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Harold M. Frost

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EVIDENCE THAT BONE RESORPTION PRECEDES FORMATION AT THE CELLULAR LEVEL*

H. TAKAHASHI, M.D.,** R. HATTNER,*** B. N. EPKER,**** AND H. M. FROST, M.D.*****

INTRODUCTION

Most of the body's organs may be considered as composite entities, made up of thousands of individual, basic, metabolically functional, and anatomically discrete, units. The metabolism of such organs must then be a summation of that of their many units. In order to understand how such organs function and are controlled, it is first necessary to understand how their individual units work and are controlled. Examples of metabolically functional units are the nephron in the kidney, the acinus in the pancreas, the alveolus in the lung, the apocrine gland in the skin, and the osteon in the bone.

It is axiomatic that when the contributions of many similar units in an organ are averaged, the composite behavior of these units may conceal meaningful and even unique characteristics of the individual unit. This is especially so if the various units are not synchronized in behavior with respect to each other. For example, study of the function of the whole kidney did not reveal that individual nephrons may in effect be turned "on" or "off" by alterations in the flow of blood through the efferent arteriole proximal to the glomerulus. Nor does the salivary output of the submaxillary gland reveal information about the total number of individual acini that contribute to it, nor the rate of production of individual units, nor the relative proportions of the gland which are engaged in producing the mucinous and serous parts of the gland's secretion.¹

This study evaluates a previously unreported property of one of the basic, metabolically functional units of human bone, the individual bone forming and bone resorbing process, examples of which are the osteon and trabeculum. This property

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**Orthopaedic Research Fellow, Orthopaedic Research Laboratory, Henry Ford Hospital. (On leave from Niigata University School of Medicine, Niigata, Japan).
***Wayne State University, School of Medicine.
****University of Detroit School of Dentistry, Detroit, Michigan.
*****Associate Orthopaedic Surgeon, Henry Ford Hospital, Detroit 2, Michigan.
can be seen only when individual bone resorbing and bone forming processes are examined. The study produced evidence that there exists a unique temporal and physical relationship between the cellular activities of resorbing and forming bone. This relationship is concealed from techniques that study the function of the whole skeleton as a unit.

**Materials**

All bones that were studied were obtained from adult humans who had been free of chronic illness and of metabolic bone disease. There were no children because we felt that growth represented an undesirable and extraneous variable. There were no cases with diabetes mellitus, rheumatoid arthritis, leukemia, congestive heart failure, osteoporosis or osteomalacia. Half of the bones were obtained at autopsy, cause of death being sudden and including accidents, myocardial and cerebral infarcts, homicide, suicide, drowning and exposure. The other half were obtained from the operating room, surgery having been performed for the diagnosis or treatment of lesions that were primarily anatomical. One hundred and fifty-seven bones from 157 persons were studied.

**Methods**

**Sections**

Fresh, mineralized cross sections were prepared by hand grinding under water. They averaged about 50 microns thick and were stained for 48 hours in 1 per cent alcoholic basic fuchsin, after which the surfaces were reground. There were an average of 3 sections per case.

**Table I**

<table>
<thead>
<tr>
<th>BONES</th>
<th>NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rib</td>
<td>107</td>
</tr>
<tr>
<td>Clavicle</td>
<td>20</td>
</tr>
<tr>
<td>Ilium</td>
<td>5</td>
</tr>
<tr>
<td>Femur</td>
<td>5</td>
</tr>
<tr>
<td>Tibia</td>
<td>7</td>
</tr>
<tr>
<td>Humerus</td>
<td>3</td>
</tr>
<tr>
<td>Radius</td>
<td>3</td>
</tr>
<tr>
<td>Fibula</td>
<td>3</td>
</tr>
<tr>
<td>Metatarsal</td>
<td>1</td>
</tr>
<tr>
<td>Phalanx</td>
<td>2</td>
</tr>
<tr>
<td>Skull</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>157</strong></td>
</tr>
</tbody>
</table>

**Measurements**

Cement lines were evaluated for scalloping caused by Howship's lacunae. Scallop­ing is a series of concavities on a cement line or bone surface which are believed to be produced by osteoclasts when they resorb bone. (Figure 1). The evaluation was done at 350X with the light microscope, using reduced aperture of the substage condenser to increase the contrast. Cement lines examined in this way in mineralized sections have a characteristic and unmistakeable appearance. (Figure 2).

*We wish to thank E. S. Zawadski, M.D. and R. H. Horn, M.D. for generously making much of this material available to us.

**Of the 107 ribs, 57 were used in studying trabeculae. All of the rest of the bones were used in studying the Haversian system. The material is listed in Table I.
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Figure 1
A Haversian system (osteon) in which a cement line separates the osteon from the circumferential lamellae. The double India ink brackets at C identify the cement line of the osteon. Mineralized, basic fuchsin stained cross section of a rib, 260X. Undulating contour of the cement line is the scalloping referred to in the text.

We studied the cement lines of a), 6000 secondary osteons in the cortex of 100 of the bones, and of b), 5,400 cement lines within the trabeculae of spongy bone of the remaining 57 bones.

RESULTS AND DISCUSSION
I: Secondary Osteons

Secondary osteons are Haversian systems that have been formed after the formation of the cortex. The kind of osteon produced by infolding of the circumferential lamellae during growth (primary osteon) and described by Ham was therefore not considered in this study; such osteons comprise less than 1 per cent of the adult's osteon population.

Secondary osteons were studied for a practical reason, to wit: In order for osteoblasts to synthesize the new bone matrix of which an osteon is made, a hole must first be made in the cortex to make room for the new bone, i.e., bone resorption must precede secondary osteon formation. It is generally believed that osteoclasts are the cells that are responsible for making this hole. It is also believed by many that scalloping of a bone surface or cement line is a reliable morphological indication that osteoclastic activity had occurred there previously. Many observers
An actively progressing resorption space, in which many osteoclasts are present. The double brackets at OC identify an osteoclast (see the tracing). The single brackets at R outline many Howship's lacunae. The arrow shows direction of progression of the resorption. Mineralized, basic fuchsin stained longitudinal section of rib, 300X plus 1¼ enlargement.
BONE RESORPTION

have shown (for example with cinemicrophotography)\(^4\) that osteoclasts can resorb bone and (in doing so) do produce scalloped surface contours. The reliability of scalloping as an indicator of previous bone resorption is in dispute\(^2\) and no test of its reliability has been published to our knowledge.

On this point the data are revealing and definite. Every one of the 6000 cement lines of secondary osteons that were evaluated revealed scalloping of contour. Thus, it may be stated that scalloping is a reliable indicator of previous bone resorptive activity, at least in osteonal remodeling. It is reasonable to infer that this applies to other modes of bone remodeling as well. It follows that in every one of the 6000 osteons evaluated, formation was immediately preceded in time by, and occurred in the same place as, a resorptive process. Therefore in this situation at least one resorption and its subsequent formation process could legitimately be measured as a basic unit of remodeling activity.

II: Trabeculae

Because of the obvious physical need that resorption precede formation inside of cortical bone, little can be inferred about the mechanism that controls the relationship between these two forms of cell activity in this situation alone.

For this reason the cement lines in spongy bone (i.e., trabeculae) were evaluated in the same manner. Trabecular surfaces are surrounded by the marrow soft tissues so that here there is no physical need for a resorptive process to precede a formative one. The data on this part of the study are equally revealing: 96.7 per cent of the 5,400 cement lines, evaluated in more than 3000 trabeculae in cancellous bone from 57 people, revealed scalloping. This is good evidence that here too a resorptive process usually immediately precedes a formative one in time, and that both take place in the same region of the bone. Since there is no obvious physical necessity for such a relationship in trabecular bone, some other cause for it must be sought.

With respect to the 3.3 per cent of the cement lines that did not show scalloping, it can be seen in trabecular bone that a formation process occasionally “flows” beyond the perimeter of the preceding and underlying resorptive process. Thus, if a section is cut correctly with respect to such a region, only the smooth part of the cement line will be included in the section. This means that in actuality more than 96.7 per cent of the trabecular cement lines had scalloping (and thus a preceding resorptive process) although it cannot be said how much more on the basis of the data given here.

III: Interpretation

In both cortical and trabecular lamellar bone of adults an individual resorptive process usually precedes a formative one. Stated in another way, a formation process does not develop until a resorptive process has appeared. This may be regarded as a cell behavioral sequence, and it means that there is some kind of functional connection between individual bone resorption and formation foci at the local, cellular level. While many biologists have reasoned that the cell environment is somehow responsible
for controlling such changes in cellular behavior, we prefer to speculate over the possibility that at least this particular sequence is predetermined by a mechanism that exists within the cell. Perhaps, as Young proposed in 1963, both osteoclasts and osteoblasts are the same cell nucleus in functionally different phases of its existence, and perhaps, as Frost proposed in 1963 this sequence of resorption — formation is determined by some form of “pre-programming” that exists and functions inside of the cell nucleus, and is determined by the time the cell division, which generated this nucleus, has been completed.

If this mode of cell behavior were to be called a behavioral sequence, one might wonder if some soft tissues exhibit analogous sequences which are concealed from the observer because studies of their behavior usually average the behavior of many units. It should be clear that this sequence (regardless of how it is effected) could not be detected by balance and tracer studies of the whole patient or bone. It should be equally clear that unless the evidence were pointedly looked for, analogous sequences would not otherwise be observed in organs such as kidney, adrenal cortex, pancreas, skin and gonads (where we suspect that analogous sequences do occur).

**SUMMARY**

More than 11,000 cement lines were evaluated in mineralized sections from 157 bones taken from 157 metabolically normal people. It was shown that, (i) scalloping of contour is a constant accompaniment to previous resorptive activity in osteonal remodeling, and by inference on any bone surface; (ii) a bone resorptive process almost always precedes a bone formative one at the cellular level. The authors speculate that this sequence of events may be determined from within the cell, and may have analogs in similar forms of cell behavioral changes in some extraosseus tissues.

**REFERENCES**