LECTURES ON

THE LIVER AND ITS DISEASES

COMPRISING THE LOWELL LECTURES DELIVERED AT BOSTON, MASSACHUSETTS, IN MARCH 1947

H. P. HIMSWORTH, M.D.

Secretary Medical Research Council
Fellow of the Royal College of Physicians of London
Late Professor of Medicine in the University of London, and Director of the Medical Unit, University College Hospital, London

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TO

T. R. ELLIOTT, M.D., F.R.S.

EMERITUS PROFESSOR OF MEDICINE IN THE UNIVERSITY OF LONDON;
FIRST DIRECTOR OF THE MEDICAL UNIT, UNIVERSITY COLLEGE HOSPITAL,
LONDON

Ignem benignissima ipse anima accendit.

PREFACE

THIS monograph is based on a series of lectures delivered at the Lowell Institute, Boston, Massachusetts, in March, 1947, and I wish to record my gratitude to the Trustees of the Lowell Foundation for the great honour they paid me in inviting me to undertake this distinguished lectureship.

The present time seems particularly opportune for reviewing our knowledge of liver diseases. The increased frequency of infective hepatitis and its complications, during the last few years, has provided unusual opportunities for clinical observation, and its prevalence in armies, by raising it to the status of a major military consideration, has compelled its intensive investigation. Almost simultaneously the experimental approach to liver disease has expanded into a new field, and it is now firmly established that serious lesions of the liver may arise, not only from the presence of noxious substances, but from deficiency of essential nutriments. The stage is set for a great advance. The immediate tasks are to assimilate the new with our old knowledge and to effect the necessary reorientation in our views required to realize its possibilities. An attempt on this task has been made in this monograph. But it has been made in the full realization that we are too close to the new knowledge to have grasped its full implications, and any suggestions made must remain tentative and subject to revision, until sufficient time has elapsed for them to be tested more completely. At this present time it can only be hoped to define some of the questions which arise and to clear the ground of some conceptions, still in current use, which are now patently obsolete. If this monograph contributes towards the solution of these necessary preliminaries it will have served its purpose.

I have to thank Dr. Balduin Lucké and the editors of the American *Journal of Pathology* for permission to reproduce Figures 42 and 43; the editors of *Clinical Science*, the *Journal of Pathology and Bacteriology* and the *Biochemical Journal* for allowing me to reproduce various figures for which acknowledgement is made in the text. I am indebted to Dr. H. C. Trowell, of Uganda, and Dr. Joseph Gillman, of Johannesburg, for material from tropical cases of liver disease. Professor G. R. Cameron and Dr. M. L. Rosenheim have read the text and given me

the benefit of their valuable advice and criticism; and I am very grateful to them. Of Dr. L. E. Glynn I can only say that we have worked together for six years on the experimental and pathological aspects of liver disease and that, although he cannot be held responsible for all the views expressed here, our ideas are so interwoven that it would be impossible now to separate them with any certainty.

H. P. HIMSWORTH.

LONDON,
June, 1947.

PREFACE TO THE SECOND EDITION

THE field of research in diseases of the liver is now being rapidly opened up and, in the two years since this book was first published, several noteworthy additions to knowledge have already been made. Of these the most important is that concerning the influence of tocopherol on experimental, dietetic, massive necrosis of the liver. Not only does this finding seem to remove the discrepancies between the results from different laboratories, but it has produced facts which promise to throw light on the fundamental biochemical reactions involved in the production of hepatic necrosis, and which may not be without significance to our understanding of the human disease as it affects malnourished races. In the pathological field the surprising observation has been adequately confirmed that the condition, long accepted as 'portal cirrhosis', is, in many cases, not primarily a lesion of the portal tracts but of the central veins—an observation which makes its development considerably easier to understand. In the clinical field the syndrome of subacute hepatitis has been clarified by further experience, and light thrown on its essential pathology by the use of puncture biopsy in its early stages. On the therapeutic side our views on the uses of dietetic therapy in the different types of hepatic disease are beginning to clear. For these reasons, to record the numerous new data which are falling into their places, and to correct certain ambiguities in the original text it has become necessary to bring the original lectures up to date in a second edition.

H. P. HIMSWORTH.

LONDON,

December, 1949.

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LECTURES ON
THE LIVER AND ITS DISEASES

CHAPTER I

THE TYPES OF LIVER INJURY AND THEIR STRUCTURAL CONSEQUENCES

A CONSIDERATION of the immediate effects of injury upon composite organs reveals that, in general, those cells which are most highly differentiated, and which endow the organ with its characteristic function, are also those which are most susceptible to damage. Nowhere is this more evident than in the liver. In this complex organ there are, in addition to the usual vascular and supporting structures, no less than three other differentiated tissues each with its particular functions. Chief of these, and entirely characteristic of the liver, is the parenchymal cell. Less characteristic, but still highly differentiated, are the cells of the biliary tracts. Least differentiated are the Kupfer cells, representatives of the widely distributed reticulo-endothelial system. Of these tissues the parenchymal cells invariably show the severest, often the only, evidence of acute damage. Whether the injury is effected by restriction of blood supply, the introduction of poisons into the circulation, or dietary deficiency, its brunt falls on the hepatic parenchyma, and it is not unusual in recent and severe lesions to see every parenchymal cell dead while the bile ducts, Kupfer cells and supporting tissues survive apparently unscathed (Fig. 2).

Thus, in the acute hepatic lesions, parenchymal damage is the most conspicuous feature. But it is not so in the chronic. In them the most conspicuous abnormality is an increase of the fibrous supporting tissues and, although the arrangement of the parenchymal pattern is distorted, the individual cells within the lobules are often, to all intents and purposes, healthy. Such hepatic fibroses have excited interest since the distant days of John Brown [6] and Matthew Baillie.[3 4] Originally attention centred on the hyperplastic nodules of parenchymal tissue with which such livers are studded and which Laennec,[32] to whom we

owe the term cirrhosis, regarded as being of the nature of new growths. Later Carswell [14] formed a more correct conception of the condition and, as a result of the importance he attached to the fibrous changes, the condition came to be regarded as an inflammatory and sclerosing hyperplasia of the supporting connective tissues.[14 15 22] It was only at the end of the last century that importance began to be attached to parenchymal degeneration.[26] At first this degeneration was merely regarded as the result of contraction of the proliferating fibrous tissue,[15 22] but later opinion steadily veered through the stages of regarding the two processes as concomitant,[1 21 29 30 40] to the view that the primary lesion affected the liver cells and the fibrosis and parenchymal regeneration were reparatory processes.[1 20 29 30 31 37 38]

This development of ideas [35] is of more than academic interest, for ideas, however abstract, are never without their influence on practice. When it was believed that the primary process in chronic liver disease was proliferation of the interstitial fibrous tissue then research in pathogensis took its start from the appearance of fibrosis. And at that stage, as clinicians well knew, a fatal train was already in progress. If, however, the proliferation of fibrous tissue is regarded as secondary to a preceding cellular degeneration, then its pathogenesis must be sought in factors making for parenchymal damage and, such lesions being often recoverable, the possibility of preventing a fatal sequence can be entertained. It is, therefore, of the greatest importance for clinicians to be clear as to the precise implications of the different pathological lesions in the liver as, according to the significance attached to each, so will clinical research and practice be influenced. At first sight it may seem surprising, even old-fashioned, to insist that in the present stage of knowledge, an understanding of the morbid anatomy of the liver is the first requisite for clinical research in this field. In recent years the dramatic advances in other fields have been the result of direct observations on patients or the development of tests of organic functions. But there are particular reasons why such a direct approach must be deferred in respect of hepatic disease, and of these the most important are the large functional reserve of the organ and its remarkable capacity for regeneration. As a result of these two attributes, lesions of its substance remain clinically latent until, the reserve being exhausted, illness suddenly appears. By that time the chance of arrest, let alone prevention, has largely vanished and the clinician is more often than not condemned to stand helplessly by, or at best, simply to palliate the relentless progress. This state of affairs will continue to exist until we clearly recognize the antecedent states of terminal liver damage; but

in attempting to do this we immediately come face to face with a particular difficulty.

The end results of many hepatic lesions resemble each other very closely. Just as many different acute lesions of the kidney terminate alike in a contracted fibrotic organ so many acute lesions of the liver terminate as hepatic cirrhosis. Many will remember the time when our knowledge of renal disease seemed to have reached an impasse and how that deadlock was broken by discarding the conception of renal fibrosis as an entity, and differentiating its types in relation to the appropriate antecedent lesion. At this present time our knowledge of chronic hepatic disease is at a similar stage of development. Just as thirty years ago 'cirrhosis of the kidney', or 'chronic interstitial nephritis' was widely considered a unity, rather than a common result of many types of renal damage, so to-day, 'cirrhosis of the liver' is still generally regarded as an entity. There are reasons for thinking that the retention of that view is one of the main obstacles to a better understanding of liver disease and, if this be so, no better contribution could be made to progress in this field than to relinquish, both in clinical medicine and pathology, the use of the term 'cirrhosis' which, not only misleads by implying an entity whose existence is doubtful, but has become so worn and defaced by loose usage as to have lost all precision. It is not proposed at this stage, however, to attempt a detailed justification of this departure from tradition. That should emerge from the subsequent discussion. All that is intended is to intimate that, when considering the types of liver injury and their sequelae, this term will not be applied to any kind of hepatic fibrosis, save in reference to the work of previous writers when the use of a new term to describe their opinions might lead to confusion.

Necrosis of the Liver

The term necrosis of the liver refers almost invariably to necrosis of the parenchymal cells. Only under the most exceptional and artificial circumstances do the other hepatic tissues die. Under all usual circumstances, experimental or clinical, the hepatic parenchyma alone suffers. Such a lesion can be produced in many different ways; but the necrosis always assumes one or other of two anatomical forms. In one, zonal necrosis, the damage is limited to a particular region within the liver lobule and according to its distribution is distinguished as centrilobular, periportal or midzonal (Fig. 1). In the other, massive necrosis, the acute yellow atrophy of older writers, the whole lobule is involved, every parenchymal cell being dead (Fig. 2), save perhaps

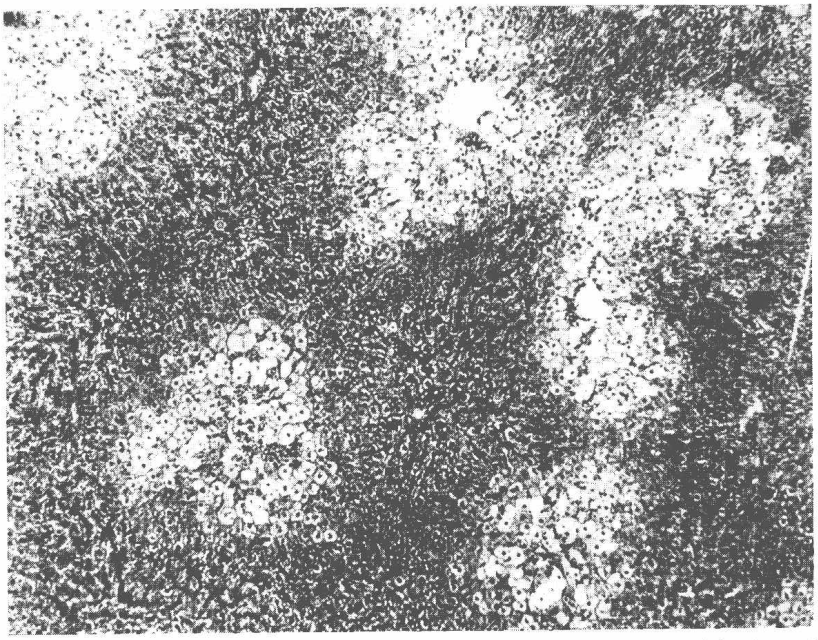

FIG. 1—Centrilobular Zonal Hepatic Necrosis. Rat. Subcutaneous injection of carbon tetrachloride 0.05 c.c./100 g. Necrosis is limited to the centrilobular zone. H. and E. × 72.

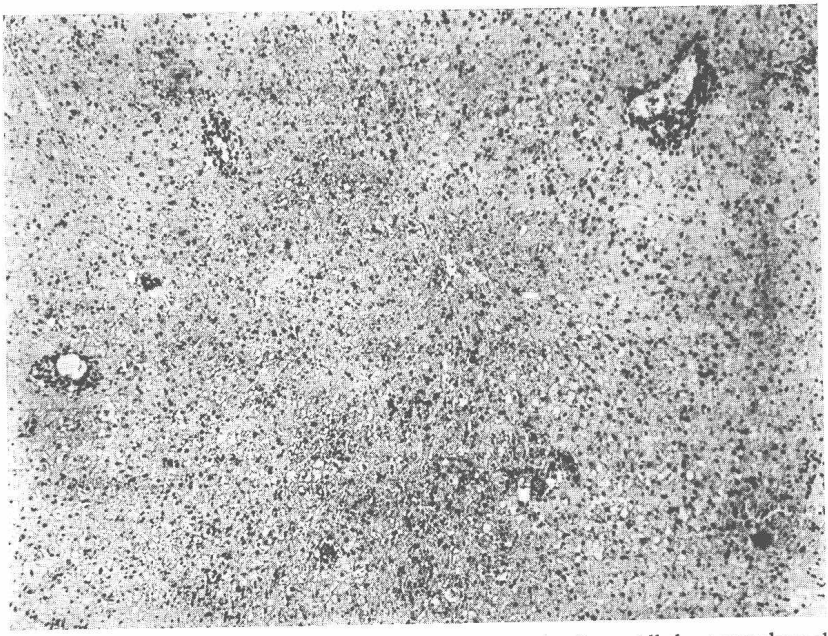

FIG. 2—Massive Hepatic Necrosis. Rat. Low protein diet. All the parenchymal cells throughout the liver are dead. The blood vessels and bile ducts survive. H. and E. × 72.

towards the edges of the areas affected where isolated, and irregularly distributed, clumps may survive. The justification for distinguishing between these two forms lies in the different course pursued by each.

Zonal necrosis is the form produced by liver poisons under ordinary experimental conditions. Its common occurrence in human disease, however, remained unsuspected until recently.[2 16 17 48] After single attacks recovery occurs with astonishing speed and completeness. If an animal is given a subcutaneous injection of carbon tetrachloride, then, a zonal necrosis, centrilobular in distribution, occurs in every lobule throughout the liver [7] and, if the dose is large, this necrosis may be of such extent that only a thin cuff of parenchymal cells survive around each portal tract. Yet within a fortnight the necrotic cells have been removed, the surviving parenchymal cells have regenerated and no trace of liver damage remains.[9] This is in marked contrast to the sequence of events following massive hepatic necrosis. This lesion differs from zonal necrosis not only in its distribution within the lobule but also in its distribution through the liver. While zonal necrosis affects every lobule to approximately the same extent, massive necrosis, when insufficient to cause speedy death, is limited to particular areas which are separated by large tracts of apparently normal liver.† Areas once affected by massive necrosis never return to normal. Fibrous tissue develops at the affected sites and the final result is a distorted organ in which irregularly distributed scars cut up essentially normal liver tissue.

The broad reasons for the different results of these two anatomical forms of necrosis are not far to seek. Although in a severe zonal necrosis, far more parenchymal tissue may be killed than in many massive necroses, yet in zonal necrosis a rim of parenchymal cells survives in each lobule. This serves a double purpose. It provides a source from which new parenchymal cells can regenerate; it holds open the reticulin framework of the lobule, the Gitterfasern, as an accurate scaffolding upon which the lobule can be rebuilt (Fig. 3). In massive necrosis no such rim of parenchyma survives. In those lobules where all the cells are dead there is nothing either to prevent collapse of the reticulum (Fig. 4) or from which new parenchyma can

† It cannot be too strongly insisted upon that the terms zonal and massive apply only to the state of affairs *within* the individual liver lobule and carry no implication as to the extent of the lesion in the liver as a whole. This point is of particular importance in respect of massive necrosis. In its most commonly recognized form, the 'acute yellow atrophy' of Rokitansky, large areas of liver are affected, but in the more frequent, but less well recognized, lesion of so-called subacute hepatitis only a few lobules are affected in each attack. Nevertheless, whether the lesion is widespread or localized, the lesions in the lobules affected are exactly the same and lead to the same sequelae.