

THE LIVER:
NORMAL AND ABNORMAL FUNCTIONS

Part A

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THE LIVER:
NORMAL AND ABNORMAL FUNCTIONS
(in two parts)

Part A

Edited by
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INTRODUCTION TO THE SERIES

Rudolf Virchow wrote in 1855 as follows:

"When we require cellular pathology to be the basis of the medical viewpoint, a most concrete and quite empirical task is at stake, in which no a priori or arbitrary speculation is involved. All diseases are in the last analysis reducible to disturbances, either active or passive, or large or small groups of living units, whose functional capacity is altered in accordance with the state of their molecular composition and is thus dependent on physical and chemical changes of their contents. Physical and chemical investigation has a very great significance in this respect, and we can do no more than wish a prosperous development to the school which is striving to form itself. But we should not conceal from ourselves that the story of metabolic interchange will be brought to satisfactory conclusion only when it is carried back to the primary active parts; in other words, when it becomes possible to describe the particular role every tissue, and every pathologically altered part of a tissue, plays in that story. Therefore, although one may begin with the outworks, the ultimate goal, beyond the urine and the sweat and the various waste products of organic activity, must never be lost from sight, nor should it be supposed that these waste products are themselves the goal. There would always be the danger of suffering shipwreck in a more or less exclusively humoral pathology, if this were to be the case."

It has taken a hundred years to start the molecular approach in a fruitful way. Modern developments in physics, chemistry, and mathematics, both conceptual and instrumental, make it now possible to exploit that new-old approach to pathology. Hence, my return to Virchow's expression, cellular pathology.

We, in modern pathology and medicine, are so involved in generating and interpreting the new research available that no one person at this stage could endeavor to write an all-encompassing treatise on the biochemistry of disease. Besides, we do not know enough yet. We can only highlight some of the most interesting details. This will be one of our objectives in this monograph series.

Underlying this are two basic roles of pathology in medicine and biology. The first and most classical role is to analyze disease processes in depth, the aim being as detailed a knowledge as possible about the causes and the cellular and

tissue development of disease. Included in this is the production of experimental disease which mimics or simulates the naturally occurring process in order to study it more easily. However, there is a second role which will assume increasing importance as we probe more deeply into cells. The molecular approach to disease has not only as its aim the study of cellular pathology but also the deeper understanding of the normal cell, both structurally and functionally. Through the induction of selected derangements in the cell, especially reversible ones, cellular pathology offers novel but essential ways to dissect the cell. The contributions of the pathologic (genetic, toxic, etc.) in the development of the molecular biology of microorganisms clearly point to an important role for such experimental pathologic systems in the molecular analysis of eukaryotic cells.

All the modern conceptual and methodologic approaches of cellular biochemistry and ultrastructural analysis must be used in such a dissection of the cell. However, our orientation is quite different. Whereas cytochemists nowadays have as their major aim the delineation of the different chemical interactions in cells, the modern cellular pathologist must continually attempt to *integrate* these into a *gestalt* that is meaningful biologically as well as biochemically. Therefore, a second important objective of this monograph series will be the presentation of model systems of higher organisms which are of particular use for the modern biologist interested in the molecular analysis of cell function in higher organisms.

Emmanuel Farber
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PREFACE

In ancient times, it was implied that the liver was the seat of the soul, although Plato decried that view and suggested instead that the organ was the vegetative center of the body. For the moment, the validity of the former concept remains unclear, but no organ deserves to be held in greater esteem. For the liver is truly a rich organ; rich in structural complexity, in diverse function, and as often follows, rich in the spectrum of malfunctions to which it falls victim. No other organ is involved in as many complex interrelationships with the host as is the liver. No other organ's functions have been so frequently probed by varied scientific methods, nor has any been used so frequently as an experimental tissue, both normal and abnormal. Often, as exemplified in studies of chemical carcinogenesis, the liver's response to challenge has been the model for others, which are more frequently the site of the disease but less accessible to study. Often, as exemplified by the studies of the agent aflatoxin, experimental studies of the liver are found to be broadly applicable to human disease. The liver's accessibility, its relative homogeneity, and its availability in varying states of development and physiologic alteration make it a biologic model *par excellence*.

Despite an enormous literature that deals with every aspect of disease of the liver from the clinical standpoint, no single work has attempted to apply these cell biologic findings and modern scientific concepts to the liver in a unified manner to examine its normal functions, the alterations of these functions as imposed by injurious challenges, and the various responses of the host to these alterations. However, the continuing series *Progress in Liver Diseases*, edited superbly by Popper and Schaffner, has been a major stimulus to the scientific approach to liver disease. It is that purpose to which this book is dedicated.

The richness of the liver's functions can be grouped roughly into three major roles; endocrine, exocrine and regulatory.

An endocrine organ can be defined broadly as that which synthesizes and secretes proteins possessing activities related to the functional modulation of other target tissues. The liver secretes numerous, immunochemically distinct plasma proteins, the total number as yet unclear. Indeed, many of these are of unknown function and others bear functional designations that may be only a partial estimate of their capacities. Several, such as those which transport hormones,

metallic ions, and other substances, interact with tissues distant from the liver. Furthermore, there are strong hints that vital interactions between other plasma proteins and distant tissues may yet be uncovered (see Chapter 5), thus approximating an endocrine activity.

The entire spectrum of liver-synthesized lipoproteins, too, can be considered as interacting in a crucial manner at many sites, especially at membrane and endothelial surfaces, although a discussion of lipoproteins and protein transport will as readily fall into the category of regulatory function.

An exocrine organ is defined as one that secretes its products to the external environment. The liver does this and more. Components of bile are produced within the hepatocytes and flow to the gut, wherein they act in a vital digestive capacity. Moreover, the liver clears the blood of exogenous and endogenous chemical substances, bacteria, and other particulate matter; processes these; and secretes them to the external environment. In this regard it is exocrine, but once again the definition between this function and that of regulation is blurred. For without the vital catabolic and alterative functions of the hepatocyte, pharmacologic agents, toxins, and carcinogens would often be fatal.

I have described the regulatory capacity of the liver above in terms of plasma protein function and metabolic elimination of many substances. But nowhere is the regulatory capacity of the liver more vivid than in its handling glucose. It is the ultimate storage depot and site of synthesis of this vital substance, smoothing the peaks and troughs of nutritional supply and energy demand. The liver then can be considered as the ultimate regulator of its host.

The liver has also been the most useful model for the rapidly expanding studies of the correlation of structure and function. The granular and smooth endoplasmic reticulum, glycogen aggregates, and mitochondria of this cell have been used in definitive studies of protein synthesis, drug metabolism, and metabolic regulation. In no other tissue has the study of injury and repair or experimental carcinogenesis been more extensively pursued. In no other tissue is the spectrum of diseases more varied, ranging as it does from abnormalities of a genetic nature, to toxic alteration, to tumors or parasitic infestation.

And last, but of crucial importance, is our rapidly expanding realization of relationships between the liver and the host other than those described above. Who would have proposed a liver defect as basic to lung pathology prior to the description of α -trypsin inhibitor deficiency? What other alterations in the structure or secretion of plasma proteins are responsible for other "distant" disease patterns? Is atherosclerosis a liver disease? Are the altered lipoprotein patterns, so much in vogue, seated in an abnormality of liver metabolism?

Therefore, this book is not written as a final word. It is written more as a landmark to indicate the progress made and to suggest some of the paths of the future.

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