An Introduction

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H. M. FROST, M.D.

In the following eight articles an attempt is made to provide an example of a novel use of bone, to wit: as an instrument for physiological research. Written in special symbols, bone contains a semipermanent record of the past behavior of its system of cells, and by reading this record some of the mechanisms of disease may be studied. It is important to understand that the bone record concerns what the cells did, irrespective of their appearance, composition, patterns or staining.

The ability to study disease through the bone “window” is based in large part on certain developments that have occurred within the past 15 years. These include simple and economical ways for making and staining thin sections of bone as it exists in its natural state; the in vivo marking of sites of new bone formation with the tetracycline antibiotics; the study of the histogenesis of cells with tritiated thymidine, and of their biochemical functions with labelled substrate compounds; and the adaptation of light microscopical measuring methods and theory to provide a system of measurement which allows accurate information to be obtained from bone in large quantities. Use of bone as a model system or window also required the systematic study and characterization of normal so that a “yardstick” would be available with which to compare diseased bone.

This series of papers required a gamble and involved a guess. The guess was that, when considered in the abstract, the cell population phenomena that occur in bone have their analogs in other tissues in the body, and that study of bone could reveal them. The gamble was the commitment, eight years ago, of the efforts of this laboratory to the paths suggested by this guess.

It is now certain that the guess was right, although it is still not clear just how large our findings and interpretations will bulk in the final understanding of disease. The gamble has already paid off in part, since our studies of the effects of the Cushingoid, thyrotoxic and hyperparathyroid states on bone agree with extensive data concerning the soft tissues in these states. Note, parenthetically, that our interpretations are still considered provocative and even controversial.

In the following articles a novel frame of reference is used, and it will aid communication if it is summarized next.
FROST

We are kept alive by the physiological work conducted by a host of different kinds of metabolically specialized cells in the body. These cells supply essentials such as absorption, secretion, impulse conduction, physical contraction, gas transport, and protein and hormone synthesis. While the metabolically specialized cells are performing these kinds of work, they do not normally undergo cell division. It is now apparent that the functional lifetimes of most kinds of metabolically specialized cells are short compared to that of man. For example, the epithelial cells of the bowel live about two weeks, and the erythrocytes 120 days. It is known that if new supplies of such short lived cells are not constantly produced, disease results. On an epithelial surface the result could be an ulcer, while in the hematopoietic system it could be an aplastic anemia.

The meaning of these facts is that a continual production of specialized cells is required for normal health in those organs or tissues whose specialized cells have functional lifetimes that are shorter than that of man. Thus, two kinds of cell behavior are absolutely essential to maintain normal health in such tissues: (1) there must be a constant production of new cells; and (2) the new cells must then provide the specific functions expected of them by the whole organism. The chemical nature, controls and behavior of these two kinds of cell activity are as different from each other as are man and moon, so that knowledge of one does not help explain the other. While a great deal is known about (2) at present, almost nothing is known about (1). Elsewhere I have called this kind of arrangement a “cell generation system,” and pointed out in part the role that cell population kinetics play in some forms of disease, as well as in normal health. This role has not yet attracted the attention it deserves by students of physiology and pathology.

Bone is a tissue whose health depends on both generation of new cells and on the specialized contributions of these cells after they have been made. Other examples of tissues with this property are the skin, all of the body’s epithelial surfaces, the gonads, hair, nails and the formed elements of the blood. Others will be added to this list as the appropriate studies are done, and will probably include all of the body’s endocrine organs, the lungs, liver, kidneys, spleen, all mesothelial surfaces, the small blood vessels, fascia, tendon and fat.

Very little is now known about the changes in behavior of individual cells with age and in disease. Almost nothing is known about the changes in generation of new cells with age and in disease. Most previous efforts at understanding diseases have been based on the assumption, or frame of reference, that disease is a disturbance in the biochemical function of the individual cell, and indeed it often is. But it seems clear at present only to hematologists that disease is also often a disturbance in the population dynamics or patterns of a tissue’s cells, and need not involve any abnormal biochemical function of individual cells at all. With respect to the table of contents of at least one highly respected book about metabolic bone diseases, it can be proved that the basis of more than half of the diseases considered in it is an abnormal cell population dynamics. This is corroborated by an extensive world
literature, whose sum is that no abnormal kind of chemical material, no abnormal enzyme, and no deficit of normal materials or enzymes, can be shown in the cells of patients with these diseases. Well!

Within the above context, we at the Orthopaedic Research Laboratory have made a study of lamellar bone physiology in patients with diabetes mellitus. This study has indicated to us that in this disease there is (1) a major defect, previously unrecognized, in generation of new cells; (2) a major defect in the behavior of metabolically specialized cells after they have been made in spite of apparently adequate treatment of the diabetes, and (3) other basic defects in diabetes than the treatable one in membrane transport of glucose. It has also shown us that when bone is studied with suitable methods and concepts it can indeed provide useful information about diseases not conventionally associated with the skeleton.

CONTRIBUTORS

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