Editorial

Role of Connective Tissue Ground Substance in Degenerative Disease

The widespread interest in the relationship between lipids and arteriosclerosis has largely obscured the relatively limited studies of the nature of tissue changes occurring in degenerative diseases. Recently, there has been an increased interest in the consideration of the possible role of mucopolysaccharides in vascular degeneration. For the most part this has been limited to an application of a few histochemical techniques of limited specificity. Frequently, these studies have not been interpreted critically in light of modern knowledge regarding the chemistry and physical chemistry of the acid mucopolysaccharides.

Several concepts lacking in experimental validation have been widely used in interpretation of histochemical changes. Among these has been the assumption that the observation of increased metachromatic staining is indicative of depolymerization of mucopolysaccharides. Whereas changes in molecular size of mucopolysaccharides may occur, changes in degree of metachromasia may depend upon many other factors.

Recent studies indicate that in cartilage chondroitinsulfuric acid-A is bound to protein by a firm linkage that appears to be covalent in nature. Chondroitinsulfuric acid-A chains of molecular weight of 50,000 are bound to a protein core to give a macromolecule with a minimum molecular weight of 4,000,000. On the basis of experience in attempting to isolate sulfated mucopolysaccharides from other tissues, it seems likely that these are also bound to proteins. Other studies indicate that hyaluronic acid is also bound to protein, although less firmly.

Another assumption that seems unreasonable on the basis of available chemical information is the release of serum mucoproteins by the depolymerization of acid mucopolysaccharides. This has resulted to some extent from a confusion of nomenclature. The acid mucopolysaccharides are linear polyelectrolytes composed of alternating units of a N-acetyl amino sugar and a uronic acid. Certain of the compounds are sulfated. As already indicated, certain of the acid mucopolysaccharides are associated with protein. Such mucopolysaccharide-protein complexes have sometimes been named mucoproteins. The same name has been used for a different class of chemical compounds which contain N-acetylg glucosamine, galactose, mannose, and sialic tightly bound to protein. Such mucoproteins have been characterized in blood but it has so far been impossible to isolate any large molecular carbohydrate fraction free of protein from these substances. It seems unlikely, on chemical grounds, that the blood mucoproteins arise from the depolymerization of acid mucopolysaccharides of connective tissues. The transformation of acid mucopolysaccharides to mucoproteins would require a complete degradation of the molecule and the change of structure of most of the hexose components. The fact that serum mucoproteins (glycoproteins) are elevated in disease which show connective tissue changes in no way proves the causal relationship of the two phenomena. Indeed, the serum mucoproteins are elevated.
in a wide variety of disease processes. This change is paralleled by a large number of other blood protein changes. The mechanism by which these changes occur in disease is not yet understood.

Recent chemical studies indicate that it is unwise to consider ground substance changes as a uniform phenomenon. At least 8 different acid mucopolysaccharides have now been isolated from connective tissues. These differ with respect to chemical composition and biological properties. The exact structure of some of these compounds is not yet known. It is apparent that there is specific localization of individual compounds. Table 1 lists the known compounds.

The mucopolysaccharide composition of the ground substance varies in specific tissues. Thus, most cartilage contains chondroitinsulfuric acid-A while skin contains a mixture of chondroitinsulfuric acid-B and a smaller amount of chondroitinsulfuric acid-A mixed with hyaluronic acid. The exact localization of individual polysaccharides in tissues is not yet known. They may play highly specific roles which depend upon both their anatomic localization and their biological activities. An example of the biological specificity is indicated by the fact that chondroitinsulfuric acid-B, which differs from chondroitinsulfuric acid-A only in the position of the OH group on C-5 of the uronic acid fraction, is antithrombic while chondroitinsulfuric acid-A has no activity on the coagulation system. This example is indicative of the many possibilities that specific localization or changes of individual compounds may result in profound physiologic and pathologic alterations.

This brief discussion is intended to focus attention on possibilities for the study of connective tissue changes in vascular degenerative disease but to warn against too ready acceptance of concepts that are not firmly based on critical evidence.

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THE PHYSICIAN

HIPPOCRATES

Greek physician, about 460-377 B.C.

For where there is love of man, there is also love of the art. For some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of the physician.—Precepts. Trans. W. H. S. Jones. From Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources. Vol. I, Boston, The Beacon Press, 1952.
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Circulation. 1959;19:801-802
doi: 10.1161/01.CIR.19.6.801

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/19/6/801.citation

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