Croonian Lectures

ON

LIVER AND SPLEEN: THEIR CLINICAL AND
PATHOLOGICAL ASSOCIATIONS

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LECTURE III

I turn now to actual diseases affecting both liver and spleen. It is manifestly impossible to deal with all of them here, and I cite merely as examples such conditions as bacterial infections, leukaemias, Hodgkin's disease, syphilis, malaria, kala-azar, and the portal back pressure of cardiac failure.

There are three important conditions about which I especially wish to speak—namely, hepatic cirrhosis, Banti's disease (so-called), and reticulo-endothelial diseases of the liver and spleen.

HEPATIC CIRRHOSIS AND SPLENOMEGALY

The relation of an enlarged spleen to the fibrotic liver in portal cirrhosis has raised endless discussion, and has been the subject of many hypotheses. In the book on *Diseases of the Liver*, by Sir Humphry Rolleston and myself, the views which have been most commonly accepted or discussed are set forth in detail, as is necessary in a textbook. In the present lectures, however, I wish to attempt something further, and to put forward other suggestions which may or may not stand the test of time. They are founded on a somewhat different outlook on the structure and functions of the two organs and their relations in disease. It is naturally a study of the commencement and gradual evolution of the pathological changes in the two organs which alone can help us, and not the end-result as seen in the post-mortem room. Before I begin, however, to discuss my views on the development of the lesion, I wish to make acknowledgement of a paper by Epplen, published in 1922, but which until recently was unknown to me. Epplen's views of ten years ago agree very closely with a number of those which I have arrived at independently, and I shall quote from his work on a number of occasions.

THE LIVER

If we consider, first of all, the gradual evolution or development of the hepatic lesion in portal cirrhosis, leaving aside for the moment the whole question of aetiology, the first point which requires discussion is the nature of the fibrosis. Is the fibrosis, as has been strongly held in the past, a primary disease of the supporting connective tissue? In other words, is the lesion a true chronic interstitial hepatitis with secondary changes in the glandular cells; or, is the lesion just the reverse—a primary atrophy or degeneration of the hepatic glandular cells followed by a replacement fibrosis? I would submit that neither of these two old views is adequate as it stands, and I agree almost completely with Epplen that in cirrhosis hepatitis the essential points in the evolution of the hepatic lesion are as follows.

The Primary Lesion

I believe that the primary lesion in cirrhosis is one which depends on slow progression but frequent repetition. It consists, first, in degeneration or destruction of liver cells, followed by regeneration and replacement by new liver cells, but with some overgrowth of fibrous tissue in

the areas which are destroyed. The essence of this view is the conception that the damage in the liver is one which is focal, but frequently repeated. Areas of liver cells die, and are replaced by new areas built up from surviving cells; these new areas are again destroyed, and again rebuilt, but increase of fibrous tissue gradually supervenes as the process of death and repair is repeatedly carried out. Finally, on this view, an entirely new liver parenchyma, containing perhaps not a trace of the old and original liver, is built up on a plan which has the appearance we describe as cirrhosis. Not only has the entire parenchyma been repeatedly destroyed and renewed, but, as is well known from the work of many pathologists (Milne, Muir), new bile ducts are made and joined up in functional relation with the new glandular cells. Even the blood vessels and their branches—both of the hepatic artery and of the portal vein—are involved, and the whole circulatory plan in the liver is markedly altered.

Alterations in Hepatic Circulation

The changes in the circulatory system of the cirrhotic liver deserve special attention, particularly in relation to what has been said in the previous lectures regarding its special anatomical and physiological features. Reference may be made first to Herrick (1907), who perfused with saline a small number of normal and cirrhotic livers obtained at necropsy. He found, on perfusing through the hepatic artery, that a larger proportion of the fluid passed out by the portal vein in the cirrhotic than in the normal liver. Guided by Gad's hypothesis, he concluded that there is freer communication between the hepatic artery and the portal vein in the cirrhotic liver, and that this must heighten the pressure in the portal vein; but these findings are equally well explained by assuming that in the cirrhotic liver there is greater obstruction to the passage of fluid through the hepatic lobule to the hepatic vein. This would be more in accord with the conclusions of subsequent workers.

It was first insisted upon by Kretz (1905) that in portal cirrhosis the hepatic artery is enlarged and hypertrophied, and there is now almost universal agreement on this fact. The hepatic artery inflow of blood is consequently increased in this disease. Some very important work on this subject has been done by McIndoe (1928), who injected the vascular system of cirrhotic livers by means of his well-known celloidin method, thereafter digesting away the tissues to leave the vascular skeleton only. By this method he was able to prove that in advanced or atrophic hepatic cirrhosis the total vascularity of the interior of the liver is much diminished, especially the portal venous tree. Many of the portal trunks are attenuated and stenosed, and the smallest portal vessels are "distorted beyond belief." McIndoe, who is also a supporter of the view that in cirrhosis the essential lesion is repeated destruction of cells followed by regeneration, states that the regenerated nodules of liver cells become almost side-tracked from the portal blood, and are finally left with a very poor portal venous supply.

It is evident, indeed, that as cirrhosis advances the liver parenchyma becomes more and more dependent on the hypertrophied hepatic artery for its supply of blood. The condition eventually but gradually produced is very similar to what is brought about suddenly by an experimental Eck fistula, in which the portal blood is diverted into the inferior vena cava and avoids the liver altogether. The work of Rous and Larimore (1920), referred to in Lecture II, on the effects of occlusion of part of the blood supply to the liver, is of interest here. It was shown that rapid atrophy ensued in the portion of liver from which the portal blood supply had been cut off, but that this atrophy was conditional to hypertrophic proliferation of

the portion of liver with an intact portal venous supply. Rous and Larimore describe the final stages of the experimental atrophy, and state:—

"As the parenchyma grows less, so do its attendant capillaries disappear, and they never survive when the liver cords [of glandular cells] are gone. Soon there remain only scattered islands consisting of a few small but healthy-looking liver cords, with the characteristic capillaries, set in a matrix of fibrous tissue."

In the liver in portal cirrhosis atrophy and proliferation of liver cells are occurring again and again.

It seems clear that the hypertrophy of the hepatic artery present in cirrhosis is a direct consequence of the defective portal circulation, and through the artery is carried, not only the oxygen, but all the metabolic products essential for hepatic function, which should normally arrive by the portal vein. This seems a far more likely view than the older hypothesis that the artery was hypertrophied to bring an increased blood supply to the new fibrous tissue in the liver. The interference with the portal inflow in cases of cirrhosis hepatis may be enormous, and McIndoe states that in such livers perfused after death 86 up to nearly 100 per cent. of the fluid perfused into the portal vein may be run off by collateral channels instead of escaping by the normal route of the hepatic veins.

The conclusion is, therefore, that in portal cirrhosis there is such dissociation of hepatic structure in consequence of the repeated death and regeneration of islands of liver tissue that a corresponding dissociation of the portal and hepatic blood also ensues. The portal blood supply is the one most severely obstructed, and the blood, being unable to flow through the liver, must be diverted through collateral channels.

THE SPLEEN

We may now turn to the splenic side of the problem. There have been two main hypotheses advanced to account for splenic enlargement in portal cirrhosis.

(a) *That the cause is passive congestion due to the increased portal blood pressure.* That there is an increased portal blood pressure is certain, and, since there are no valves on the portal or splenic veins until the ellipsoids are reached, the back pressure must quickly reach the spleen. This hypothesis is, however, inadequate for a variety of reasons. First, there are cases in which the spleen is enlarged before cirrhosis in the liver is at all advanced—and certainly the spleen is usually enlarged before any ascites or other definite signs of portal back pressure supervene. Secondly, it is only in about 80 per cent. of well-marked cases of cirrhosis that the spleen is enlarged at all.

(b) *That the spleen enlarges as a result of "toxins" circulating in the blood and reaching the spleen by its arterial supply.* Hitherto no very adequate reasons have been offered in support of this view, the chief suggestions in its favour being the claim that in so-called Banti's disease the splenic enlargement occurs before the hepatic cirrhosis. I am of opinion that this second hypothesis of the cause of the splenic enlargement is the more important one, but in a sense not previously considered.

If the view just put forward of the evolution of portal cirrhosis, with the accompanying distortion and obstruction of the portal venules, is correct, then two conditions must result which could affect the spleen. First, the increased portal pressure must be thrown back to the spleen and obstruct its venous outflow. Secondly, since the portal blood flow is obstructed and diminished, the metabolic products coming from the intestine which should be arrested by the liver and "detoxicated" are, instead, carried past the liver into the general circulation, and reach the liver and spleen simultaneously in the arterial blood.

"ANGIOSTOMIE"

Are there any metabolic products which normally go to the liver, but in which the spleen might be considered "interested," and might even hypertrophy to deal with them? We know little about this matter at present, but we should certainly quickly aim at knowing far more. It seems to me that the so-called method of "angiostomie," elaborated by E. S. London and his colleagues in Russia from 1919 onwards, should give us one of the best possible opportunities of studying experimentally the metabolic substances which are normally carried from the intestine or from the spleen to the liver. By his method London is able to bring up closer to the surface, and to fix permanently in position, deeply seated veins such as the portal, hepatic, and splenic. Silver cannulae of an ingenious type are placed in position with one end over the vein and the other at the surface of the body. The animals survive in perfect health for many weeks or months, and repeated samples of blood may be taken without trouble and without pain to the animals from any or all of these veins simultaneously. A fair amount of metabolic research has already been carried out by London and his colleagues in Russia, and by Haberland (1926) and György and Kleinschmidt (1927) in Germany. By this or other methods we may discover much that is unknown at present of the various metabolic substances carried to the liver, many obviously necessary for the body, but some almost certainly toxic.

HAEMOCHROMATOSIS, HEPATIC AND BILIARY CIRRHOSIS

One fact on which we have already a considerable amount of information is that both liver and spleen are certainly much interested in the metabolism of iron and of haemoglobin. Here a number of important, but in many ways as yet unconnected, points arise, some of which may suggest the clue to the problem we are attempting to solve. I give them now in sequence in the hope that they may excite interest and encourage future work.

1. The histological structure of the enlarged spleen in hepatic cirrhosis is interesting. There are few actual degenerative changes, and the cells of the reticulo-endothelial system are active. Deposits of iron pigment or haemosiderin are constantly found in both liver and spleen in hepatic cirrhosis. Blood destruction is in excess in advanced cirrhosis, and both anaemia and latent jaundice may be present.

2. The extraordinary type of cirrhosis hepatis known as bronzed diabetes, or haemochromatosis, must be remembered. In this disease there are enormous deposits of organic iron in the liver, spleen, and lymph glands, and a cirrhosis of both liver and pancreas. Mallory's suggestion that this disease is in some way related to copper poisoning comes to mind, as does also the recently described close association of copper and iron in the treatment of anaemia.

3. Certain points concerning biliary cirrhosis and the so-called hypertrophic biliary cirrhosis of Hanot are of much interest. There are grave and growing doubts whether this condition ought to be described as a separate disease at all, but this point need not detain us. Here, however, we have at any rate a type of cirrhosis occurring in young people with great enlargement of liver and spleen, little portal obstruction, and early and persistent jaundice. The resemblances to some forms of chronic haemolytic or acholuric jaundice are striking, and are also enhanced by the fact that both diseases have a pronounced familial incidence. Finlayson (1899) has reported three cases of biliary cirrhosis in one family, and Boix (1893) and Boinet (1898) have described splenic enlargement without symptoms in other members of a family in which a case of biliary cirrhosis occurred. Moreover, in biliary

cirrhosis "crises" occur (just as in acholuric jaundice and Addisonian anaemia), with increase of the hepatic and splenic enlargement and deepening of the jaundice. Chronic pancreatitis is said to be a constant feature of biliary cirrhosis, a point of resemblance to haemochromatosis.

It is curious that manganese salts bring about biliary cirrhosis in animals (Findlay, 1924, Hurst and Hurst, 1928). Casamajor (1916) has also reported biliary cirrhosis in a fatal case of manganese poisoning. It is still more curious (Rolleston and McNee, 1931) that the symptoms of manganese poisoning are very similar to those of progressive lenticular degeneration, a remarkable nervous disease associated with cirrhosis hepatis, and which, moreover, is commonly familial but not hereditary. All these facts are merely set down as parts of a jig-saw puzzle still to be solved. They all touch at various points, and by future work we may find the key to fit them together.

In concluding this section I feel I must do justice to Epplen's earlier work (1922) by a direct quotation from him:

"In closing I cannot resist the temptation to give expression to a thought, growing into a conviction, that we must regard cirrhosis of the liver as a disease closely allied to diseases of the blood."

If this be true, we can see how liver and spleen must be intimately associated in cirrhosis of the liver.

BANTI'S DISEASE

I have previously touched on this problem in papers dealing with diseases of the spleen, in one of which (1929) I wrote:

"The actual account of Banti's own cases is far from clear, and various alterations in description were made by him in his subsequent papers. It would require much space to give an adequate and comprehensive account of Banti's disease as he described it, and to contrast it with other forms of splenomegaly. It is hoped that this question may be dealt with in a later paper."

The disease being one affecting both liver and spleen, now seems a suitable occasion to deal with it in some detail. Banti, as must again be emphasized, did not adhere rigidly to his opinions in all the papers written by him, in several languages, from 1894 onwards. Two of his most important contributions were published in German in Ziegler's *Beiträge* (1898), and in *Folia Haematologica* (1910). The latter, which is his final communication, is the most detailed of all, and at the end of it he attempts to answer the many criticisms which had been levelled at his preceding papers. There is actually, as I have gradually realized, very great confusion and indefiniteness among British physicians as to what Banti himself claimed as the essential clinical and pathological features of this disease. This is no doubt in part due to Banti's own variations in description, and I feel that a short time spent here in describing his observations will not be out of place.

Banti admits that the term "primary," or "cryptogenic," is "a collective name for a genus of diseases, including many species"; but he always holds strongly that the disease described by him has such definite clinical and histological characters as to separate itself clearly from the others. His own observations began in 1882, but it was not until 1894 that he was able to pick out from the group of primary splenomegalies the type soon to be associated with his name. In his final paper (1910) he summarizes the main characters of this affection, basing his conclusions chiefly on fifty cases observed by himself.

AETIOLOGICAL FACTORS

Sex: Thirty-two females; eighteen males. Age: Two, 10 to 15 years old; seventeen, 15 to 25; fifteen, 25 to 35; eleven, 35 to 45; and five, 45 to 55. The youngest was 12 years, and the oldest 55 years old. Previous diseases:

Nothing characteristic. Malaria, syphilis, hepatic and gastric disease, alcohol, dietary factors, and locality—all could be excluded or were without influence. *Heredity*: No two cases occurred in one family. *Locality*: No difference between the mountains and the plains.

SYMPTOMATOLOGY

The disease always follows a chronic course, extending over several years at least. For clearness of description Banti divides the clinical course into three phases or stages, but he notes that this division cannot be held too rigidly.

Phase I

Onset gradual. A feeling of weight or pain in the left hypochondrium finally leads to the discovery of an enlarged spleen. In other instances the signs and symptoms of anaemia lead to investigation and discovery of the splenomegaly. Splenic enlargement slowly but gradually increases, until in some instances the organ may reach the pelvic brim. The spleen is smooth and painless (except when perisplenitis occurs), and the shape, with the characteristic notch, is retained. The symptoms associated with the splenomegaly during this phase are anaemia, weakness, and dyspnoea.

The anaemia is important, and of three types: (a) of slow development and progress, with remissions and exacerbations (haemoglobin may be down to between 30 and 50 per cent.); (b) appearing very late only, with haemoglobin never below 60 to 70 per cent.; (c) no real anaemia present, but only weakness and dyspnoea. The liver during this phase is unchanged, and gastro-intestinal symptoms are absent. The common duration of this first phase is three to five years, but may be as long as twelve years.

Phase II

The onset of this period is shown by changes in the urine, which is diminished in amount, of high specific gravity, and contains urobilin. The liver begins to enlarge, is smooth and painless, and soon extends to two to three fingerbreadths beyond the costal margin. No jaundice or ascites. Anaemia often increased. The size of the spleen remains as in the first phase. The duration of this phase is inconstant. At first Banti believed its average length was twelve to eighteen months, but from experience he recognized that this was often an underestimate.

Phase III

This period is marked out by the onset of ascites, unassociated with pain or fever. The liver decreases in size and recedes behind the costal margin. The size of the spleen remains unaltered. Urine scanty, and contains urobilin or, rarely, bilirubin. Skin often lemon yellow, but never deep jaundice. During this stage haemorrhages from the stomach or bowel are frequent. Death ensues in this phase from haemorrhage or hepatic insufficiency. Banti freely admits that patients in this third phase cannot be distinguished from those suffering from advanced atrophic alcoholic cirrhosis.

HAEMATOLOGY

Banti made very complete observations on the blood, but admits that there is not any characteristic blood picture. The red corpuscles are diminished, but not below three millions per c.mm. The haemoglobin percentage is reduced more definitely, and the lowest figure recorded is 35 per cent. The colour index is always less than 1. Morphological changes in the red blood cells are rare, but at times anisocytosis and poikilocytosis are found. The leucocytes are generally diminished (leucopenia) to between 1,500 and 3,500 per c.mm., with a relative lymphocytosis. Nothing was found to suggest active blood destruction, and this was confirmed according to his observations by the absence of haemosiderin in the liver or spleen.

PATHOLOGICAL ANATOMY

"The characteristic lesions are in the spleen, liver, and almost always in the splenic vein and portal vein." It is often forgotten that a lesion in the wall of these veins was well recognized by Banti. The changes in the spleen are distinctive. The organ is enlarged, smooth, and of normal shape. The capsule is often unchanged or may be thickened. The weight is seldom below 1,000 grams, but may be up to 3 kilos. In section, the parenchyma is firm and red and

the Malpighian bodies are well seen. The histological appearances are identical in all the three clinical stages of the disease.

"*Fibroadenie*."—The chief change affects the splenic reticulum, the fibres of which become thickened so as to form a distinct meshwork. As the fibres become thicker the meshes are narrowed until finally only tiny holes are left. This is the change named by Banti "*fibroadenie*," because, as he states (1910), "*das lymphatische Stroma sein reticuläres und adenoides Aussehen behält*." This term, as used by Banti and quoted without explanation by all subsequent writers, requires some consideration. *Adenia* (Fr. *adenie*) is an old word to express enlargement of lymphatic glands, but we are now more familiar with the terms "*adenitis*" (inflammation of lymphatic glands) and "*adenoid*" (gland-like). In Banti's time the spleen was still considered as one of the lymphatic organs of the body, so that by "*fibroadenie*" he presumably meant a fibroid enlargement of the spleen, the fibroid change affecting the reticulum. It will be noted that the term "*fibroadenie*" is retained even when Banti is writing in a language other than French. He makes a strong point that the change in the spleen is not an *adenitis* or inflammation, and that the *adenoid* or gland-like structure of the organ is perfectly retained. There is not any formation of granulation tissue, and there is an absence of all cellular reaction. The lesion appears to be the result of "*einer chronischen Reizung [irritation] der lymphatischen Organe*." The characteristic change of "*fibroadenie*" thus affects the splenic reticulum, and occurs in two situations—namely, in some of the Malpighian corpuscles only, and scattered irregularly throughout the whole pulp. In any affected spleen the process is always seen at different stages of development, and this is especially true in the Malpighian follicles. Banti is of opinion that the lesion begins just outside the follicles in the penicillar arterioles and spreads into the follicles gradually. The arteriole may be normal, but is often the seat of hyaline change. It is, however, just surrounding the arterioles that the reticular fibres are thickest and the meshes smallest. The last stage of the process, which is rarely seen, shows the whole follicle converted into a sclerotic nodule. The only other changes noted in the spleen consist of swelling and degeneration of scattered cells in the pulp and in the follicles.

The Liver

The liver in the first stage of the disease is unaltered. In the second stage it is definitely enlarged and the intrahepatic branches of the portal vein are thickened and sclerosed. At this period, also, the connective tissue in the portal canals begins to increase greatly. In the third stage the organ is markedly diminished in size, and its surface is uneven and nodular. Banti simply describes the changes of this stage as identical with those of an ordinary portal cirrhosis of the Laennec type. Siderosis is absent in both liver and spleen.

Splenic and Portal Veins

Very often, but by no means constantly, patches of "*chronic sclerotic endophlebitis*" are found in the splenic vein and even in the portal vein. These changes have been found even in the first clinical stage of the disease, and in the third stage slight changes of similar type have been discovered in the mesenteric veins. No mention is made of complete thrombosis of the splenic or portal veins in any of his cases.

BANTI'S CONCLUSIONS

In concluding his description of the pathology Banti affirms that the "*fibroadenie*" of the spleen: (1) precedes the onset of hepatic cirrhosis; (2) is not proportional in severity to the hepatic cirrhosis; and (3) is not influenced in any way by the cirrhosis. Attempts by bacteriological and other investigations to elucidate the cause of the disease were negative, and he finally states his hypothesis of the pathogenesis as follows. An unknown infective agent localizes itself in the spleen. In the reticulum it produces a "*fibroadenie*," while in the cells of the pulp and of the lymph follicles purely degenerative changes ensue. Since the changes in the reticulum are more severe and more intense than the cell degeneration, and since they are most marked around the penicillar arterial branches, it may well be considered that the lesion begins in this last situation. The causative agent on the basis of this hypothesis would be one brought to the spleen by the arterial

blood. Whatever the agent be, it induces neither cellular exudation nor granulomatous tissue formation.

It will be noticed that this hypothesis does not quite agree with his previous view that the lesion results from some "*poison*" actually produced in the spleen itself.

CRITICISMS OF BANTI'S DESCRIPTION

Since Banti's various descriptions of his disease as a clinical, and especially a pathological, entity were published, criticism in many forms has arisen. Eppinger rather amusingly divides the literature into two groups: (1) those who accept Banti's views—generally clinicians—and (2) those who reject them—generally pathologists.

To this suggested generalization there must be many exceptions, and one of the earliest and best known among the clinicians was the late Sir William Osler, who wrote:

"Banti's disease is simply chronic splenic anaemia plus features of cirrhosis of the liver, which represent a terminal stage of the disease. Banti's merit consists in calling attention to this important aspect, but, after all, these secondary changes in the liver are somewhat rare, and, as my records show, the haemorrhages, ascites, and even the jaundice may be present without existing cirrhosis."

Why do pathologists reject Banti's disease as an entity?

The reason is because the changes in the spleen which Banti described in his last paper as pathognomonic of his disease occur in many different types of enlarged spleen, even in the spleens of patients suffering from ordinary alcoholic cirrhosis. Banti himself writes that similar changes may occur in leukaemia and "*polylymphomatosis*." The spleen changes are thus not peculiar, although in the spleens studied by Banti they were evidently well marked. I have personally never seen a case which agrees really closely with Banti's clinical and pathological description, and Continental authors such as Eppinger (1920) have also emphasized its extreme rarity.

Banti's clinical description and his criteria for diagnosis are far too rigid, and it seems certain that "*Banti's disease*" should be classified simply as the late stage of splenic anaemia, or, what is perhaps even more apt, as an unusual type of ordinary portal cirrhosis in which high portal blood pressure and changes in the spleen precede the onset of marked fibrotic changes in the liver.

The writer wishes to suggest again, as he has already done elsewhere, that the term "*Banti's disease*" should be deleted from our nomenclature, and all suitable cases classified in the category either of splenic anaemia or of hepatic cirrhosis.

RETICULO-ENDOTHELIAL DISEASES OF THE LIVER AND SPLEEN

This group of diseases, which affects the liver and spleen, and, in addition, the bone marrow, has already been referred to at the beginning of these lectures as that in which the greatest progress in elucidation has been made during the twenty years which have elapsed since the description of the reticulo-endothelial system. It was to this group especially that Eppinger devoted his monograph in 1920, but great advances in our knowledge have taken place since he wrote. We are still far from possessing a complete insight into the functions and metabolic activities of this system of cells, but one function which is very striking is their power to ingest various substances, especially pigments and lipoids, which are formed within the body during the activities which we call metabolism. These cells act as phagocytes, and possibly in other ways in the defensive mechanism of the body; they are also concerned in the establishment of immunity to infections, whether by ordinary pathogenic bacteria or by protozoa.

As a result of overactivity in any of these functions, the reticulo-endothelial cells proliferate and increase enormously in number. The hyperplasia in the bone marrow

is seen only by the pathologist, but indirectly may show itself to the clinician by changes in the blood picture as seen in stained films. Proliferation of these cells in the spleen, which in man is their chief situation in the body, results in splenomegaly, and this group of splenic enlargements is of great importance because of its frequency. In the human liver the reticulo-endothelial system is represented by the cells of von Kupffer, which form a very incomplete lining to the portal venous sinusoids or capillaries. Proliferation of these cells cannot be expected as a rule to lead to great hepatic enlargement, but nevertheless the liver may sometimes be considerably increased in size in this group of diseases. The conditions are different in the livers of some experimental animals—especially in birds, in which the spleen is relatively very small and the liver large. It was in the liver of birds that I was first able to demonstrate the enormous proliferation of reticulo-endothelial cells that may occur in an experimental haemolytic anaemia (McNee, 1914).

In man, as has been stated, reticulo-endothelial hyperplasia in the spleen is recognized clinically by splenomegaly, and in my Lettsomian Lectures on diseases of the spleen (1931) I made an attempt to describe and differentiate histologically the main types, and the characteristic lesions, of the splenomegalies associated with reticulo-endothelial disturbances. I have not, as will be ultimately essential, investigated the bone marrow systematically in this group of diseases. For this purpose it is evident that a large number of complete necropsies in such cases would be required. In the liver, proliferation of the reticulo-endothelial cells only rarely causes hepatic enlargement, and the changes which usually ensue are brought about through the transference by the Kupffer cells of the material which they have ingested to the contiguous polygonal glandular cells. In this way the glandular cells may be damaged in varying degrees of acuteness and severity, leading to marked pathological changes in the liver.

There are three chief divisions of the human diseases which affect the reticulo-endothelial system in liver and spleen.

HAEMOLYTIC ANAEMIAS

Pernicious (Addisonian) anaemia and chronic haemolytic (acholuric) jaundice may be taken as examples of diseases in which an excessive destruction of red blood corpuscles occurs within the body, but we have no reason for suggesting that the cause of the haemolysis is in any way the same in the two conditions. At the present time our position with regard to both of these diseases can fairly be described as exciting. I need not refer to the recent great advances in the treatment of pernicious anaemia, while the clinical cure of chronic haemolytic jaundice by splenectomy has been emphasized recently by our President (Dawson, 1931) in a most important contribution to the literature of this disease.

It is instructive to contrast some of the points illustrated by these two diseases. Both are obviously haemolytic anaemias, and both are therefore instances of haemolytic jaundice—in the one, the disease generally latent, in the other, commonly overt. In both diseases red blood corpuscles are destroyed in the body, chiefly, we believe, by ingestion within cells of the reticulo-endothelial system. In Addisonian anaemia the cells which are destroyed are defective in size and shape, but not in any other way which we recognize at present. In acholuric jaundice the cells destroyed are apparently normal in shape and size, but to us appear defective only in respect of a purely artificial test of fragility, applied to them outside the body and when separated from the plasma. I refer, of course, to their undue fragility in descending dilutions of solutions of sodium chloride when compared with the red cells of a normal individual. It is interesting to remember that in both of these diseases the periods of

haemolysis seem to be intermittent, and there must be some good reason for this if we could only find it. The main difference which we know at present in the pathology of the two diseases is that in untreated Addisonian anaemia the bone marrow is very abnormal, whereas in acholuric jaundice there is simply a moderate erythroblastic reaction.

The pathological histology of the liver and spleen in these two diseases shows an interesting contrast. In acholuric jaundice the liver is unaltered in size, and the only abnormality found is an increase in the number and size of the Kupffer cells, which contain the pigment and debris of broken-down red blood corpuscles within them. In Addisonian anaemia identical changes are seen in the Kupffer cells, and the only additional point often noted in the liver in this disease is the presence and multiplication of erythroblasts in the sinusoids (myeloid metaplasia).

In the spleen from a patient suffering from acholuric jaundice the histological appearances are remarkably constant and unmistakable. The pulp spaces are engorged with red blood corpuscles, so numerous that the actual structure can only be made out satisfactorily when the spleen has been removed by operation and allowed to empty itself of blood before fixation. The blood sinuses are then seen to be relatively empty, while the pulp is absolutely stuffed with red blood cells of normal size and shape. Many of the reticulo-endothelial cells contain red blood corpuscles, whole or broken up, or the haemosiderin pigment derived from them. In Addisonian anaemia the filling of the pulp spaces with erythrocytes, even in cases in which the spleen is considerably enlarged, is less marked; but phagocytosis by reticulo-endothelial cells is abundant, and haemosiderin can always be demonstrated by the prussian blue reaction. Here again the main contrast is the presence of islets of active blood regeneration (myeloid metaplasia), the amount of which, however, varies considerably in different cases of the disease.

In both of these diseases, therefore, the liver and spleen are involved in one way which we know—namely, through the activities of the reticulo-endothelial system in the destruction of red blood corpuscles and the metabolism of haemoglobin. So far as we are aware, the glandular cells of the liver are not damaged in either disease. The two diseases are both well known, and are therefore taken as contrasting types, but it is evident that there are many other haemolytic anaemias affecting mankind in which the reticulo-endothelial cells are also involved.

DISEASES CHARACTERIZED BY LIPOID CHANGES IN RETICULO-ENDOTHELIAL CELLS

This group of diseases is of very great interest, and includes such conditions as Gaucher's disease, Pick's disease, Niemann's disease, and the hypercholesterolaemic splenomegaly sometimes found in diabetes mellitus.

The fact that the cells of the reticulo-endothelial system readily take up cholesterol esters was first shown in animals by Anitschkow (1914), but it had been noted as early as 1889 by Coats of Glasgow that in some cases of diabetes associated with lipaemia the spleen pulp was full of large foamy cells. Since these observations a number of spleens from cases of diabetes mellitus have been found to contain abundant cholesterol esters in their reticulo-endothelial cells, and an excellent account of "hypercholesterolaemic splenomegaly," with a full bibliography, has been given by Dyke (1928). A particularly interesting point for us is the frequent association of this splenic change with biliary cirrhosis of the liver. In Dyke's case this was well marked; but the polygonal cells of the liver appeared undamaged, and the Kupffer cells did not contain any fatty or lipid material. This last fact is in a way contrary to expectation, and the cause of the biliary cirrhosis with hepatic enlargement remains a

puzzle. A further point of interest in these cases is Dyke's claim that in his case the hypercholesterolaemia, or lipaemia, was due to the existence of a chronic interstitial pancreatitis. This at once recalls to us the clinical and pathological features of bronzed diabetes or haemochromatosis—pancreatitis; hepatic cirrhosis, and enormous deposition of haemosiderin. Here again are remarkable points of contact, but the puzzle remains to intrigue us.

In Gaucher's, Pick's, and Niemann's diseases the reticulo-endothelial system is involved in the metabolism of lipid substances, which are apparently different, although closely related compounds in each disease. The splenic enlargement is due to enormous hyperplasia of the reticulo-endothelial cells, which are filled with the special lipid characteristic of the disease. Here again we are dealing with diseases involving both liver and spleen, for in the liver the Kupffer cells proliferate enormously, and, unlike Dyke's description of the changes in hypercholesterolaemic splenomegaly, contain the lipid material. In all of this group of diseases the liver cells may be extensively damaged, and hepatic cirrhosis may result. I have referred elsewhere to an unpublished case of A. R. Rich of Baltimore in which not only the liver and spleen were extensively involved, but the bone marrow was so infiltrated with lipid-containing reticulo-endothelial cells that the ivory bone was invaded and a pathological fracture resulted.

DISEASES, ASSOCIATED WITH CHRONIC SPLENOMEGALY, WITH MARKED RETICULO-ENDOTHELIAL HYPERPLASIA AND GIANT-CELL FORMATION

This group has interested me very greatly, since included in it are some of the largest splenomegalies in my own extensive collection. No one, so far as I am aware, has been able to make a complete examination of such cases. My own observations so far are confined to spleens removed by operation, and I am unable to give any histological account of the changes in the liver. It is certain, however, that in several instances the liver was cirrhotic at the time of the operation. The histological changes in the spleen are almost characteristic. There is enormous proliferation of the reticulo-endothelial cells associated with increase in the reticulum, so that, as I have described it, the spleen becomes a large heavy solid organ. In association with these changes giant cells appear, which may be very numerous and may almost suggest the appearance of a myeloid sarcoma. The causation of this condition affecting both liver and spleen is quite unknown, and I have only been able to suggest that the changes might be due to some chronic inflammation of unknown aetiology and of very long standing.

CONCLUSIONS

In these lectures I have tried to interest physicians in a somewhat difficult problem of clinical medicine. It will be observed that my whole thesis centres around "the portal circulation," and some of the organs connected therewith. I have confined myself here to a consideration of two organs—the liver and the spleen—on which I have carried out personal observations, and about which I therefore have something to say. But the scope could obviously be extended to include diseases of the whole intestinal tract.

We know a good deal about the dynamics of the systemic and pulmonary circulations, but far less about the portal. We are familiar with the clinical results of alterations in the systemic and pulmonary blood pressures, but so far we know only the very gross and late effects of increased portal pressure. The metabolic problems with which the systemic and pulmonary circulations are concerned are, on the whole, simple and clear-cut, and

have been very fully investigated. In the portal circulation, in which all the substances derived from the intestine are carried to the liver, the problems of metabolism are much more intricate and difficult to investigate. So far as the liver and spleen are concerned, the liver is obviously dominant in all ordinary metabolic functions; but the spleen, on the other hand, surpasses the liver in its reticulo-endothelial activities.

Much experimental work has been carried out on different aspects of our subject, but, as usual, the results have gone far ahead of their immediate and direct application in clinical medicine. Isolated researches have, however, already given us valuable clues which we must follow. I have collected some of the most important experimental results in my first two lectures, and in my last lecture have attempted to show how some of them may be applied. I am convinced, from my study of diseases of the liver and spleen, that a new chapter in medicine will ultimately have to be written concerning derangements of the portal circulation and their causes.

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THE PROGNOSTIC VALUE OF SPINAL ANAESTHESIA IN VASOSPASTIC DISEASES OF THE LOWER LIMBS

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In any study of the circulatory disturbances of the limbs there arises at once the difficulty of estimating with sufficient exactness the degree to which the disease has progressed and the functional value of the circulation in the affected limb.

Viability and function of a limb are possible within a wide range of variations in the amount and pressure of the blood which flows through it. Although colour changes and claudication may indicate roughly that all is not well with the circulation, it is essential to have more exact knowledge as to what extent the diseased vessels are still pervious and remain able to react to nervous im-