in the face of continued T_4 and corticoid secretion should inevitably lead to an osteoporosis. It is possible and plausible that so-called senile and postmenopausal osteoporoses are results of disproportionate decline in STH effect with increasing age, the comparison being with thyroid and adrenal cortical hormone effects at the cellular level. Such a thesis explains the known failure of sex hormone therapy to cure the bone disorder in these osteoporoses.[41,76,82,83]

K) With exception of the parathyroid, no feedback mechanisms between bone and endocrines are known. Bone is at the mercy of the endocrine milieu and cannot modify this milieu defensively and directly in any known way. As a matter of biological philosophy, such a situation is unusual; in time feedbacks connecting bone with the endocrine milieu may be found.

L) Note the radical de-emphasis of gonadal hormones. They are assigned indirect functions and are absolved of direct effect on bone formation or resorption.

III: Some General Endocrine Physiology

Hormones in general do not create new chemical reactions. They modify reactions that would occur withhout endocrine control. Hormones act by affecting enzyme synthesis, enzyme blockade, critical enzyme ratios or by affecting membrane permeability selectively. There may be other modes of action. The result of these actions is modification of the routes of energy flow in cells. Some hormones have target organs whose cells are unusually sensitive to the effects of the hormone. Other hormones exert effects on most or all of the body's cell complement.

Hormones are bound to proteins in the blood and extracellular fluids. To act they usually must be hydrolysed from these proteins. The free hormones enter cells, or fix on cell membranes, exert their specific effects, become chemically altered, are further degraded or excreted as conjugated metabolites.

In many ways the actions of hormones are uniquely explainable in terms of the engineering concepts that deal with servomechanisms[a] and with oscillation. A brief discussion of these matters is included in the glossary because of the potential applicability of computer techniques to the analysis of endocrine effects and interrelationships. This approach has already been suggested by Danziger and Elmergreen[23] and is inherent in analyses by authors such as Bauer, Ray,[7] Roston,[91] and Szilard.[109]

In the hypophysectomized animal, metabolism in cells occurs at basal rates on the order of a few percent of rates characterizing the intact animal. One of the difficulties in studying and interpreting hormone effects in hypophysectomized animals is the fact that many of their effects are markedly diminished by the presence of the basal state.

Note that insulin, gonadotrophins, adrenalin and norepinephrine are not included in the synthesis, although they may well exert significant effects. Note that no

mention is made of possible antihormone effects, although it is probable that eventually they must be accorded a place in our schematic.

1) Somatotrophic Hormone (STH)

STH is a polypeptide secreted by acidophil cells of the adenohypophysis. There is ascending species specificity of STH from different animals, hormone from an animal high on the evolutionary scale usually being active in one lower but the reverse is not usually true. The age changes reported are not well documented at this time, and not uniformly related. By the latter is meant failure to relate — or inability to measure — total output consumption of hormone per day to the total amount of DNA^a and RNA^a. Due to gradual decrease in body water proportion with age and change in body fat proportion, total DNA and RNA cannot be estimated from body weight alone.

STH accelerates protein synthesis throughout the body, acceleration of bone formation apparently being one facet of this activity. Accompanying this action are nitrogen, calcium and phosphorus balances in excess of unity and increased calorigenesis.

Most gross effects of STH require the presence of T_4 for full effect.

STH induces net loss of fat in tissues. Beta cells of the pancreatic islets are directly stimulated to produce extra insulin. Blood sugar is lowered. Epinephrine is necessary for this effect.

STH decreases the intracellular amino acid pool.

STH is necessary for the evolution of normal tissue repair responses to injury and for mitotic activity during growth and repair.

T_4 accelerates secretion of STH. Secretion of STH has also been shown to drop during fasting and some work indicates that excess of dietary protein, or something in such a diet, induces a decline in STH secretion.

(References: 16, 18, 28, 55, 56, 60, 86, 87, 98, 102, 113, 117.)

Table I

	THYROXINE	CORTICOIDS
Protein Synthesis	In.	De.
Protein Catalysis	In.	De.
Nitrogen Balance	Negative	Negative
Fat Catalysis	In.	De.
Carbohydrate Catalysis	In.	De.
Calorigenesis	In.	De.
Adrenal Corticoid Effect	De.	De.
Thyroxine Effect	De.	De.
Skeletal Senescence	De.	In.
V_1	In.	De.
B_{sk}	<1	<1

In.=Increased
De.=Decreased

2) Thyroid Stimulating Hormone (TSH)

TSH is a glycoprotein secreted by basophil cells in the adenohypophysis.

TSH increases the rate of iodine uptake from the blood by the thyroid, the rate of synthesis of iodinated thyronines and the rate of release of T_4^a into the blood.

Centers near the median eminence of the hypothalamus secrete a TSH stimulating substance, which stimulates the adenohypophyseal basophils to secrete TSH. The level of T_4 secretion induced by TSH depresses the hypothalamic center.

(References: 6, 63, 76, 97, 98, 99, 102, 113.)

3) Adrenocorticotrophic Hormone (ACTH)

ACTH is a simple polypeptide protein with molecular weight of about 4500. It contains 39 amino acid residues.

ACTH induces synthesis of adrenal cortical steroid hormones, the effect appearing within minutes of administration. The biochemical locus of hormone action is after synthesis of cholesterol.

ACTH is known to alter membrane permeability selectively on the basis of chemical structure in some cells. ACTH, like STH, has some direct effects upon cells which are not mediated through adrenal cortical synthesis.

A center near the median eminence of the hypothalamus secretes an ACTH stimulating factor which in turn stimulates secretion of ACTH by cells (probably basophils) in the adenohypophysis. The resulting increase in plasma steroid levels inhibits the hypothalamic center.

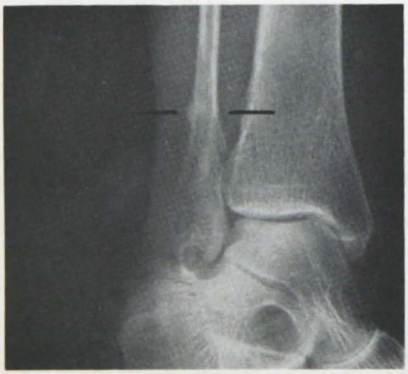

Figure 13

An example of fatigue failure in the fibula of a 26 year old woman in the second trimester of pregnancy. In this instance the hypercortisonism is endogenous and complicated by the presence of adjustments in function and in effect of the other endocrines. It is not claimed that this hormone effect is the *only* cause of this condition.

Epinephrine stimulates increased ACTH secretion, promptly and independently of the adrenal cortex. As with TSH, destruction of the hypothalamic center induces a drop of ACTH secretion to basal levels, which maintain adrenal cortical activity at higher levels than occur after hypophysectomy.

(References: 9, 25, 72, 100, 102, 113.)

4) Thyroxine

Thyroxine is tetraiodothyronine with symbol T_4. 3, 5, 3' — tri-iodithyronine, a partially deiodinated form of T_4, is designated T_3.

T_4 increases BMR. While the nitrogen balance effect is negative, there is an absolute increase in protein synthesis, offset by the larger increase in protein catabolism. Negative nitrogen balance induced by T_4 is larger than that induced by adrenal corticoids; see Fremont-Smith Iber and Plough.[31]

It is believed T_4 uncouples oxidative phosphorylation, meaning it impairs transport of energy from Kreb's cycle respiration to ADP. As a result there is excess energy which appears as excess body heat. This explanation is not wholly satisfactory. T_4 opposes the rate retarding effect of the corticoids, an effect illustrated by Alterman.

T_4 potentiates the action of STH on the body cells, decreases sensitivity of the thyroid to TSH stimulation, accelerates maturation of ossification centers, increases resorption and fibrous bone formation in the enchondral ossification apparatus. T_4 accelerates lamellar bone formation and bone resorption generally.

T_4 increases STH secretion.

T_3 is more active physiologically than T_4 but in the body over 90 per cent of the thyronine is present as T_4. See Table I.

TSH stimulates synthesis of iodothyronine and secretion of T_4 into the blood by the gland. T_4 depresses the hypothalamic center, causing it to diminish secretion of a TSH stimulating factor.

The action of TSH on the thyroid is depressed by the adrenal corticoids. Cellular use of T_4 is depressed by estrogen.

Some metabolic effects of the thyroid and adrenal cortical hormones are compared in TableI.

T_4 accelerates rate of synthesis of adrenal cortical steroids and their rate of tissue use.

(References: 1, 4, 18, 22, 28, 31, 56, 58, 63, 64, 65, 87, 97, 98, 99, 101, 104, 113, 118.)

5) Adrenal Corticoids

Aldosterone will not be considered.

The cyclopentanoperhydrophenanthrene nucleus is the basis of the adrenal cortical and sex hormones. These hormones are synthesized partly de novo from acetate and partly from exogenous cholesterol by the adrenal cortical cells.

DOC is considered a mineralcorticoid because it has salt retention and other effects similar to aldosterone. It is only 0.05 as potent as the latter.

The corticoids cause increased tissue and liver glycogen, decreased cell sensitivity to insulin, increased urinary nitrogen; a net excess of gluconeogenesis over protein synthesis, negative nitrogen balance, an absolute decrease in extrahepatic protein synthesis. Corticoids suppress the effect of TSH on the thyroid, pituitary secretion of ACTH and secretion of ACTH stimulating factor by the neurohypophysis.

The corticoids suppress chondrogenesis during growth, growth, skeletal incorporation of Ca^{45}, Ca^{47}, Sr^{85}, P^{32} and S^{35}. Fat synthesis from carbohydrate is depressed.

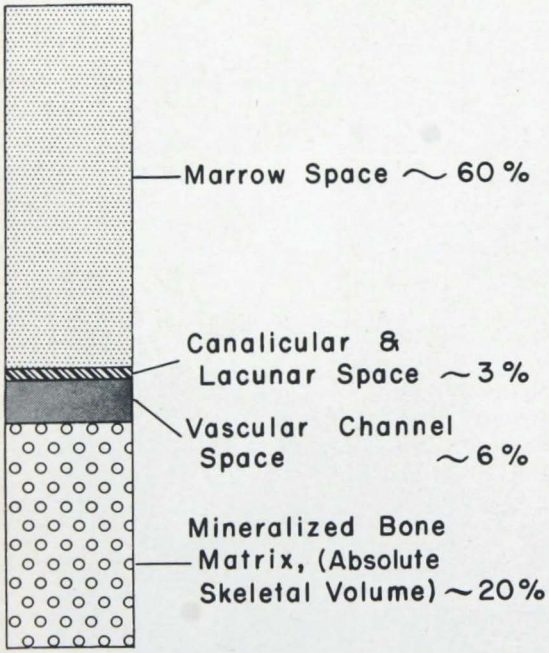

Figure 14

ASV (absolute skeletal volume) is diagrammed. The total volume of the bar represents the total volume of space encompassed by the periosteum of a bone or of all the bones in the skeleton. Part of this space is filled with non-bony substance, such as the marrow, the lacunae, the canaliculae and the blood vessels. When all of the non-bony spaces are subtracted from the total apparent volume, the remainder is termed by the writer ASV.

ABV designates absolute bone volume and may refer to one bone or part of any bone. ASV refers to the absolute volume of the entire skeleton.

Alteration in adrenal cortical secretion patterns may occur in congenital or acquired affections causing virilization or premature sexual precocity (Table I).

Adrenal corticoids are inactivated in the liver by conjugation. Hepatic inactivation differs in the sexes, being more active in the female. The conjugates appear as 17-oxysteroids in the urine and are often used as indices of cortical synthesis.

In the absence of the adenohypophysis adrenal cortical function occurs at a basal level that is from 1 per cent to 5 per cent of normal. Aldosterone synthesis is relatively insensitive to ACTH secretion enabling the hypophysectomized animal to survive better than the adrenalectomized animal.

ACTH action on the adrenal cortex is potentiated by STH. In thyrotoxicosis increased amounts of corticoids are synthesized and degraded and ACTH suppression by plasma corticoid level is retarded.

Adrenal hyperplasia occurs during pregnancy and may be induced experimentally by large doses of exogenous estrogen. Adrenal glands are larger in women than

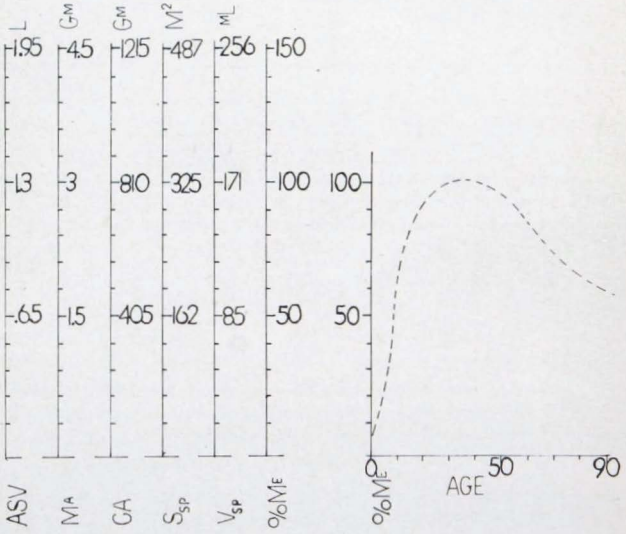

Figure 15

A diagram comparing the mean ASV against the corresponding mass (Ma) of the dried, degreased skeleton, the mass of calcium (CA) in the skeleton, the specific surface of the entire skeleton (S_{sp}), the specific volume of the entire skeleton (V_{sp}) and the mean as percent, 100 being the norm. L: liters. Gm: grams. mL: milliliters.

On the right the dashed line represents approximately the normal variations in ASV with age. Perhaps the maximum of the curve should lie further to the left; unfortunately we do not know.

in men. These and other facts indicate increased adrenal cortical function induced by estrogen.

(References 1, 4, 9, 11, 14, 15, 17, 25, 29, 31, 59, 64, 65, 67, 70, 72, 74, 76, 79, 96, 100, 101, 103, 105, 113, 118.)

6) Epinephrine and Norepinephrine

These hormones are secreted by the adrenal medulla and also by nerve endings and ganglion cells in the sympathetic nervous system. The effects are synergistic in many instances and opposed in some others.

Epinephrine stimulates the neurohypophyseal center that stimulates ACTH secretion. Epinephrine decreases liver and muscle glycogen, increasing blood glucose and lactate.

Epinephrine is necessary for the lowering of blood glucose produced by direct STH effect. Norepinephrine increases some adrenal cortical synthetic activity.

(Reference: 113.)

7) Parathormone

This is a simple protein with molecular weight of about 9500. While it appears unlikely that there is more than one parathyroid hormone, the matter is not settled.

Parathormone induces proliferation of mesenchymal cells in the bone spaces, induces differentiation of these cells into osteoclasts and induces increased resorptive activity by the osteoclasts.

It depresses renal tubular reabsorption of phosphate, leading to increased urinary phosphate and decreased serum phosphate in the hyperparathyroid state. The hormone increases absorption of calcium from the gut, as does vitamin D.

The level of parathormone secretion seems to be determined by the level of ionized calcium in the arterial blood entering the glands. Increased ionized calcium depresses hormone secretion while decrease leads to more secretion.

(References: 76, 80, 101, 110, 113, 117.)

8) Estrogens

The nucleus of the estrogen molecule and of its associated precursors and metabolites is the cyclopentanoperhydrophenanthrene nucleus around which the adrenal corticoids are built. Progesterone is one of the estrogen precursors. The most active hormones are estrogen and estriol.

Estrogen decreases tissue sensitivity to T_4. Accordingly, with estrogen present there is a slight increase in the PBI and decrease in the BMR. TSH secretion rises slightly as does the uptake of iodide by the thyroid.

Estrogen, and perhaps other ovarian secretions, induce adrenal hyperplasia which need not be dependent on ACTH secretion. Accompanying the hyperplasia is an increase in adrenal cortical secretion. Estrogens cause negative nitrogen balance and on large continued dosage cause or accentuate osteoporosis.

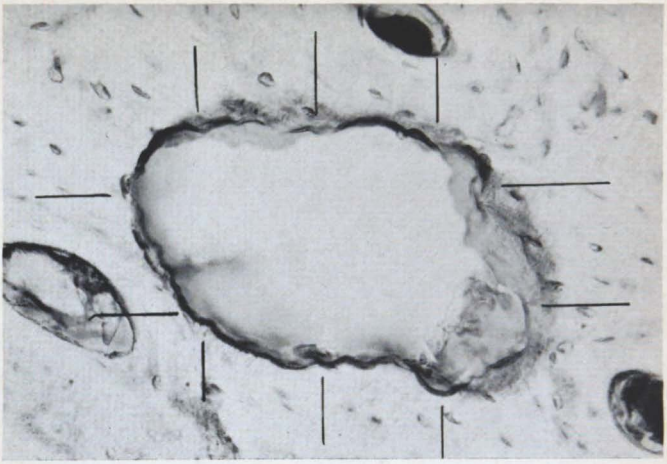

Figure 16

A resorption space in lamellar cortical bone is illustrated, outlined by the India ink brackets. The walls of the space are gently scalloped, each hollow being termed a Howship's lacuna and being the residium of the action of a specific cellular activity termed osteoclasia. This particular space would shortly have become the site of formation of a new Haversian system if the patient had not died of intercurrent disease.

Most investigation of estrogen effect on animals has been done in non-adrenalectomized animals so experimental separation of estrogen and adrenal cortical effects is seldom possible with the available facts. The effects noted are: Estrogen (in animals with adrenal cortex intact) retards maturation of ossification centers, retards growth, retards resorption of the chondrooseous complex under the epiphyseal plate, retards the rate of release of isotopic ions from the prelabelled skeleton, has no, or a retarding, effect upon skeletal uptake of isotopic ions, and retards S^{35} uptake by aorta and cartilage.

Estrogen retards the rate of weight loss of denervated limbs.

Feedback between estrogen and FSH, and progesterone and ICSH, exists. The liver is an important site of estrogen metabolism.

Little is known about interaction of adrenal cortex and ovary. In particular, it is not known if inhibitory adrenalcortical effects induced by estrogen affect the proportionality of normal corticoid effect upon synthesis and catalysis or not.

(References: 9, 13, 14, 19, 24, 26, 56, 61, 65, 76, 83, 90, 93, 101, 113, 117.)

9) Androgens

The chief androgens are testosterone and androsterone. Chief metabolites are 17 ketosteroids which are excreted in the urine. Since urinary 17 hydroxyketosteroids

are chiefly metabolites of the corticoids, urinary analysis of the keto — and hydroxy — products is used as an index of the functions of the adrenals and the gonads.

Apart from the effects of the androgens upon the target organs (male sex characteristics), positive nitrogen balance is induced in the body in general by androgens. The increase in protein synthesis in the soma is less than that induced in target organs. The protein anabolic effect of STH is potentiated by androgens. Androgens have been observed to decrease skeletal uptake of S^{35}, Ca^{45}, and P^{32}.

In the male, adenohypophyseal ICSH (interstitial cell stimulating hormone) stimulates secretion of androgens by the Leydig cells of the testis. Feedback between androgen secretion and ICSH secretion exists.

Little is known about the mutual interactions of the testis and adrenal.

(Reference: 113.)

IV Second Synthesis

It is now possible to superimpose some additional factors upon the diagram already discussed in figure 1. See figure 10. These are the feedback mechanisms occurring between the endocrines in response to endogenously or exogenously induced variation in secretory activity of one or several of them. However there are so many variables here that a true understanding of events cannot be given. In order to do so, accurate measurements of time-dose-response relationships would be needed.

A) While STH appears to be the only hormone that can induce a B_{sk} in excess of unity, the presence of T_4 is necessary for the full effect. In the Hypothyroid immature mammal, there is not only retardation in maturation of ossification centers; there is also a retardation in rate of bone production with maintenance of relatively normal ratio of diaphyseal width to diaphyseal length. The mutual dependence of STH secretion and effect on T_4 secretion and effect seems to be inherent in the mammalian organism.

B) Excess STH secretion seems to have little adverse effect on levels of thyroid and adrenal cortical activities. The reverse is not true, as was indicated in the preceding paragraph.

C) An excess of thyroid function leads to an increase in STH secretion of unknown magnitude and an increase in adrenal cortical function and effect of unknown magnitude.

D) An increase in estrogen secretion apparently enhances adrenal cortical activity by direct action of the estrogen on the adrenal. There may also be an effect through the pituitary. Estrogen depresses thyroid activity directly while decreasing tissue sensitivity to T_4. The compensatory adjustment occurring in the pituitary to these events is unknown, but important in understanding observed events.

E) Simultaneous increase in thyroid and adrenal function induces a nitrogen and skeletal balance much less than unity. Maximum corticoid effect on the skeleton, in the absence of thyroid and gonadal adjustments and with T_{f50} and T_{r50} of five years, could not produce a negative calcium balance over 200 mg. per day. Larger negative balances than this would mean some adjustment has intervened which has increased remodelling rate while maintaining or accentuating the imbalance between

Figure 17

A silver stain of an undecalcified, fresh section of human lamellar bone. A group of osteocyte lacunae and their canaliculae are illustrated, outlining a small island of bone in the center where the canaliculae and part of the lacuna have become filled with mineral. This is a condition termed micropetrosis.

Canaliculae in lamellar bone always run towards the original source of blood supply, always perforate the lamellae perpendicularly to their main plane of symmetry, and number about 50 per lacuna. At the upper left corner of the figure is part of an Haversian canal seen in cross section. Compare the lacunae here with those in figures 16 and 22, where a stain to reveal the lacunae specifically was not done.

formation and resorption. In the light of this model, this means increased thyroid effect. In clinical interpretation of events, the importance of the time constant[a] must be remembered. The adrenal can adjust within minutes but thyroid effect requires days to appear due to the long half-time of T_4 in the plasma.

F) The purpose of the second synthesis has been well served if the need for measurements of hormone effects in controlled circumstances without confusing adjustments of other endocrines has been illustrated. The use of the living skeleton as a tool for investigation of these effects appears logical in view of the relative simplicity of the methods of studying it that are available.

Discussion

The model presented raises numerous questions and problems, some of which are not only provocative but potentially rewarding avenues of investigation or thought. Some of these questions will be discussed. For obvious reasons, discussion will be brief.

A-Nondependence of Balance and Absolute Rates

The concept that rate of internal remodelling need not bear fixed relationship to the net balance of synthesis and catalysis is important in other fields than bone remodelling and merits repetition.

For example: net increase in gluconeogenesis following administration of cortisone is well known. It was assumed the net increase was the result of an *absolute* increase in the rate of gluconeogenesis. Yet in vitro, where measurements of the sort that could reveal absolute changes in rates are made, cortisone causes no absolute change in rate of gluconeogenesis. In vivo catalytic activity (gluconeogenesis) is normally balanced by synthetic activity (protein synthesis). When both are depressed, but asymmetrically with net excess of catalysis, observed events are accounted for. Cortisone seems to exert the same effect upon extraskeletal, cellular protein synthesis and catalysis that it exerts on bone formation and resorption.

Another example: cortisone decreases iodine uptake by the thyroid gland in the hypophysectomized, thiouracil treated animal but increases (over short periods of observation) the rate of release of T_4 to the blood, seemingly unexplainable and contradictory events. Yet in the thyroid the processes of molecular synthesis and catalysis of thyroxin-thyroglobin complex are continually going on with hidden rate of internal turnover,[a] much like bone. In the situation described, iodide incorporation is almost arrested by experimental design. Internal turnover in the thyroid continues without TSH, and when the synthetic side is depressed more than the catalytic side (an apparently characteristic effect of cortisone) net balance less than unity results and T_4 is released into the blood because it cannot be reincorporated in the thyroglobin molecule as fast as it is hydrolysed from it.

This concept has other applications that will be delt with separately.

B-Supreme Importance of STH

STH is accorded unique importance in the model control system described. It is the only hormone that could place a skeleton into balance in excess of unity. The gonads are relegated to an indirect role in skeletal physiology by this model, a

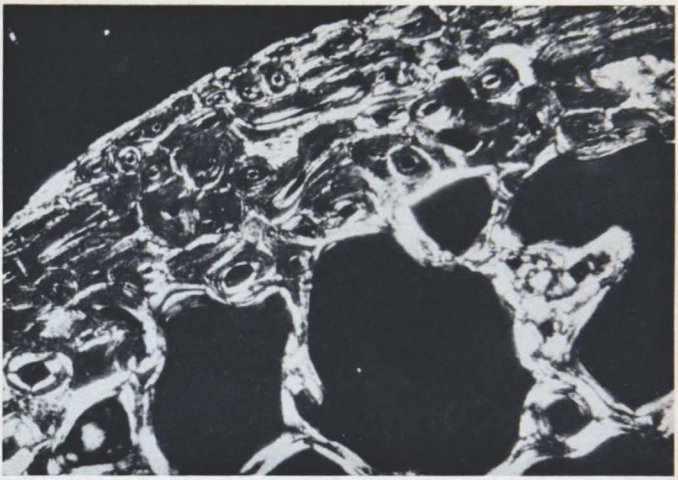

Figure 18

Cross section of human rib, undecalcified, between crossed polars. The cortex lies above, the marrow spaces with some trabeculae of cancellous bone below, the middle of the plate. The periosteal surface lies at the top, and the lamellae not of Haversian origin immediately under the periosteaum are termed circumferential lamellae. The non-Haversian lamellae lining the marrow spaces are termed endostal lamellae.

radical departure that will not be readily accepted in spite of growing assent with the present deemphasis; see McLean and Urist,[76] Nordin,[83] Heaney and Whedon,[58] and the writer.[41,42]

C-The Cause of Senile and Postmenopausal Osteoporoses

If STH deserves the position given it in this model, it is apparent why senile and postmenopausal osteoporoses have proved refractory to treatment with sex hormone and dietary factors as far as the osseous disease is concerned. Simple: the wrong hormones were employed (Figure 11).

In the terms of the present model these two osteoporoses would be the result of one of the following possibilities: declining STH secretion with age; increasingly defective synthesis of the STH molecule with increasing age; an increasing tissue refractoriness to STH molecules with increasing age, or a combination of these possibilities. The resulting decrease in STH protein anabolic effect would leave the skeleton exposed to the unshielded actions of the thyroid and adrenal cortex, both of which tend to produce osteoporosis. The difference is the thyroid produces it quickly, the adrenal cortex slowly.

It is belaboring the obvious to point out that purified human growth hormone

is scarce so there is still no commonly available treatment of these osteoporoses, assuming the present synthesis correct.

D-Need for Measurements

Figure one is reasonably simple in concept. In spite of this simplicity, qualitative but not quantitative predictions can be made on the basis of the diagram. To be able to make quantitative predictions of remodelling behavior under the most favorable, controlled experimental circumstances, information not currently available must be obtained. The use of this information would be in the programming of a computer. The types of information needed are as follows:

1) Dose-response relationships; Between formation and resorption rates and individual hormones. In controlled circumstances, how much new lamellar bone will be formed as a result of an administered dose of one microgram of STH per gram of tissue or per gram of DNA? How much additional new bone will be formed when the STH is supplemented by 5 micrograms of T_4? How much inhibition will occur when corticoids in known amounts are added? What are the damping and instability factors of each in this servomechanism?[a]

2) Time constants:[a] It is necessary to know the average time required for endogenous synthesis of a hormone, the average period of its existence in the blood and the average period of its effective existence in the cells upon which it acts. The The effectiveness of an army depends on the rate firepower is delivered at the front, not on its total membership or the part on the way to the front.

3) Proportionality factors: What happens to absolute rates and net balance when normal proportions of adrenal cortical steroids in plasma are altered? Similarly for thyroid thyronines? Similarly for the gonadal hormones?

4) "Gaposis": The preceding text certainly does not contain the complete story of the effects of hormones on bone remodelling rate, nor does it note all of the important indirect effects that result from interactions of the endocrines with each other. These gaps in knowledge must be filled and it will require an enormous amount of labor to do so. For example, exactly how much insulin is needed for corticoid effect? How much epinephrine is needed for STH effect? Is there such a thing as a pure, isolated STH effect?

Skeletal remodelling should be a rewarding field for investigation of these factors because of the ease with which dose-response and time-response factors may be measured by methods already developed. In a way the skeleton is a living record of effect, a record conveniently preserved for considerable periods of time because of relative stability of bone compared to stability of intracellular protein and enzymes.

E-Organ Remodelling and Senescence

Several advantages resulted when nature combined cells to multicellular organisms; additional advantages resulted when this aggregation developed into multiple organs, composed of multiple cells, in one organism. One of these advantages was longevity. Longevity accompanied emergence of something less easily defined which is simply

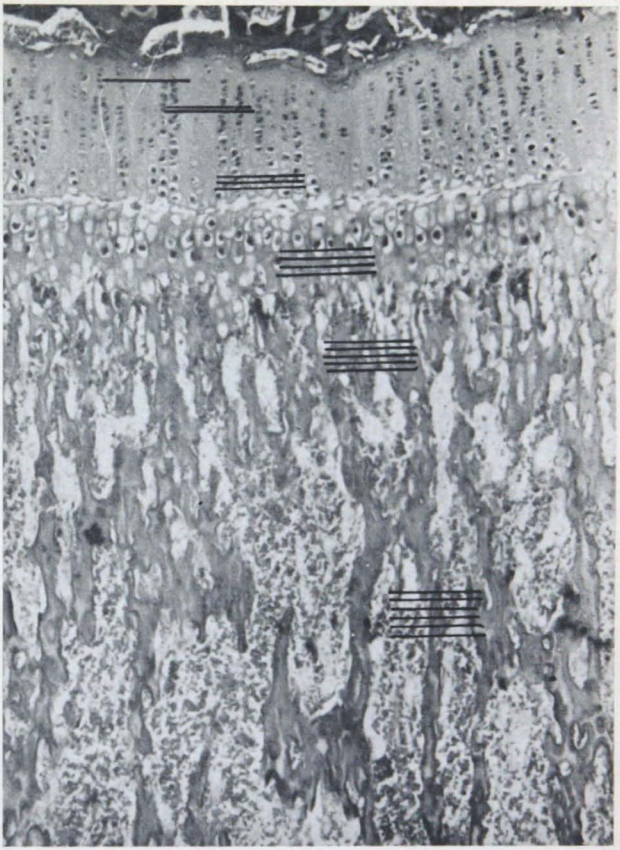

Figure 19

A longitudinal section through the proximal tibial epiphysis of a young rat. The epiphyseal plate is at the top, the diaphysis below.
The single India ink bar at the top identifies the germinal layer of the plate.
The double bar identifies the proliferating cells of the plate.
The triple bars identify the plane of hypertrophying cells of the plate.
The quadruple bars identify the plane of the calcifying cartilage lacunar walls of the plate.
The quintuple bars identify the plane of vascular invasion of the calcified cartilage and the deposition of fibrous bone on the remaining walls of the cartilage lacunae.
The sextuple bars identify the resorption of the chondroosseous complex and its replacement with blood-forming marrow and an occasional lamellar trabeculum.

termed a personality. Personalities inhabit bodies. Parts of the body die continually and are replaced by new parts; the personality remains relatively unaffected by this cell turnover.

One way of looking at aging is to think in terms of an organism endowed with a fixed number of cells. With increasing time, an increasing proportion of these cells die and eventualy the organism and personality will also die. This is the current popular view of aging. A good discussion of this view is outlined by Szilard.[109]

Skeletal remodelling suggests another way of regarding aging: an incomplete replacement of senescent or damaged cells by newly generated cells. If it were possible to improve on the replacement that already occurs, it would be possible to keep skeletons younger, using the word in the sense of functionally more capable. The adult skeleton does remodel itself. Why? And why is it that other organs, such as liver, or blood vessels, appear to be less competent in this regard than bone? It is assumed the reader is familiar with the facts supplied by isotopically labelled nucleotides indicating that there is some remodelling in adult visceral organs.

F-Bone Remodelling and Fatigue Failures

T_4 accelerates remodelling and thus retards senescence. It follows that in thyrotoxicosis, pathological vertebral fractures or excessively brittle traumatic fractures should be significantly less likely than in a senile osteoporotic, assuming the thyrotoxicosis has been present long enough to produce the alterations in quality suggested under remodelling kinetics.

Hyperadrenalcorticoid function accelerates senescence of bone; should retard repair of whatever wear-and-tear phenomena actually occur, and should thus exhibit several intriguing associations: brittle fractures; spontaneous fractures of vertebrae and ribs; fatigue fractures under physiological loads.[a] These associations actually occur. Consider (and these thoughts are presented for consideration, not as proven cause-effect relationships):

1) In endogenous or exogenous hypercortisonism there are spontaneous fractures of ribs and vertebrae, even in children (Figure 12).

2) Traumatic fractures in hypercortisonism are usually brittle with comminution.

3) In this text the gonad is assigned the role of an adrenal cortical stimulator. It is interesting that march fractures are usually encountered in vigorous, young people who are in full gonadal function and whose adrenal cortical function is known to be active. These fractures are less often encountered in aged people or children. It is significant that the slowest rates of skeletal remodelling found in a normal life occur around ages 25-45.[44,48] The writer has seen three pregnant women in the past four years with fatigue fractures of the fibula, and one 45 year old male with the same affection, in the absence of unusual physical activity (Figure 13).

Rutishauser and the writer have demonstrated the normal existence of microscopic fatigue cracks in cortical bone in dogs[85] and in patients.[39] These cracks must

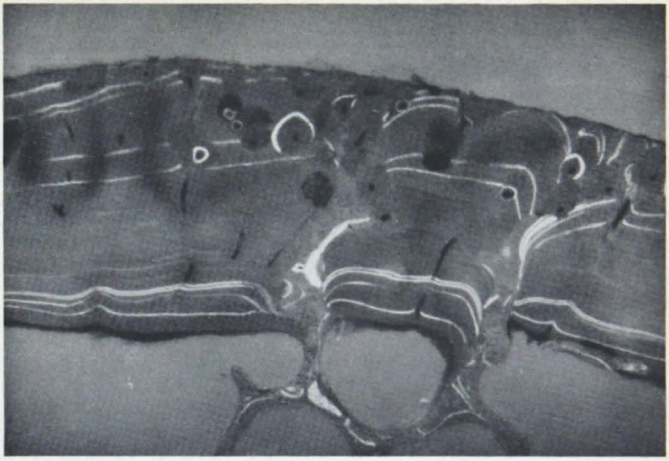

Figure 20

Cross section of rib of a child who received tetracycline antibiotics on five occasions, four of which were at known times and for known durations. Undecalcified, blue-light fluorescence, about 20 X.

The periosteum is at the top, the endosteum at the bottom. Compare with figure 22. The bright lines are tetracyclines that were deposited in newly formed and mineralizing bone. Note that bone was being formed much more rapidly at the periosteal surface than at the endostal surface. Note how well the circumferential and endosteal lamellae are identified by the tetracycline label.

normally be repaired. If they were not, skeletons should (like the one-hoss shay) exhibit more spontaneous failures than they do.

4) Aseptic necrosis of the femoral and humeral heads may occur in patients under treatment for long periods with corticoids.[59,74] It is plausible to suppose that the corticoids retard repair processes in critical areas so that with continued load — and decreased irritability of the joint tissues — cumulative, poorly healing microscopic injuries add up to a spontaneous aseptic necrosis. The term "aseptic necrosis" is a misnomer in these cases because histological examination of such heads (obtained at arthroplasty) reveals that they are well vascularized and not dead. It is these two observations that made the condition so puzzling.

G-Push-Pull

The presence of push-pull has been mentioned. Consider the following:

In thyrotoxicosis an osteoporosis develops. The skeleton, being in balance of less than unity, adds calcium to the blood. If there were no factor withdrawing more calcium from the blood, the serum calcium would rise until the increase in concentration were enough to increase rates of urinary and fecal loss and restore balance.[61]

Usually serum calcium does not rise in thyrotoxicosis. Therefore, a factor must exist which accelerates removal of calcium from the blood (by kidney, stool or both), or which retards its absorption from the gut. There are several possibilities which will not be considered. The point is that the push-pull way of looking at some things indicates where and what else to look for.

There should be similar mechanisms present in the hypercorticoid state, in the acromegalic state and in other examples of pathophysiology and biochemistry in general.

Conclusion

While the reasoning could continue, it is time to stop. It is hoped that the foregoing material provides thought-provoking and some understanding, and stimulates work radiating out from the basis established. Problems of growth, senescence, interpretation, kinetics and synthesis have been dealt with, with these factors in mind.

ACKNOWLEDGMENT

Appreciation is expressed to the following individuals without whom this work would not be possible: Dr. E. J. Collins and Dr. R. Johnson of Kalamazoo, with whom the initial synthesis of events was made; Dr. C. L. Mitchell, Dr. J. Fleming, Dr. C. White, Dr. R. Horn and Dr. G. Fine for creation of a climate in which basic research is possible, in an institution devoted to the practice of medicine; Mr. J. Kroll for the photography, Mr. J. Gray for the art work, Mr. A. Bowden for the photomicrographs and Miss E. Bosanko and Mrs. B. Hentschel for the large amount of typing, and to Mr. G. Scimieni, Mr. P. Santori, Mr. A. Villanueva and Mr. R. Hattner for a most rewarding and stimulating association.

GLOSSARY

ABSOLUTE BONE VOLUME: The volume of bone remaining after subtraction of all the marrow, vascular, lacunar and canalicular spaces. The important feature of a unit absolute bone volume is that the amount of matrix in it remains unchanged during its biological lifetime, whether this be a week or 60 years. It is the matrix that is manufactured by the osteoblasts. It is the volume of matrix manufactured in a given time period by all of the bone-forming loci in a reference absolute volume of bone that constitutes a true statement of rate. Robinson and Elliott[88,89] and the writer[41] have discussed the desirability of adopting volume rather than mass as the standard of reference in skeletal measurements (Figure 14).

ABSOLUTE SKELETAL VOLUME: The volume of all the bone in the skeleton after subtracing all of the marrow, vascular, lacunar and canalicular spaces from it. Measurement of the canalicular and lacunar volumes in human bone have been published by the writer. Average values of vascular space in cortical bone has been determined by the writer also; Currey has done measurements on beef bone.[21] (Figure 14).

The mean mass of dried, degreased skeletons has been determined by several groups of authors, notably Lowrance and Latimer,[69] Trotter, Broman and Peterson[111,112] and Mertz,[77] and Baker.[5] A mean value for U.S. skeletons would be 3200 — 3500 grams. The density of dried, degreased bone has been measured to be about 2.3 by Robinson[89] and Elliott.[88] Similar values are quoted in McLean and Urist.[76]

With these figures it is possible to calculate average absolute skeletal volumes and masses. Some of the data of the above authors has been used in the construction of figures 5, 6, 15.

ACTH: Adrenocorticotrophic hormone of the adenohypophysis.

ACTIVITY COEFFICIENT: See Neuman and Neuman[90] for a discussion of this concept. Briefly, ions in solution are not completely available for reaction with other ions, molecules or surfaces. Ions attract a shell of water molecules about themselves, and occasionally shells of other ions; some ions exist in combination with their homologues as unionized molecules; some ions chelate with other substances. For these and other reasons, all of the ions in solution are not available for various reactions. Rates of reactions depend upon ions present in utilizable state, not upon ions that may be shielded from reactants. An activity coefficient is a number that, when multiplied by the total ions present will predict reasonably well the chemical reactivity that will be observed.

Figure 21

Undecalcified section of rib. Some remnants of lamellar bone may be seen (compare with figure 23). The major part of the plate, however, is composed of fibrous bone which literally fills the marrow spaces. The fibrous bone is revealed by the "warp and woof" appearance of the anisotropic lamellae.

This is a specimen from a case of metastatic carcinoma of the stomach with osteoblastic metastases to the skeleton. As is usually the case, the "blastic" aspect of this process is the filling up of the marrow spaces with fibrous bone, *not* lamellar bone, in response to some stimulus from the tumor.

Crossed polars, about 200 X.

APATITE:[54,80] A lattice. A lattice is a three-dimensional structure of the positions of atoms in a crystal. The apatite lattice has a certain relationship of calcium, phosphate and hydroxyl ions to each other. Substitutions may be made for these ions by others of like size and charge, for example Sr++ for Ca++, with preservation of the lattice.

A lattice is not a chemical compound or identity but a method of arrangement in space of atoms of particular charge, and of given ratios in number, to each other.

Some formulas of bone apatite follow, from McLean and Urist:[76]

$3Ca_3(PO_4)_2 \cdot H_2(OH)_2$ (Dallemagne) (alpha tricalcium phosphate)

$Ca_{10-x}H_{2-x}(PO_4)_6(OH)_2$ (x=vacant lattice points in the apatite) (Posner)

$Ca_{10}(PO_4)_6(OH)_2$ (Apatite)

The role of carbonate, citrate, magnesium, sodium and water in the mineral phase of bone are not settled. Vacant positions in the ideal apatite lattice occur, as do substitutions. An hydration shell surrounding the crystallites like a cloud or halo occurs, and some ions are in this shell or adsorbed on the surface. The function of the carbonate remains unsettled, although its importance is granted by all concerned.[71,73]

Apatite crystals are small, about 100 X 150 X 300 Angstrom units in size, larger crystals being found in older bone and after heating, smaller ones in young and fresh bone. The total surface area of the apatite crystals in the body is enormous, being over 100 M^2 per gram of apatite. There are about 2000 gm. of apatite in the whole skeleton.

APPOSITION: Bone Formation.

BALANCE: As used here, the state of balance between the opposing activities of synthesis (formation, manufacture) and catalysis (resorption, destruction). A negative balance is the same as a balance less than unity. A positive balance is the same as a balance in excess of unity.

BONE FORMATION: This term herein means the formation of a given volume of matrix by osteoblasts. In a normal skeleton lamellar bone matrix becomes mineralized about a week after its formation, existing as an osteoid seam in the week between formation and mineralization. Fibrous bone mineralizes more irregularly and faster than lamellar bone.

BONE RESORPTION: Herein means resorption of a given volume of bone by osteoclasts. When osteoclasts resorb bone, they remove both mineral and organic phases simultaneously, at least at the level of resolution of light microscopes. Resorption of bone matrix and hyaline cartilage matrix is not seen until the matrix has become mineralized. Osteoclasts and chondroclasts appear unable to destroy the tissue unless the mineral is present. This suggests the physical chemistry of resorption is dependent on some function of the mineral ions (Figure 16).

The exception to the above occurs in pyogenic infections where destruction of unmineralized cartilage occurs.

BONE MATRIX: The organic phase of bone. It is composed of 95 per cent collagen and 5 per cent cement substances. There is a large amount of water in newly formed matrix which is replaced by crystallites as mineralization begins.

A) Bone collagen appears to be the same as collagen in other parts of the body. Collagen is a crystalline, fibrous organic solid composed of ultramicroscopic tropocollagen molecules. The tropocollagen molecules associate with each other in parallel bundles visible with the light microscope.

B) Bone cement substance contains a small organic fraction that is as yet uncharacterized chemically. The major part of the cement substance is composed of chondroitin sulfates A and B, with some C also present.

Chondroitin (A) is composed of D-galactosamine, D-glucuronic acid and sulfuric acid. Chondroitin (C) is similar but (B) contains L-iduronic acid instead of glucuronic acid. The chondroitins are present in bone matrix in polymerized form with an indefinite molecular weight. The relationship of the chondroitins to the bone collagen is probably specific and an important factor in the ability of bone and hyaline cartilage to mineralize. Mineralization of bone and cartilage matrix seems to begin by a process of nucleation in which small seed crystals of apatite are formed in special matrix centers.

BONE MINERAL: All the inorganic material deposited in the bone matrix. This includes the apatite, the carbonate, and also Mg, Sr, F, Na, Cl, K, traces of other ions such as Pb and Zn, and citrate and carbonate.

B_{AL}: See Skeletal balance.

CANALICULAE: Small tubular holes in bone that connect osteocyte lacunae to a vascular channel, such as an Haversian canal. The canaliculae are about 0.35 microns in diameter in human bone, number over 1,000,000 per mm^3 and comprise about 5.5% of the volume of lamellar bone.[45] The average length of a canalicula is 115 microns (Figure 17).

CANCELLOUS BONE: Spongy bone, on cut surface appearing much like the cut surface of the natural or synthetic household sponge. The individual bars of cancellous bone are termed trabeculae. Cancellous bone is usually found in the medullary spaces at the metaphyses of long bones, and in the medullary spaces of the flat bones and vertebrae. In the normal adult cancellous bone is made up entirely of lamellar bone. Fracture callus and the chondroosseous complex of enchondral ossification contains trabeculae made up of fibrous bone (Figure 18).

CHONDROITIN SULFATE: See Bone Matrix.

CIRCUMFERENTIAL LAMELLAE: The outer layers of lamellar bone in the cortex. If the outside layer of an onion can be visualized, it may be pointed out that this is the onion's circumferential lamellae. Circumferential lamellae are by definition lamellar bone. Like all lamellar bone, circumferential lamellae contain lacunae and canaliculae and vascular channels (Figure 18).

CORTICAL BONE: Long bones are tubular structures with gross form known to everyone. The visible wall of the tube is cortex and is termed cortical bone. Like all bone of all types, cortical bone is formed only by osteoblasts. As a rule, cortical bone is lamellar

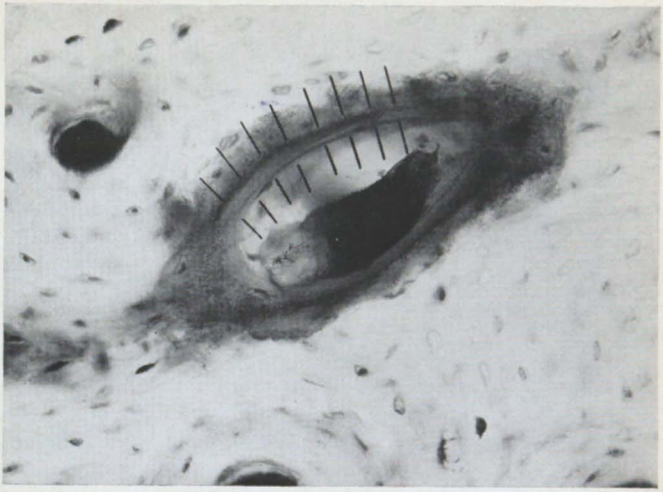

Figure 22

A cross section of a new Haversian system in the process of formation. The Haversian canal lies in the center of the plate. Its perimeter appears slightly dark because it is still fuchsin permeable, thus is stained somewhat in this fresh, undecalcified section.

Between the India ink bars lies an osteoid seam. The seam is new bone matrix which has not yet begun to mineralize, at least in any way detectable with the light microscope. The demarcation between seam and mineralized bone is a relatively sharply defined plane known as the zone of demarcation. This zone is about 4 microns thick and in it, in the course of about four days, initial mineralization occurs so rapidly that about 70% of all the mineral that can ever be laid down in this bit of matrix is deposited.

bone. By definition any bone contained within the tubular, cylindrical walls of a long bone is not cortical bone. The term therefore is a purely descriptive, locative term without any inherently attached quality or quantity (Figure 18).

DENSITY: The physicist uses the term to mean mass of a unit absolute volume of material. If the material contains pores or holes, volume of these holes is subtracted to obtain the true volume. In symbols, where (M) = mass and (V) = absolute volume, Density = $\frac{M}{V}$.

Physicians, being medically rather than physically oriented, misuse this term and cause confusion as a result.

Specific Gravity (Sp.G.) is the ratio of mass of a unit volume of material to the same volume of water. True density and Sp.G. are nearly the same, the difference due to the fact that a cubic centimeter of water does not quite weigh one gm.

DIFFUSE EXCHANGE: Radioactive, inorganic, bone-seeking ions in the plasma establish an equilibrium with bone. At equilibrium about as many ions leave the blood to enter bone as leave the bone to enter blood in unit time. Mutual entrance and departure of ions from these two compartments is exchange. Studies of rates of exchange and of differences exhibited by different ions under differing circumstances is a potent investigative weapon.

Bone is not homogeneous at any level of resolution. Inhomogeneities lead to differences in exchange behavior which can be associated with physiological and physical

factors. For example, old bone exhibits less and slower exchange with blood than young bone. Dead bone exhibits less exchange than living bone.

There is a diffuse uptake of isotope from blood by bone, the term diffuse being used because no morphological resolution has been possible that would reveal where or in what part of the mineral at the molecular level the major part of the diffusely taken up isotope is deposited. Diffuse uptake is not associated with bone formation or bone resorption. Little effort has been made to investigate histological localization of this diffuse exchange material, although the work of Strandh,[107,108] of LaCroix,[66] and of the writer[40] suggest this would be informative.

DIFFUSION IMPEDENCE: When a drop of ink falls into a tank of still water under isothermal conditions, in a few hours the ink will have permeated throughout the tank. This occurs by the migration of ink molecules between water molecules. This is diffusion and is distinct from mixing produced by stirring or circulation of the water.

Diffusion is ions or molecules gradually permeating and distributing themselves through relatively fixed molecules of some other substance. Diffusion occurs in gases, liquids and solids, and diffusing material may also be gaseous, liquid or solid.

The rate of diffusion under given circumstances is governed by many things, among them being temperature, size of diffusing atoms, charge, mass, pressure, nature of the material being permeated, interactions between the two substances or between separate atoms of each substance and so on. Diffusion is not a free process; there is a resistance to permeation.

Diffusion impedence[40] means the resistance a diffusing atom encounters to permeation of a substance, analogous to the electric sense of the term impedence. Diffusion impedence is the sum of the impedence or resistance offered by numerous additive factors.

DNA: Desoxyribonucleic acid, the material constituting the chromosomal content of the cell nucleus which contains the chemical and steric coding necessary to the production of species specific proteins. DNA is responsible for synthesis of cellular enzymes and for their continued presence during the cell life. Removal of DNA from the cell leads to gradual death.

DNA governs the synthesis of RNA, which is ribonucleic acid. RNA located in the ribosomes (also termed microsomes) of the cytoplasm is responsible for the actual synthesis of cellular protein. A separate RNA component termed transfer RNA brings specific amino acids to the synthesizing RNA where the amino acid sequences comprising protein structure are formed.

ENCHONDRAL OSSIFICATION: The mechanism by which cartilage is transformed to bone. Enchondral ossification is a complex series of events. These events must be known if adequate interpretation of experimental histology is desired. The events involved in enchondral ossification in man and in common mammalian experimental animals are as follows: refer as needed to figure 19.

A) A germinal layer of chondrocytes lies along the surface of the epiphyseal plate farthest from middiaphysis. These cells divide, adding new cellular material to the epiphyseal plate. Recently divided chondrocytes lie within single lacunae. The cell division described is polarized so the direction of division is always away from middiaphysis. Nucleotide incorporation occurs here.

B) Shortly after division new cartilage matrix gradually intrudes between the two daughter cells, eventually producing separate cartilage lacunae with a single chondrocyte lying in each. In this phase the production of new cartilage matrix and incorporation of amino acids is a prominent molecular event. The polarization mentioned in (A) is retained in this and subsequent events, the addition of new material or the removal of material occurring predominantly parallel to the long axis of the bone.

C) After separation of the daughter cells and lacunae, enlargement of individual lacunae and degeneration of chondrocytes within begin to occur. In the later phases of this part of the enchondral sequence alkaline phosphatase is elaborated by the chondrocytes and inorganic SO_4 is bound to the matrix.

D) Then the enzyme phosphorylase appears in large amounts in the chondrocyte cytoplasm. Accompanying appearance of this enzyme the glycogen granules present in large amounts in the preceding phase disappear. Simultaneously mineralization of the cartilage walls of the chondrocyte lacunae occurs.

At the conclusion of this phase, chondrocytes are largely dead and are surrounded by calcified cartilage lacunar walls.

E) From marrow spaces on the diaphyseal side of the epiphyseal plate, capillaries invade the calcified cartilage, causing erosion of the floors and roofs of calcified cartilage

Figure 23

Lamellar bone under crossed polars, about 300 X. Note the alternating bright (anisotropic) and dark (isotropic) bands. The relatively straight bands are circumferential lamellae. An Haversian system lies at the top middle of the plate and is also composed of lamellae. Compare with figures 21 and 22.

lacunae but, in accordance with the polarization referred to, leaving the side walls of lacunae relatively undisturbed.

At present it is disputed whether all of the chondroclasia referred to is produced by specific cells termed chondroclasts, or whether some cartilage erosion occurs by endothelial cells of the invading capillaries. There is no dispute about the presence of chondroclasts. These cells resemble osteoclasts and are probably similar biochemically. They exhibit increased amounts of an acid phosphatase and glutamic oxalacetic transaminase. The obligatory presence of mineralization for resorption suggests the mineral plays an essential role in the physical chemistry of resorption.[36]

F) Osteoblasts differentiate from the primitive mesenchymal cells accompanying the vessels that invaded the spaces between the calcified cartilage bars. These osteoblasts deposit fibrous bone on the walls of the calcified cartilage bars. The resulting trabeculae have a distinctive appearance histologically, the scalloped cartilage bars being covered on all sides by new fibrous bone.

While the fibrous bone (also termed fine-fibered bone, fetal bone, woven bone, primitive bone and others) is often termed osteoid, or osteoid seam, such usage should be discouraged. In fresh, undecalcified material true osteoid seams are not seen in the formation of fibrous bone.

G) Next, the chondroosseous complex is in turn resorbed.

The chondroosseous complex is the trabeculae of calcified cartilage covered by fibrous bone already mentioned in (F). Its resorption is accomplished by osteoclasts which make no functional distinction between calcified cartilage or mineralized fibrous bone.

H) The space resulting from resorption of the chondroosseous complex is filled with hematopoietic marrow and to a lesser extent by new trabeculae of lamellar bone.

I) Accompanying the above processes is a constant remodelling of the metaphyseal cortex by the process of deposition of new bone on the endosteal surfaces and resorption on the periosteal surfaces.

J) Finally, a similar but reversed process occurs in diaphyseal remodelling. There is periosteal deposition (circumferential lamellae) and endosteal resorption. In many long bones diaphyses not only grow by centrifugal expansion; they grow in a lateral direction, or anteriorly, or posteriorly, so that after a period of months the original central axis of a bone may have been left behind, or in front, and have become completely exteriorized. These processes, well known in laboratory animals,[117] are beautifully revealed in humans with tetracycline labels (Figure 20).

ENDOSTEAL LAMELLAE: Onion-peel-like layers of bone lining the marrow spaces. See Figure 18, 20. Endosteal lamellae are parallel to the circumferential lamellae and both are parallel to the periosteum. Separately identifying them is an artificial abstraction which may be confusing but is useful.

EXTRAHAVERSIAN BONE: This term designates all cortex that is not functioning, intact Haversian systems. This includes circumferential lamellae, endosteal lamellae, fragments of partially remodelled-out Haversian systems, outer members of concentric systems and the occasional layers of fibrous bone lying parallel to the circumferential lamellae and described by Currey.

FIBROUS BONE:[42] A primitive, rapidly elaborated, structurally inferior bone elaborated by osteoblasts (Figure 21).

Fibrous bone under crossed polars lacks overall order in orientation of collagen. There is no lamellar structure. There is no apparent polarization of structural units by physical loads imposed upon the part. Osteocyte lacunae are irregular, lack polarization in shape, are large and number about 80,000/mm^3. The lacunar specific volume[a] of fibrous bone is about 11 percent.[45]

Canaliculae in fibrous bone lack polarization by load or blood supply. The canaliculae number about 400,000/mm^3 and the canalicular specific volume[a] is about 2 per cent. The mineral phase in fibrous bone appears to be the same as in lamellar bone. Crystallites are oriented with (C) axes parallel to the long axis of the collagen fibrils in lamellar bone.[85] Little specific is known about the cement substance of fibrous bone. While it may be different in some way from lamellar bone, it is also possible that differences between the two are merely in assembly, structural units possibly being identical.

Osteoblasts forming fibrous bone are accelerated by T_4, are little accelerated by STH and are little inhibited by corticoids, the latter an important physiological attribute. Fibrous bone formation is induced by trauma, somewhat accelerated by trauma. Exposed fibrous bone surfaces in tissues in some manner induce replacement by lamellar bone. Fibrous bone is found normally during enchondral ossification. Pathologically, it is the major constituent of fracture callus, and is used to wall off inflammatory, neoplastic and physical processes. Occasionally some is found between bands of circumferential lamellae.[21]

GROWTH REMODELLING: See **REMODELLING.**

HAVERSIAN SYSTEM AND CANAL: Just as a long bone is a macroscopic tube containing a central canal termed the medullary space, so the Haversian system is a microscopic bony tube containing a central canal. Haversian systems are commonly a cm. in length, branch frequently, average 250 microns in diameter and have central canals termed Haversian canals about 70 microns in diameter.[46] Haversian systems may comprise none of the cortex (characteristic of the new born) or as much as 70 per cent of it in the elderly.[36] There is a gradual increase in the proportion of cortical bone made up of Haversian systems with age (Figure 22).

Haversian systems are invariably composed of lamellar bone and from the evolutionary standpoint are ancient structures[27] (Figure 23).

HOWSHIP'S LACUNA: When osteoclasts resorb mineralized bone or hyaline cartilage they produce a shallow excavation in the surface of the solid. At light microscope resolution the organic and inorganic phases are resorbed simultaneously, rare exceptions occurring. In the exception collagen of the matrix is resorbed last and obtrudes into the space between the osteoclast and the bone as a **brush border.**

The excavation is termed a Howship's lacuna and is illustrated in figure 16.

INTERNAL REMODELLING: See **REMODELLING.**

LACUNAE: Small holes in cartilage or bone in which the cells characteristic of the material reside. In cartilage they are termed chondrocytes, in bone osteocytes. While cartilage lacunae have no canaliculae, bone lacunae always do. After death of osteocytes the canaliculae, and more rarely the lacunae, may become filled with mineral so completely that they may not aerate in undecalcified sections even after heating. Large amounts of bone with its porosities plugged in this manner is termed micropetrotic bone[37] (Figure 17).

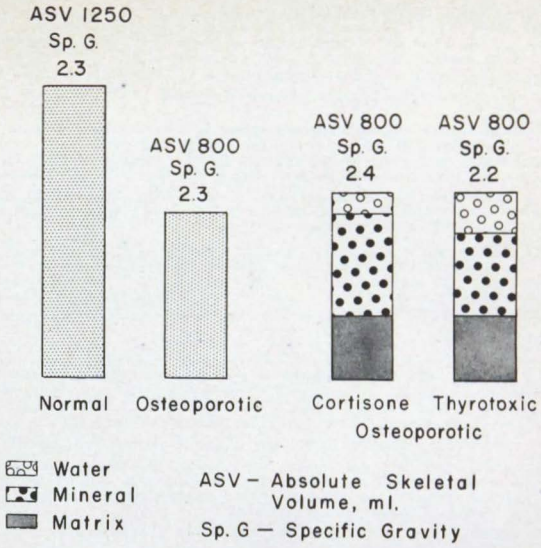

Figure 24

A diagram illustrating the nature of an osteoporotic skeleton, and the fact that the quality of a given osteoporotic skeleton has nothing to do with the state of its being osteoporotic. The quality rather is derived from and characteristic of the cause of the particular osteoporosis under consideration. The two examples discussed in the text are illustrated.

It is quite possible for the same skeleton to be both osteoporotic and osteomalacic, a concurrence that has needlessly confused matters at times in the past. Keep in mind that an osteoporosis is a disturbance in volume of bone, while an osteomalacia is a disturbance in quality: both may coexist just as readily as they may exist independently.

LAMELLAR BONE: A mature, slowly elaborated, structurally superior bone elaborated by osteoblasts.

A) Under crossed polars lamellar bone exhibits order, there being an alterating series of isotropic (dark) and anisotropic (bright) bands. These bands are the lamellae which gave this type of bone its name (Figure 18, 23). The plane of lamellae is in some manner polarized by the physical loads on the part, the orientation in three-dimensional space being such that maximum resistance to load is offered by the bone. Lamellar bone has a tensile strength of about 11,000 lb./in.^{2}, a compression strength of about 14,000 psi and a shear strength of about 8,000 psi. It contains about 20,000 lacunae and 1,000,000 canaliculae/mm^3. The lacunar specific volume is about 1.5 per cent and the canalicular 5.5 percent. Lacunar specific surface is about 24 mm^2/mm^3 while canalicular specific surface is about 225 mm^2/mm^3. [36,45]

B) Collagen bundles in lamellar matrix are regularly oriented in the lamellae and the crystallites are in turn oriented with respect to the collagen, the (C) axis parallel to the collagen long axis. The structural basis for the isotropy of the isotropic part of a lamella has not been explained.

C) Lacunae in lamellar bone are polarized by the lamellar planes, being flattened between them and having long axes parallel to the lamellar elongation of the region. Canaliculae in lamellar bone always perforate lamellae perpendicularly and always run

towards the original source of blood supply. See figure 17. As with fibrous bone and calcified cartilage, once formed there is no significant physical distortion throughout life. Grossly and microscopically observed changes in morphology occur by the device of removing some material and replacing it with new material.

D) Lamellar bone formation is stimulated by T_4 and STH and is strongly inhibited by the adrenal corticoids. Estrogen does not significantly accelerate or induce lamellar bone formation.

E) Mineralization of lamellar bone proceeds at an exponentially decaying rate. As a result, old moieties of bone are more highly mineralized than young ones. Accompanying an increase in mineral density is an increase in diffusion impedence which is maximal in the most highly mineralized bone observed: that of micropetrosis[37] (Figure 17).

A given skeleton may be said to possess an average age which is the mean of the sum of its myriad moieties formed at different times. Accompanying average skeletal age there is an average diffusion impedence.

LOAD: A force applied to a structural member. The force might be an obvious physical mass, or it might result from bending, compression, tension or torsion applied by various means, muscle pull being an example. The resistance to an externally applied load developed within the matter of a structural member is termed stress. Obviously the meaning of these terms is restricted here to the engineering application.[30]

MATRIX: See **BONE.**

ORGANIZERS: Cells are governed by factors producing numbers of generically different effects. Organizers may govern functions of cells that are mature and relatively stable. Such regulation is one of the functions of the endocrine system in the adult. Organizers also affect the division and proliferation of cells under non-steady state conditions. Such regulation is a less appreciated function of the endocrine system.

A) Steady state organizing factors may accelerate or retard certain cell functions.

B) Non-steady state organizing factors may initiate cell division (as after trauma), may end cell division, may cause or induce differentiation of cells actively or recently divided along certain lines (parathormone induces the appearance of osteoclasts; lowering 0_2 tension induces differentiation of osteoblasts).

In addition to these two types of organizing factors there is another group of factors which is extremely important but to which little attention has ben devoted. These are space polarizing factors.

C) Space polarizing or orienting factors are responsible for orientation of biological activity in 3 dimensional space. Such factors govern the enchondral ossification apparatus. They govern growth and internal remodelling of bone and are responsible for the fact that many membranes transport various molecules preferentially in one direction.

OSTEOBLAST: The cell responsible for synthesis of bone matrix. It appears by differentiation from dividing mesenchymal cells. Functionally there are at least two types of osteoblast: those that form lamellar and those that form fibrous bone. The two types respond differently to local and systemic factors and they exhibit different reactions to various induction factors. The same mass of osteoblasts always forms one or the other type of bone but never both. The occasional osteoblast trapped in the matrix being formed becomes an osteocyte. This entrapment is not a haphazard process, a conclusion indicated by the relatively constant number of lacunae per unit volume in lamellar bone.[36] The physical chemistry responsible for this entrapment is unknown.

OSTEOBLASTIC ACTIVITY: Bone formation.

OSTEOCLAST: A cell that resorbs bone. The definition is functional, not morphological. Osteoclasts may have one or 100 nuclei. They appear by differentiation from dividing mesenchymal cells. There is no presently known difference between osteoclasts resorbing lamellar or fibrous bone or calcified cartilage. The obligatory mineralization of these tissues for resorption to occur has been mentioned. There are steady-state organizing factors governing osteoclastic activity; there are also space polarizing factors whose nature is unknown.

Osteoclasts contain increased amounts of glutamic oxalacetic transaminase, and form appreciable amounts of an acid phosphatase.

A controversy has raged over several generations over whether resorption is accomplished by osteoclasts. Microcinephotography has conclusively shown that they do and controversy now revolves around the lesser question of whether or not nonosteoclastic resorption may occur. In other words, can bone be "dissolved" in vivo without the

presence of osteoclasts? The weight of evidence indicates osteoclastic activity is the only manner in which bone is resorbed in vivo.

OSTEOCLASTIC ACTIVITY: Bone resorption.

OSTEOID: As a single term, not used in this text because of its many meanings.

OSTEOID SEAM: Lamellar bone formation proceeds in a definite sequence of events, as follows:[43,47,48]

A) Elaboration of a speck of new matrix by osteoblasts (Figure 22).

B) A period of quiescence from the standpoint of light microscopy, during which more new osteoid material is added each day by osteoblasts. So, the original speck becomes buried under an increasingly thick layer of newer matrix.

C) About 7 days after formation, beginning of mineralization is seen with light microscopes.[43] A preceding nucleation or "seeding" of the matrix appears to occur at molecular levels but is invisible with light microscopes.

Mineraliazation of lamellar bone begins in a plane parallel to the lamellae of which the matrix is constructed. This has been termed the zone of demarcation by LaCroix,[66] Ponlot,[84] Vincent,[114] and others, an excellent term.

D) In the next 4-5 days about 70 per cent of all the mineral ever deposited appears.[3] Progressive mineralization occurs at an exponentially decaying rate so that there is some minute increment in mineralization even after decades of in vivo existence.

New bone matrix is termed **osteoid seam** during the time between formation and initiation of microscopically visible mineralization. After mineralization convention is to term the bone matrix simply the matrix, justification being that there has been subtle chemical and steric change in the matrix which permitted or induced mineralization, so mineralized matrix is different from osteoid seam.

Confusion is caused by the fact that many pathologists feel osteoid seams are not normally found in healthy skeletons (they always are),[47,48] or that osteoid seams are found only in osteomalacic states (this is false),[48] or that the osteoid seams found in osteomalacic states are idfferent from those found in the normal skeleton (no difference detectable with the light microscope; none known at the molecular level).[36]

OSTEOMALACIA: A disease, meaning an entire patient is included in the definition with factors in history, physical examination, laboratory examination, x-ray examination and histological examination that lead to the diagnosis of osteomalacia. No precise definition of osteomalacia is agreed upon. Here the working definition will be the presence of typical chemical abnormalities commonly associated with osteomalacia, associated with the presence of osteomalacic bone in the skeleton.

OSTEOMALACIC BONE: An abnormal qualitative state of bone. Not a disease any more than an hematocrit of 26 per cent is a disease; it is a sign, and thus one of the features present in a patient with a disease.

Osteomalacic bone is defined as bone containing more osteoid seams than are present in similar normal bones or skeletons. The writer and Villanueva measured normal numbers and normal widths of seams in a series of humans.[36,48]

OSTEOPOROSIS: Like osteomalacia, a disease, one of whose signs is a decrease in absolute skeletal volume of the patient. A decreased absolute skeletal volume by definition establishes the presence of **an** osteoporosis.

The quality of bone in the osteoporoses varies markedly. The qualities that are found are characteristic of the nature of the disturbed physiology causing them, and not characteristic of the osteoporotic state itself. Thus, in thyrotoxicosis the bone is of slightly low average density, there is much new bone and considerable feathered bone,[34] there is little micropetrosis and there is little osteocyte death.[35,36]

In hypercortisonism the bone is of slightly increased average mineral density, there is very little new bone, there is little feathered bone, there are appreciable amounts of micropetrotic bone and considerable osteocyte death.[36]

These qualitative features, which are actually observed, are characteristic of thyrotoxicosis or of hypercortisonism respectively, but are not characteristic of and need not be associated with all osteoporoses (Figure 24).

OSTEOPOROTIC BONE: An abnormal quantitative state of bone characterized by low absolute bone volume compared to similar normal bone.

It is essential that this be realized: quality of the bone has nothing to do with whether it is osteoporotic. Failure to recognize this in the past, coupled with analytical methods that were inherently inadequate, has created much confusion over this point.[41] Many texts (whose excellence are **not** denied) contain erroneous statements concerning this point.

POLARS: The Nicol prisms or the Polaroid polarizer and analyser of the polarizing microscope. Crossed polars merely means that the directions of vibration of the polarizer and analyser are at 90° to each other so the field is dark. A birefringent material placed in focus between crossed polars rotates the light transmitted through it so that in certain positions light is also transmitted through the analyser.[37]

PUSH-PULL: In this text the meaning is the presence of multiphasic energization of transport of biological substances through biological compartments. See Figure 9.

Example: Cortisone causes skeletal balance to drop below unity. As a result there is an excess of calcium being released to the blood due to excess of bone resorption over formation. This excess would elevate serum calcium. However, cortisone impairs renal tubular reabsorption of calcium, accentuating urinary excretion. The efficiencies of these processes are such that no significant change in blood level usually occurs. Calcium "pushed" into the blood from bone is simultaneously "pulled" from the blood by the kidney.

While the blood level does not alter, increased amounts of calcium are carried by blood from bone to kidney in unit time. This may be paraphrased by stating that transport rates are increased by push-pull mechanisms.

RATE: In this paper the absolute change in unit time in a unit reference volume of original substance. Since bone is the topic, rates here mean absolute bone volume formed or resorbed in a unit reference volume in unit time (Figure 3).

REMODELLING: Several types of remodelling are referred to in the text.

A) Growth remodelling: that part of bone formation and resorption processes peculiar to the processes of growth. This includes osteoclasia of endosteal surfaces in expanding diaphyses, bone formation on periosteal surfaces of expanding diaphyses, osteoclasia of the periosteal metaphyseal surfaces and bone formation on the endosteal metaphyseal surfaces.

B) Internal remodelling: **Histological** internal remodelling is the ceaseless resorption and formation of bone that continues throughout life in healthy skeletons. The result of these processes is continual renewal of the cortices and trabeculae without significant change in shape, size or absolute volume of the skeleton. Making a distinction between (A) and (B) is not as artificial as it may sound because there is evidence that different trigger factors and different induction factors are present in the two, in addition to factors in common.

C) Internal remodelling: In **remodelling kinetics concepts** this is the total volume of bone formed and resorbed without external evidence by means of balance changes.

The symbol V_i means kinetic internal remodelling. An example would be a 60 year old woman with T_{r50} and T_{r50} of 5 years. In a 5 year period this woman would have formed half as much new bone as she had at the start, and would have resorbed a similar amount. The V_i would be the sum of the two, or a volume equal to the total absolute skeletal volume. V_{i1} would be the internal remodelling in one year.

D) Total remodelling: In remodelling kinetics concepts this is the total amount of bone formed and resorbed per year. It is equal to the internal remodelling per year plus the net total change in volume.

V_{t1} is the symbol for total remodelling per year. V_t would be the total remodelling in an unspecified time.

RESORPTION: SEE BONE.

RIBOSOME: An ultramicroscopic cytoplasmic body containing the protein synthesizing part of the RNA and significant amounts of phospholipid. Protein synthesis appears to occur in the ribosomal fraction of the cell.

RNA: See DNA.

SEAM: An osteoid seam.

SEEDING: Also termed nucleation.[54,80] It is believed that matrix is prepared for mineralization by the formulation of specific cationic and anionic binding groups which have a stereospecific relationship to the lattice constants of the apatite crystal unit cell. The spacing of the organic binding groups is very similar or identical to the spacing in the apatite lattice. It is easier for an apatite crystal to form on such a prepared bed than it is for it to form de novo out of solution. The preparation of such a bed is termed epitaxy. Thermodynamic concepts find ready application in explanation of these events.

Once seeding of the bone matrix has occurred, subsequent mineralization seems to be able to proceed without additional specific preparation and with less difficulty.

SENESCENCE: The progressive functional deterioration of cells or structures. If the tissue termed senescent is bone, then senescence consists of structural weakness or failure, loss of elasticity, inability to exchange electrolytes and buffers with the blood, inability to heal, etc. If the tissue is kidney then senescence is inability to reabsorb phosphate, or inability to retain polorization of ion transport.

Senescence in other words does not deal with the chronological age of the tissue but only with function deterioration, a purely arbitrary usage adopted herein.

SERVOMECHANISM: A device so arranged that change in one part (input) produces a change of proportional magnitude in another part (output). Servomechanisms may be machines, hydraulic mechanisms, electronic circuits, chemical reactions, or the act of transportation. The essential thing about a servomechanism is that there is a means by which an alteration in input is reflected by a proportional change in output.

Servos may exist in one-to-one ratios, as in antenna rotators. They may exist with positive or negative response meaning that a clockwise rotation might be arranged to produce an anticlockwise or clockwise rotation of the output.

Feedback is necessary for a servo system. There must be some arrangement to enable the output to sense the position of the input and adjust to it. There is a limit to the sensitivity possible with such an arrangement.

The existence of feedback between input and output creates the possibility for oscillation or instability. Deliberately induced and controlled instability is a necessary and useful phenomenon in electronics. Such an instability is responsible for the menstrual cycle of women and the hibernation of certain animals.

Positive feedback promotes oscillation while negative feedback inhibits it.

The system of endocrine relationships is a large mass of feedback mechanisms. Many isolated hormone effects may be interpreted in terms of servo analysis. This is very useful because servo analysis is a suitable problem for analog computer technique.

SKELETAL BALANCE: The symbol is B_{sk}. The term defines the rate at which the absolute skeletal volume is changing. To permit use of the term in computation, additional qualifications have been introduced into the meaning. Skeletal balance is defined as the proportion of the original absolute skeletal volume present one year later, given constant T_{r50} and T_{s50} obtained by measurement or inference (Figure 8).

B_{sk} is expressed as a decimal fraction, or as a percentage. B_{sk} of 1.05 for example means that after a year of the formation and resorption rates assumed, the absolute skeletal volume will be 1.05, or 105 per cent, of what it originally was. Naturally this also applies to skeletal mass unless there is a disease producing abnormal quality of bone in the interim.

SPECIFIC VOLUME: The proportion of the grossly evident volume of a material that is porous rather than solid material. For example, glass is a complete solid without any specific surface. A blotter, or a container full of dry sand, contains holes in which there is no material other than air, in addition to the solid contents.

Bone is a porous material containing lacunae, canaliculae, vascular channels and marrow spaces. Figures for bone specific volume are given under fibrous and lamellar bone (Figure 15).

SPECIFIC SURFACE: Just as bone contains a certain proportion of its volume made of holes or porosities, so walls of these porosities have a certain area in a unit volume of bone. The total area of the walls of the pore spaces in a unit volume of material is the specific surface. This is stated in terms of area per volume, an example being the 205 mm^2/mm^3 which is the canalicular specific surface in human lamellar bone (Figure 15).

STH: Somatotrophic hormone of the adenohypophysis.

TETRACYCLINE LABELLING: See Figure 20. Any of the currently available tetracycline antibiotics become permanently deposited in newly forming and mineralizing bone, hyaline cartilage and teeth. This tetracycline may be seen by microfluorescence methods in suitably prepared undecalcified sections immediately or many years after deposition. When the time and duration of administration are known, accurate measurements of bone formation rates can be made by methods published by the writer. Study of tetracycline labelled human bone has greatly advanced knowledge of bone physiology.[44,50,51,52,53,78]

TIME CONSTANT: In a servomechanism the ratio between the quickness with which output responds to signal from input, and the quickness with which input variation is transmitted

to output, determine how quickly the system adjusts to change. If output can adjust only slowly, rapid fluctuations in the input will not be adapted to. The system "ignores" them. Proportional values of time constants are important in governing instability or oscillation.

TRABECULUM: SEE CANCELLOUS BONE.

TRANSDUCER: A device that converts alteration in one physical modality or form of energy to another. A loudspeaker converts electrical energy to sound. An ear converts sound to electrical energy. Bone in some manner converts physical loads imposed upon it into polarizing factors governing the activity rates of osteoblasts and osteoclasts in space. This is the sought-for- space orienting transducer.

TURNOVER: While this word means much the same as remodelling, it has been withheld because it has come to mean molecular remodelling. Turnover occurs, in the sense that thyroglobin and iodinated thyronines are constantly being synthesized and hydrolysed in the colloid of the thyroid gland. Amino acids are constantly being synthesized into protein and then degraded into unit amino acids again. Turnover in bone mineral occurs in the sense that a given calcium atom enters the bone now, and returns to the blood later.

In this text then remodelling is the histologically evident tissue turnover, while turnover itself is molecular remodelling and is not microscopically visible.

TSH: Thyroid stimulating hormone of the adenohypophysis.

T_{f50}: Bone formation half-time, or times in years to form half as much bone again as started with.

T_{r50}: Bone resorption half-time.

T_3: TRIIODOTHYRONINE.

T_4: Tetraiodothyronine.

VOLKMANN'S CANAL: A small canal transverse to the diaphyseal long axis and transverse to the long axis of Haversian systems which carries transverse blood vessels in the bone. One of the types of vascular spaces normally found in bone.

V_i: Internal remodelling, kinetic sense. Not evident by positive or negative calcium or nitrogen balance.

V_t: Total remodeling. In both instances remodelling is preferably expressed in volume rather than mass.

V_{t1}: The total amount of bone formed anew, and the total amount of bone resorbed, in one year, expressed as a volume.

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