Horizons in the Study of Liver Disease

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Changing concepts and approaches in pathology are reflected in the study of the liver. The shape of the organ attracted interest long before it was related to disease processes. It was studied in sacrificial animals by Babylonian and Etruscan diviners in order to foretell the future. The development of rational empiric medicine by the Egyptians, Babylonians, Greeks, and Romans led to concern with structural alterations of the liver and their relation to human diseases. However, only after the foundation of clinical-pathologic correlation by Morgagni and the Italian School was an energetic attempt made to recognize the gross anatomic and subsequently microscopic substrates of diseases developing in the liver. During the following classical period of pathology, the concept of the different hepatic diseases was established without special application as yet of pathologic knowledge to the individual patient. Cirrhosis was subdivided on the basis of morphologic criteria. Acute yellow atrophy was described, and during World War I, it was recognized to be related to catarrhal jaundice. Only during World War II was the role of viral hepatitis as the etiology of both conditions appreciated.

Present-day clinical pathology of the liver

The classical period of hepatic pathology was succeeded by modern pathology about 25 yr. ago, when liver biopsy permitted evaluation of the alterations in the living patient, when the use of hepatic tests was widely expanded, and when finally various types of human liver diseases—particularly those related to malnutrition—were reproduced in experimental animals. All three approaches, as well as improvement in knowledge of the physiology of the liver, allowed correlations to be made between structural alterations and functional changes. Gradually, the application of hepatic pathology shifted from the broad concepts of liver...
diseases to diagnosis in the individual patient, in an attempt to provide objective clinical aids based either on morphologic or functional methods. This appearance of hepatic pathology at the bedside helped in the understanding not only of diseases primary in the liver but also of the hepatic reaction to a disease process elsewhere in the body, and the concept of nonspecific reactive hepatitis was thus proposed. Correlations established some factors of etiology in liver diseases, but many remained unsolved. For instance, the etiology of cirrhosis in many patients is still a riddle. We can thank modern pathology, however, for therapeutic leads in the treatment of some of the side effects of hepatic injury such as ascites or electrolyte imbalance. Portal hypertension is now being attacked surgically as a result of studies of vascular alterations in cirrhosis. However, rational therapy directed toward restoration of the basic functions of the damaged liver cell still does not exist.

THE COMING ERA

In the last few years, the hepatic pathology of the future seems to have arrived. As the result of the introduction of biophysics and fine structural cytochemical and submicroscopic technics, structure and function are being identified. If the intracellular mechanism of the failure of the liver becomes known, a rational therapy may be developed, dispelling much of the mystery surrounding liver disease today. Moreover, many basic studies on nucleic acids and their relation to genetics and to normal and abnormal protein synthesis, as well as to metabolic pathways and the alterations resulting from enzyme defects, are being carried out using the liver as a model. These fundamental studies may eventually give us the key to the understanding of many diseases not really related to the liver.

The attempts in this pathology of the future are fragmentary and come from many groups. In the following, we would like to emphasize those in our own laboratory, where the attempt is being made to supplement our knowledge based on the foundation of modern clinical pathology of the liver by electron microscopic, histochemical, immunocytochemical, and biochemical methods directed towards a careful observation of the patient.

INTRACELLULAR SITES OF HEPATIC INJURY

A variety of drugs, most of them proved metabolic poisons, regularly and predictably injure the liver cells. Newer knowledge indicates the specific sites of this injury. The liver cell, like any cell, and particularly those of parenchymal type, contains mitochondria, the organelles that