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An Analysis Of The Relative Complexity Of Cell System Dynamics In Bone

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AN ANALYSIS OF THE RELATIVE COMPLEXITY OF CELL SYSTEM DYNAMICS IN BONE*

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I: Introduction

1) *Purpose: To identify the easiest cell system to understand in bone, so that it can serve as a Rosetta stone in understanding its more complex systems.*

Granting that the production and maintenance of bone is done by a group of cell systems, then there is no accepted basis for concentrating study on any one system in order to understand the cell population physiology that is involved in the health and diseases of this tissue. This has led to much disagreement over the formation, function and fate of bone cells in health and disease. This includes our concepts of metabolic bone disease, which for the most part are not concepts: they are simply statements of the fact (that disease exists), and are often based on such unclear ideas of cause and effect that there is no logical connection between anything the pathologist describes in diseased bone, and current ideas about the nature and cause of the disease. While this may seem harsh, with a few exceptions it is true. To improve this state, it would be helpful if *simplest-case,* and/or *steady-state* forms of cell behavior were known and understood, for this knowledge and understanding would then serve as a wedge or foothold in advancing our understanding of nonsteady state and more complex behavior. But such knowledge is not, and to get it these systems must first be *identified.* As cyberneticists† (See Ashby,[3] Pask[15]) point out, such systems offer the best chance to make a quick and successful analysis of the behavior of a system. It is easier to understand steady state than nonsteady state behavior, and it is clear that simple behavior can be more easily understood than complicated behavior. With these things in mind, this article presents an analysis of *some* of the cell behavior that occurs in bone, and which is actively under study the world over. While some cells are not considered here, it is because this omission

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†One definition of what cybernetics is: it is the art and/or science of understanding what controls the changes in behavior (or what prevents changes in behavior) in dynamic systems.

does not alter the nature or outcome of the argument. The analysis uses simple cybernetic and information theory concepts[13,15,17,21] *which allow us to determine the relative complexities of a group of cell systems,* even though we are ignorant about most of the details of their composition, structure and internal behavior.

2) *The Context of the Analysis:* Like many other publications out of my laboratory, this article will pose a communication problem to some readers. The reason is simple and basic, and it is engendered by the fact that the behavior of dynamic systems can be represented by abstractions (such as differential equations) which have their own structure, laws, internal relationships and dynamic behavior. When the correspondence between the physical behavior of a real system and some abstract *model* of it is very good, the model is very good. When the correspondence is based on a true measure of understanding of the system, the model will *predict* its behavior, and can be used to devise new ways of changing it. Thus, making models can be a constructive activity.

The first step in making a model of a system is to identify its important functional parts, *and then assign a symbol to the function of each part. In the mind of the model builder the real part and the symbol for its function tend to become synonymous,* leading sometimes to phraseology that confuses, rather than transmits intelligence. In this paper some ordinary words are used in very special ways, so that in order to get the meaning of the analysis over better, some definitions are needed before we proceed further. The words are: cell dynamics, state, change, variety, and minimum variety. *Cell dynamics* means the changes that occur over time in cells, in cell populations and in cell systems. In this analysis, we shall focus more on *what* cells do, and on *changes* in what cells do, than on how or why they do this. In bone, as noted in Putschar's excellent summary,[15] and also in part by Johnson[14] and me[6-8] (see Table I), these cells include chondroclasts, fibrous osteoblasts, lamellar osteoblasts and osteoclasts as well as the parent mesenchymal (i.e., progenitor or stem) cells that make or generate them. We shall be concerned here with *state, change in state, and choices between alternative states,* as these concepts have been used by Ashby,[3]* by Pask[15] and by Wiener.[21] For example, in this text when the cells called osteoblasts make bone, this represents the *state* of making bone (other states in this sense are destroying bone, not making bone or making new cells). We are unconcerned here with *how* or *why* bone is made. If osteoblasts disappear, it interests us as a *change in state* (or a change in the kind of function) because it tells us that a *choice* was made in the control apparatus between two alternative states (i.e., making, or not making bone). We shall not discuss the molecular basis or the mechanism for this change here, we merely recognize that it occurs. This restriction of scope is essential because: (*i*) we do not know enough about cells to explain their changes in biochemical terms in the broad sense, and (*ii*) our immediate aim is to achieve, not an understanding of specific changes, but an identification of the ones we should tackle first. That this *is* a problem is shown by this sampling of facts: Tonna[19]

*Ashby's book is recommended to the reader who knows arithmetic and simple algebra, and wants to understand what cybernetics is. The book is unusually lucid, clear and well organized, and it is recommended most strongly to anyone engaged in any phase of research in medicine or physiology.

concluded that osteoblasts are made before, and may change into, osteoclasts; Young[22] found that both of these cells seem to be made simultaneously by progenitor cells; Jee and Arnold[11,12] observed that osteoclasts were made before osteoblasts, while Jee and Nolan[13] found that intra-arterially injected carbon particles eventually appeared in the cytoplasm of osteoclasts but even after 200 days they did not appear in osteoblasts. These facts can imply variously that (*i*) osteoblasts change to osteoclasts

Table I

		Lamellar	Fibrous	Sources
Effect of Endocrine Agents	Hypercorticoid state	Inhibits profoundly	Little or no effect	Follis, R. H., Proc. Soc. for Exptl. Biol. and Med., 76:722, 1951.
	Estrogen therapy	Inhibits profoundly	Little or no effect	
	Thyrotoxic state	Accelerates profoundly	Little effect	Day, H. G., Follis, R. H., Endocrinol., 28:83, 1941. (6) (9)
	Hyperparathyroid state	Accelerates profoundly	Little effect	
Occurs as:	Initial reaction to trauma	0	+	(9) (20)
	Initial reaction to infection	0	+	
	Initial reaction to non-osteogenic neoplasm	0	+	
Structure, Microscopic	Tissue culture can produce this kind	0	+	
	Lamellae present	+	0	(8) (9) (6) Ascenzi, A. in L'Ostéoporose, Masson Paris, p. 42, '64.
	Regular geometric organization of collagen	+	0	
	Regular orientation of hydroxyapatite crystals	+	0	
	Structure oriented parallel to physical forces on the bone	+	0	(20) (8) Wolff's law
	Can be laid down directly on calcified cartilage	0	+	(9) (20)
	Fate in body	Stable for decades	Always replaced by other kinds of tissue	(9)
	Physical durability	Strong, fatigue-resistant	Weak, fatigue-prone	(9)

Elsewhere (Henry Ford Hosp. Med. Bull., 8:199, 1960) I have proposed that the production of lamellar bone is a different kind of cellular behavior than is the production of fibrous bone. This idea is being increasingly accepted but is still not understood by some. This table lists some differences in lamellar and fibrous bone physiology, which are factual (i.e., observed directly, not inferred) and representative. I am classifying all kinds of bone which show alternating, parallel isotropic and anisotropic planes under the polarizing microscope as *lamellar*. This includes secondary osteons, circumferential lamellae and endosteal lamellae. I am classifying all other kinds of bone as fibrous bone. This includes the bone found on calcified cartilage, in fracture callus, in acute bone infection and in osteosarcoma. Fetal bone, as is found for example in ribs of new born infants, is not considered or included in this analysis. Not only is the *structure* of these two kinds of bone different; the *behavior* of the cells that make each kind is different. I conclude that *functionally* they are different kinds of cells. While this may beg the question (i.e., why?), it does not invalidate my logic.

(*ii*) or vice versa (*iii*) that they are separately made and unrelated to each other. What will reconcile these conflicting implications, based on the findings of respected investigators? And how can one develop a consistent theory of the role of cell behavior in metabolic bone disease when the factual basis for any theory seems to be so confused? Q.E.D.: a problem *does* exist.

The term *variety* will be used below. It has a specific meaning in both cybernetics[3,15,21] and information theory, as outlined by Shannon and Weaver.[17] We will use a paraphrased definition: The variety in a system is the number of *choices* between alternative actions that are used to control its behavior. One choice is one unit of variety (technically, one "bit"). For example, either bone is being resorbed by osteoclasts in a given place, or it is not. This may be thought of as reflecting the exercise of a choice between two alternative or possible states (i.e., resorbing, or not resorbing bone). We shall seek the *minimum variety* which various cell systems in bone can have. While one cannot tell how large a variety a real system actually has, one can usually describe some lower limit with respect to some form of behavior, *less than which it cannot have;* this is its minimum variety. Thus a control scheme with a variety of three (i.e., it provides three binary choices which can control a maximum of eight unique states), cannot represent the control machinery of a system whose changes in behavior reflect a minimum of four units of variety (which can control 16 different, unique states). Paraphrased, the control mechanism cannot have less variety than the behavior it controls.

To sum up, the analysis will concern changes in behavior, with whose aid the simplest and steady state* mode(s) of cell behavior in bone will be identified. The details of histogenesis of individual cells, the mechanisms by which transitions in function occur and the nature of the relationships between the transitions, will not be discussed; they are not the subject. The subject is to identify which of the several cell systems involved is the easiest to understand. This would then be studied, and once "cracked" the general problem of all the cell behavior in bone should prove much easier to understand because the "cracked" case would provide valuable clues about the general nature of the general case. While the cybernetic approach does not guarantee a valid analysis, it is far more likely to be valid than is pursuing an essentially random approach, which has been done in the past. To prepare for the analysis, a factual resumé of the major, dynamic cell processes that occur in bone growth, modeling, and remodeling, follows next. These processes or functions are to

*By steady state is meant a mode of behavior which tends to continue in a stereotyped way, changing in a minimum amount in the presence of minimum or zero guidance from outside of the system. Keep in mind that the system is bone, so the body's soft tissues are, in this analysis, outside of the system. Keep in mind that the steady state refers to a group of *changes,* and not to chemical or thermodynamic equilibrium.

be thought of as states* in the bone system, while their variations are changes in state *which reflect the presence of variety in their control apparatus,* whatever this apparatus may be.

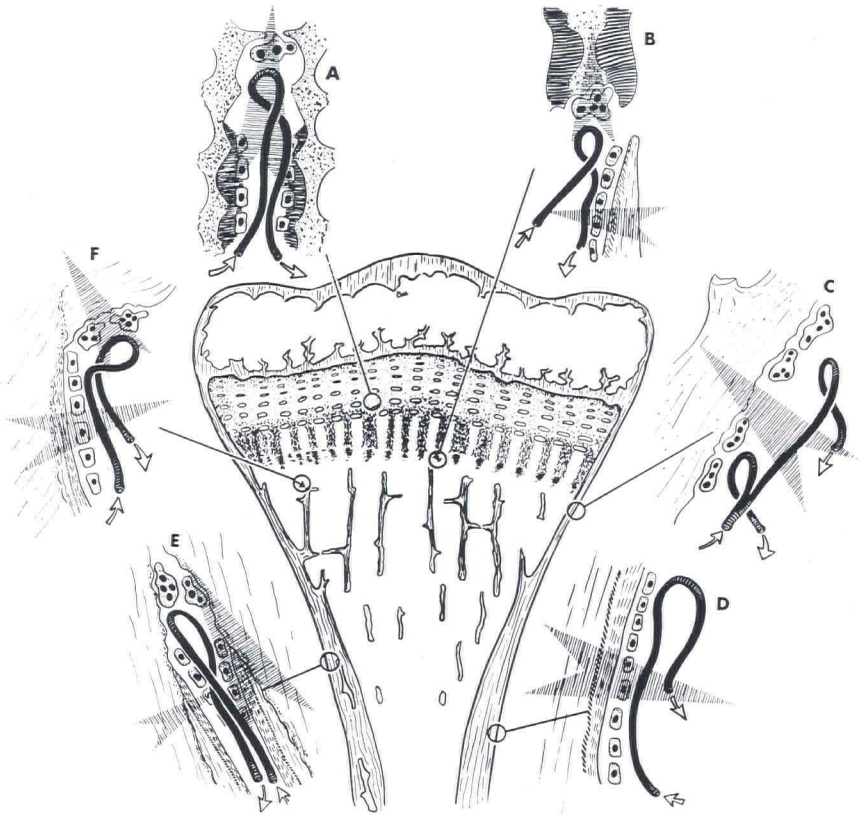

Figure 1

In the center of the figure is a longitudinal section through the tibia of a growing animal. The epiphysis is at the top. The separate diagrams surrounding this part of the figure are the various, separate cell systems or BMU referred to in the text. (A) shows the columns of cartilage cells (top), the calcified cartilage (middle) and invasion of the calcified cartilage by chondroclasts, with subsequent deposition of new fibrous bone on the walls of the unresorbed bars of calcified cartilage. The bars plus the bone deposited on them are the chondroosseous complex. (B) shows the removal of the chondroosseous complex, and its replacement by trabeculae of lamellar bone. (C) shows the osteoclastic drift which usually occurs at the metaphyseal flare during growth. (D) shows the osteoblastic drift which enlarges the outside diameter of the shaft during growth. (E) shows the tunneling of the compact bone which is the first step in depositing a new osteon inside the cortex. (F) shows the remodeling of a trabecular surface, an activity (turnover) which also occurs at the endosteal and periosteal surfaces of the cortex.

*One kind of cell behavior, such as making bone, is considered as a kind or state of function, and thus simply as one state. It should be pointed out that each state is a functional entity and as such is an absolutely real thing. But as we focus on smaller and smaller structures in bone, we become less and less certain of the correspondence between function and structure. The work of the future will be partly to define this correspondence. For the present purpose the analysis is confined to function, and its changes. Thereby we adhere to reality as best we can at this time. Incidentally, one of the reasons for the power of the cybernetic approach is its habit of mentally transforming a *process,* such as cell metabolism, into a *state* which can be given symbolic representation and manipulated by the formal rules of various logical systems.

II: *The Cell Systems and Behavior of Bone Growth and Remodeling*

The cell systems that will be described are built around three basic kinds of cell behavior, and thus around a minimum of three states. These are: (*i*) the generation of new cells (*ii*) the cell-engendered resorption of calcified tissue (*iii*) the cell-engendered formation of new calcified tissue. These three states are found combined in six distinct cell systems, which provide two age-related classes of behavior: (*i*) behavior present primarily during growth, and (*ii*) behavior present throughout life. A cell system here means a *group* of different kinds of cells and cell functions which (a) functions as a unit independent of neighboring cells and cell systems (b) which is consistently found in nature, and (c) which as a group has some properties that are lacking in its individual cells, and lacks others that are present in its individual cells.*

Figure 1 shows the cell systems that seem to me to be essential to making and maintaining bone. There are six, which might be called cell "microsystems". The first four of them (1,A-D) are active primarily during growth, while the last two (1E,F) are active throughout life. Their real order of development in time is the order in which they are described. Most of them are well known, and are more than adequately described by Weinman and Sicher,[20] Putschar,[16] Enlow[4] and Johnson.[14]

At the ends of most bones in children there is an epiphyseal plate made of hyaline cartilage (see figure 2). In it, a special layer of cells makes new cartilage cells, some of which are left behind by the growth, to eventually become surrounded by calcified cartilage and die. This initial production of calcified extracellular matrix may be thought of as the priming of a pump, whose subsequent history is a series of paired "packages" of resorption-followed-by-formation of calcified tissue. Were there nothing present to be resorbed initially, the first (resorptive) member of the first "package" could not occur, and the whole sequence would "die aborning". While the cartilage layer in which new cells are made is not relevant to our subject, the calcified cartilage it indirectly makes is, in this way:

(A) *Production of Chondroosseous Complex*:† A proliferating capillary advances towards the calcified cartilage from the midshaft side of the bone. New, usually multinucleate cells called chondroclasts) appear ahead of this vessel and partially resorb the calcified cartilage (see (A) figure 1). Then other new, mononucleate cells (fibrous osteoblasts[9]) appear alongside the vessel, where resorption has already occurred, and lay down new fibrous (i.e., woven, reactive) bone on the surface of the unresorbed cartilage (see Table I). Both kinds of cells are nourished by the same capillary, and these cells and vessels act as a functionally independent

*Some of these systems have been given distinct names by anatomists and histologists, others have not as yet.

†Also known as primary spongiosa.

unit or cellular microsystem, which I will call a *Basic Metabolizing Unit*** of cell activity, and abbreviate thus in the future: BMU.[9,18] It has some special properties that none of its individual cells have. The function or state of this particular BMU is that of replacing cartilage with calcified trabeculated structural material (the chondro-osseous complex).

(B) *Replacement of Chondroosseous Complex.* This complex of calcified cartilage bars covered by fibrous bone is the *chondroosseous complex* (or primary spongiosa).[20] It is left progressively farther behind in the metaphysis (see figure 2) as the epiphyseal plate grows away from it. The complex is then approached by a second, separate system of capillaries which arises from the midshaft side of the medullary cavity of the bone, and which is preceded by multinucleate cells called osteoclasts which resorb the chondroosseous complex*. Following this, osteoblasts appear that make lamellar trabecular bone in the medullary cavity,[9] and are also nourished by this system of vessels (see (B) figure 1). Lamellar bone differs in several ways from the fibrous bone laid down on the surfaces of the partly resorbed calcified cartilage that was described in (A) above.[6,9] This second kind of cellular microsystem or BMU also acts like an independent system, whose function or state is that of replacing primary spongiosa with lamellar trabeculae.[9] These two integrated processes (i.e., A and B), and the separate systems of cells involved in them, add new length to, and new trabeculae in, the metaphysis of a bone during growth. For practical purposes they stop at the time of maturity ($\pm$20 years).†† Both (A) and (B) occur in special regions of bones; they are neither widely nor randomly located in space. There are regions where (A) and (B) *cannot* occur.

During growth two other special kinds of changes occur on many external and internal surfaces of bone, and each involves a special cell system. Their functions seem to be to cause systematic motions of bone surfaces through space during growth. They are:

(C) *Osteoclastic Drift.* An example of this occurs under the flare of the metaphysis on the periosteal surface, and is well described by Enlow.[4] Here there is continual resorption of bone (see figure 1C), during the 15 - 20 years needed to make the adult bone, which makes this surface move in three dimensional space. This is called *drift.* During growth, surfaces undergoing this state are continually being removed by osteoclasts, so this will be called *osteoclastic drift.* When growth stops, so does osteoclastic drift for practical purposes. The function or state of osteoclastic drift is provided by a system of nourishing capillaries and osteoclasts, which function as an independent unit or BMU.[9]

**The reasons for this (another!) new term will appear in greater detail and with more force in other publications that are being prepared. Although most assuredly known to others, these ideas or facts have not been specifically stated before in any published work known to me. The reader may feel free to check on these, or to disagree with my interpretations, which are deliberately provocative, which I certainly *believe* are right, but which are far from sacrosanct.

*A genetic defect in this cellular microsystem or BMU causes the disease known variously as marble bones, osteopetrosis, or Albers-Schoenberg disease.

††Some low order activity continues throughout life, as has been described by L. C. Johnson in several articles.

(D) *Osteoblastic Drift.* One example of this occurs at the midshaft of a typical, growing long bone, where an increase in outside diameter is had by adding layers of new lamellar bone on to the outer surface (see (D) figure 1). This addition is done by lamellar osteoblasts*, and the new bone is called circumferential (or endosteal,

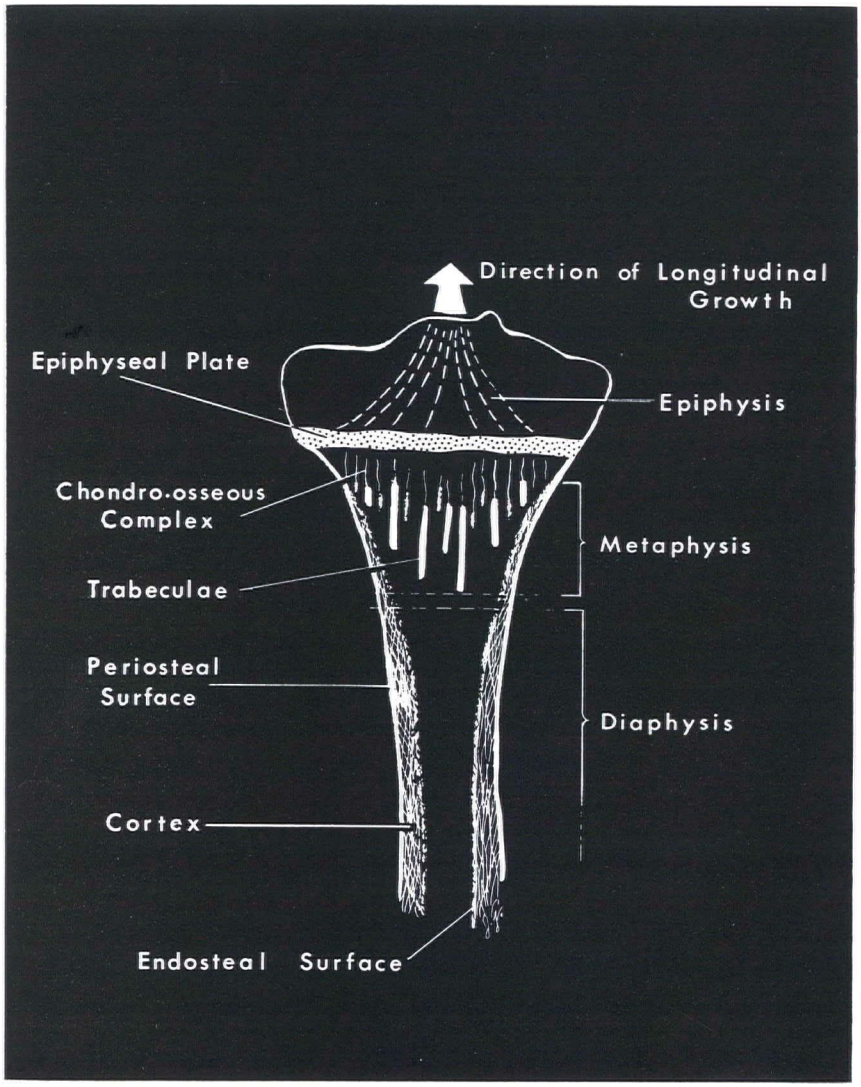

Figure 2

This diagram shows the location of the various parts of a bone which are referred to in the text, so that there need be no confusion about meaning, even if there is some disagreement over the selection of terminology. It is a sketch of a longitudinal section cut through the tibia of a growing animal.

*Functionally speaking, there are two kinds of bone-forming osteoblasts whose physiology differs in many important respects. See Table I.

when it occurs on the walls of the marrow cavity) lamellae. This function or state is called *osteoblastic drift* here, and it also stops at skeletal maturity for practical purposes. Here too a system of nourishing vessels is present, and vessels and cells are a BMU.[9] Both kinds of drifts are distributed in special ways on bone surfaces, and they are not randomly placed. There are regions where each kind of drift *cannot* occur. Next we will describe two processes which continue throughout life.

(E) *Osteonal Remodeling.* This occurs primarily inside of compact bone. First, osteoclasts appear and "drill" a cylindrical hole through the cortex which is called a resorption space. See (E), figure 1. A proliferating capillary follows behind the osteoclasts, and then lamellar osteoblasts appear on the walls of the resorption space, make new bone, and thereby partly fill the hole back up. In this way a new, *secondary osteon* or Haversian system is made.[4] Replacement of cortical bone with new osteons occurs throughout life. It neither stops, nor changes its basic pattern, at skeletal maturity. The vessels and cells that provide the function or state of osteon formation act as a functionally independent system and are another BMU.[9] Osteonal remodeling occurs in all cortices thick enough to contain them, so that they are randomly distributed in bone. This is true in spite of the fact that the *amounts* of osteonal remodeling do vary in a systematic way in bone. In other words, there is no part of compact bone where osteons *cannot* occur.

(F) *Surface Remodeling.* The trabeculae of lamellar bone left behind by step (B) of the enchondral ossification process are also remodeled throughout life,[20] as are all periosteal and cortical-endosteal bone surfaces.* Here, too, the functional package of cell activity is resorption first and formation second, as shown by Takahashi et al.[18]. The function or state of surface remodeling continues after maturity, and is provided by a system of vessels and cells that are functionally independent and so have the properties of a BMU.[9] All bone surfaces are subject to remodeling so that, like osteonal remodeling, its distribution is general. While amounts differ from region to region, there is no lamellar bone surface that *cannot* be remodeled.

III: The Analysis

We have just described six behaviorally distinguishable, cell-vessel microsystems, or BMU. By combining them in the right places, directions, sequences and amounts, the morphology of the normal skeleton can be completely explained. For example, the size and transverse geometry of the periosteal and endosteal envelopes (i.e., spaces, volumes) are fixed by the patterns and relative rates of osteoblastic and osteoclastic drifts. These drifts also determine whether a bone will be straight(ulna), monotonically curved (femur) or S shaped (clavicle). The balance between endosteal and periosteal processes fixes the thickness of the cortex. The direction of osteonal remodeling is one factor in determining the grain of bone, while the enchondral ossification apparatus fixes bone length, its width at its ends, its orientation in space and the amount of trabecular bone with which we enter adult life.

*Remodeling is used in the sense of turnover, which is simply a combination of both resorption and formation. It does not mean modeling or reshaping of bone.

We will now identify: (1) the steady state and (2) the minimum variety cases in these six.

1) The Steady State

Only two microsystems are normally active throughout life: osteonal and surface remodeling. The others exist only (or almost exclusively) during growth, or in abnormal situations (see column (3), Table II). So by definition, in the cybernetic sense and with respect to both age and growth, osteonal and surface remodeling are the only steady state cases*, and should be easier to understand first than the other four cases or kinds of BMU.

2) The Simplest Case

Only two of the six BMU continue throughout life. The other four are in effect "turned off" at maturity (some basal activity persists, but as a fraction of a per cent of the activity that occurs during growth), a change that means variety is present (column 5 of Table II). The variety needed to make the new cells, and to direct an activity through space, is the same for all cases and so is not listed in the table. But variety must exist in BMU (A) through (D) to explain their systematic locations in space, and the fact that in some places they cannot occur. This is shown

Table II

BMU	Present in: Child	Adult	Steady State	Age Change, Variety	Location in space limited, variety	Choice of kinds of cell behavior	Sum of variety, binary choices
1) Making Chondroosseous Complex	+	0	0	1	1	2	4
2) Replacement of Chondroosseous Complex	+	0	0	1	1	2	4
3) Osteoclastic Surface Drift	+	0	0	1	1	1	3
4) Osteoblastic Surface Drift	+	0	0	1	1	1	3
5) Osteonal Remodeling	+	+	+	0	0	2	2
6) Trabecular Remodeling	+	+	+	0	0	2	2

*Note that most metabolic bone diseases in adults involve *only* osteonal and surface remodeling. Therefore we can learn to understand and treat this group of diseases only by studying these two activities, and we specifically cannot accomplish this through study of the first four activities that were discussed: making the chondroosseous complex, replacing it with lamellar trabeculae, or both kinds of drift. No end of confusion has arisen in the past because this was not appreciated. It was such a misunderstanding that led to the unsuccessful efforts to treat osteoporosis with estrogens and androgens, and osteogenesis imperfecta with androgens. And lest you think I consider myself above such things, I confess to having made similar mistakes.

in column 6 of Table II. The kinds of cell behavior (i.e., destructive or formative) are two in all BMU except the drifts, in which it is one each. This variety is shown in column 7. In column 8 the varieties are added by rows, which shows that the enchondral ossification states have minimum varieties of four, the drifts three, while the other two have a minimum variety of two, *and so are the simplest cases to analyse.** In fact, they are half as hard to analyse as the drifts, and one quarter as hard as the enchondral ossification processes.

Thus, osteonal and surface remodeling of lamellar bone are the least complex forms of remodeling, modeling and growth activity in bone, and should therefore be the easiest to understand*.

IV: Discussion

1) *The Mesenchymal Cells: A Common or Diverse Group?*

If one kind of mesenchymal** cell makes all of the cells involved in the six different kinds of BMU, the two systems that were selected are the best to study. But if six kinds of mesenchymal cells were to make the cells of the six kinds of BMU, then each BMU would have to be analysed by itself, because what was learned of one BMU (for example osteon formation) would not help to understand any of the other BMU. My present opinion is that BMU (C-F) inclusive are the products of one mesenchymal cell system, while BMU (A) and BMU (B) are each from different ones; but, this opinion needs study and confirmation.

2) *One Source of Lack of Agreement*

Using this analysis, we can now understand better the apparent disagreement which was recorded earlier. Tonna[19] studied negative drifts (i.e., situation C of figure 1). Young[22] studied BMU (A) and (B) simultaneously, possibly unaware that he was observing the products of two different sets of mesenchymal cells (and besides, his attention was focused on another problem). Jee,[10] Jee and Arnold,[11,12] Jee and Nolan,[13] and Jee and Arnold in a series of publications in the Anatomical Record over the past 10 years, have studied osteonal remodeling (i.e., BMU (E)), and recognized what seems at present to be the true sequence of cell dynamic events.[7,8] Thus, these authors studied different cell systems, a fact whose meaning was concealed by words: because we call five different kinds of bone formation by the same term, "osteoblastic activity", we tend to assume they *are* the same thing, when in fact, and speaking functionally, it can easily and definitively be shown that they are not.

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*It should be observed that at present, osteon physiology provides the *only* case in which the behavior of a synchronous group of human cells can be studied with complete assurance that the observing act and technique will not affect the cells. This study reveals some basic but hitherto concealed properties of human cell function.

**Mesenchymal cells here are simply the parent or progenitor cells that make the osteoclasts and osteoblasts.

3) *The Meaning of Variety*

One choice or bit of variety can choose between two different states or actions. Two units of variety can control twice as many; a third unit of variety again doubles the number of states that can be controlled, or selected. In other words, if the number of units of variety is made the exponent to which the number two is raised, the resulting number will be the *maximum* number of states that can be controlled by that variety. This is why a system with minimum variety of four is twice as complicated as another with a minimum variety of three, and one with three in turn twice as complicated as another with two.

SUMMARY

A cybernetic analysis indicates that the dynamic logic of surface and osteonal remodeling of lamellar bone is easier to analyse than the other forms of modeling and remodeling that occur in bone growth and in normal health. Of the two, for practical reasons, the best to study first is osteonal remodeling. Using what is learned from it, the other kinds of bone cell behavior could be understood faster than if (*i*) they were the initial choice for study, or (*ii*) the present random approach to these problems were to continue. Similar analyses of cell behavior in soft tissues might prove instructive and helpful to physiologists generally.

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