Croonian Lectures

ON

LIVER AND SPLEEN: THEIR CLINICAL AND
PATHOLOGICAL ASSOCIATIONS

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LECTURE I

The early observers in clinical medicine must have recognized the frequent association of enlargement of the liver and spleen, but there could be no real progress towards discovery of the reasons for this association until the development of the compound microscope made possible the study of cellular pathology. The enormous simultaneous enlargement of the two organs in the disease that we now recognize as leukaemia must have been a great puzzle. Hardening of the liver in cirrhosis was noted by Vesalius, Harvey, and Morgagni, but changes in the spleen in this disease did not at first attract attention.

When cellular pathology developed in the time of Virchow the main characters of the lesion in cirrhosis hepatis were soon made out; but the nature of the frequently associated splenic enlargement has remained obscure even to the present day. The introduction of Ehrlich's methods of staining the cellular elements of the blood and blood-forming organs enabled rapid strides to be made in haematology, and the different types of leukaemia were soon identified. It was later found that in some diseases resembling leukaemia on account of the hepatic and splenic enlargement the characteristic changes of leukaemia were absent from the blood. Such diseases, at first known as pseudo-leukaemias, have now been to some extent differentiated from one another, and include, for example, the clinical conditions known as splenic anaemia and chronic haemolytic (acholuric) jaundice. Among the early investigators of this group was Banti of Florence, who claimed to be able to distinguish, both on clinical and on histological grounds, a variety of pseudo-leukaemia or splenic anaemia which has since remained associated with his name.

It thus gradually became evident to clinicians and pathologists that there were at least two great groups of diseases in which the liver and spleen were commonly involved together. On the other hand were diseases of the blood and blood-forming organs (anaemias and leukaemias of different kinds), and on the other were diseases, such as hepatic cirrhosis, in which the association of a lesion in the two organs was evidently of an entirely different nature. Progress in our knowledge of the interrelations of the spleen and the liver in hepatic cirrhosis has been, and still remains, very slow.

DISEASES INVOLVING RETICULO-ENDOTHELIAL
SYSTEM

The clue, however, to the second group of diseases was given by Aschoff and his pupils (1911 onwards) in their development of the conception of what is now universally known as the reticulo-endothelial system of cells. As soon as the physiological activities of these cells were recognized it at once became possible to link up a number of diseases, some of great interest for our subject, which previously had not appeared to bear any direct relation to one another. The three chief situations in the body in which reticulo-endothelial cells are numerous are the liver, the spleen, and the bone marrow; but the relative abundance of the cells in these situations is not identical in all animals. This, as will be seen, has an important

bearing on the interpretation of animal experiments. The first, and up to now the only, attempt at a reasoned correlation of the diseases involving the reticulo-endothelial cells in these three situations was made by Eppinger, who in 1920 published a monograph entitled *Die hepato-lienalen Erkrankungen*, with a subtitle *Pathologie der Wechselbeziehungen zwischen Milz, Leber, und Knochenmark*. The manuscript of this monograph, as Eppinger states, was first sent to the publishers in July, 1914, but delay due to the war ensued, and the manuscript was revised, and added to, before publication more than five years later.

It is in a sense unfortunate that no concise title has been found in our language to describe adequately diseases involving the reticulo-endothelial cells in liver, spleen, and bone marrow. The term "hepato-haemopoietic diseases" has been suggested, but is too cumbersome for ordinary usage. "Liver-spleen diseases," the exact translation of the chief title of Eppinger's book, is ugly, but for lack of something better has already come into fairly common use. It is inaccurate, or rather incomplete, in that it fails to include the important third organ which is involved—namely, the bone marrow. Since 1920, when Eppinger's monograph appeared, the activities of the reticulo-endothelial cells in many processes of normal and pathological metabolism have been extensively explored. This is particularly true in relation to the metabolism of haemoglobin and its derivatives, such as bile pigment, and also in relation to various lipid substances. The group of diseases in which the liver, spleen, and bone marrow are intimately associated in virtue of the reticulo-endothelial cells which they contain is now fairly easy to define, and good progress in their elucidation can be reported. In the light of much new work, in some fields of which I have myself been interested for a number of years, a reconsideration of the problems and associations of these diseases is now due.

DISEASES WITHOUT INVOLVEMENT OF RETICULO-
ENDOTHELIAL SYSTEM

The other large group of diseases affecting liver and spleen in which, so far as we know, the reticulo-endothelial system of cells does not play any important part, provides problems which are much more difficult to solve. Two main lines of thought occur in considering the possible explanations of this group.

The association of disease in the two organs might depend on: (1) Some *anatomical* interrelationship which has been disturbed. The two organs concerned are in a particular and peculiar relation to one another in their vascular connexions. Both are organs on the portal venous system, which is devoid of valves, and the blood from the spleen must pass through the liver before reaching the vena cava and the heart. (2) Some *metabolic* interrelationship which has been disturbed. In order to deal fully with this possibility a complete knowledge of the functions of the two organs would be essential, and that we do not possess as yet. The much-discussed problems of the action on the liver of metabolic toxins or poisons, using these terms in the widest sense, are obviously included here. On general grounds it would be expected that the liver, which is by far the more important organ of the two in metabolism, would play the predominant part and be, in most instances, the primary seat of disease. But, as will be seen, although the order of involvement is not yet clear, there are diseases in which the question of whether the liver or the spleen is implicated first is of great clinical and therapeutic importance. There is, in fact, no reason to exclude the possibility that some metabolic activity of the spleen, known or as yet unknown, may be the cause of a primary splenic disease which subsequently affects the liver.

INTERRELATIONS BETWEEN LIVER AND SPLEEN

It is thus very evident that, in approaching the very difficult problem of the interrelations between the liver and spleen in disease, we must summarize and take stock of our knowledge, or lack of knowledge, of certain important fundamental points. These include, first, details concerning the essential histological structure of the two organs involved, including the reticulo-endothelial elements contained within them; secondly, a knowledge of all the vascular connexions of the two organs, which implies a thorough study of the whole mechanism of the portal circulation and of the factors controlling the blood flow through the liver and spleen; and thirdly, a consideration of some of the important physiological activities of the two organs.

In these lectures it is proposed first of all to consider carefully the fundamental problems which I have just referred to, and then to apply the existing knowledge, so far as we are able, to the clinical problems of diseases of the liver and spleen in man. While doing so, special attention will be paid to the condition generally known in the past as Banti's disease, since there has been great controversy concerning the exact status of this affection.

Whereas it might well be thought that the microscopical anatomy of all the important organs in the body was completely and exhaustively worked out, it must be recognized that this is far from being so. In the latter half of last century, with the advent of the compound microscope and the consequent rapid development in knowledge of normal and pathological histology, the chief facts concerning the structure of most organs were soon known; but during the present century, in consequence of the attention directed to the advances in biochemistry, bacteriology, and allied sciences as applied to medicine, the study of disease from the purely morphological standpoint has tended to fall into the background. Great strides have indeed been made in the study of pure physiology, but it still remains as necessary as before to correlate disordered function with abnormal structure in order to understand the origin and natural history of disease. Both in the liver, and more particularly in the spleen, there is still much room for improvement in our exact knowledge of structure.

THE LIVER

In this country we are chiefly indebted for our knowledge of structure to two observers—Kiernan (1833) and Beale (1856-89). There are various discrepancies between the views of these two men, particularly about the structure and importance of Glisson's capsule, but in the main their writings have formed the basis of the descriptions given in all textbooks of histology for many years. It has become necessary, with the development of experimental work and new knowledge of hepatic physiology, to re-examine the observations of these older writers with much more perfect technique than was available to them. All the essential parts of hepatic structure require review. In 1925 I reinvestigated the structure of the hepatic lobule in order to support hypotheses concerning the relations of the liver to bile pigment formation, and published a schematic plan to illustrate as simply as possible the principle on which I believed the hepatic lobule to be built up. One of the main alterations from the descriptions of Kiernan and Beale lay in the addition of the reticulo-endothelial cells (first described by von Kupffer in 1876) to the essential lobular structure and their anatomical relations to the portal blood capillaries and the polygonal glandular cells.

The peculiar double vascular supply of the liver by the large portal vein and smaller hepatic artery naturally

attracted attention long ago, and the first attempts to solve the problem of how and where these two streams meet within the liver were made by Betz in 1863, and by Johannes Gad ten years later. So important has the question of the interrelations of the portal vein and hepatic artery circulations proved in recent experimental work on hepatic disease, and so impossible is it to separate the purely anatomical from the physiological problems, that a separate section is devoted in these lectures to the vascular circulation through the liver in all its aspects.

The supporting tissues of the liver also require consideration, particularly in reference to their influence on the vascular supply of the organ in normal and pathological circumstances. Cameron and Mayes (1930) give a most interesting account of the historical views concerning Glisson's capsule, the chief supporting structure of the liver. They state, following Kiernan's work chiefly, that the older writers seem to have had "a singularly clear view of the importance of Glisson's capsule as the basis of the vascular architecture of the liver." First referred to by Waleus (1640), the true capsule of the liver received its classical description by Glisson (1654), who fully recognized it as a structure separate from the peritoneal coat of the liver, and suggested that its intrahepatic prolongations might be concerned with supporting the weight of the heavy glandular organ. Glisson, it must be remembered, was unaware of the lobular structure of the organ, which was not pointed out until Malpighi (1699) described the shape of the lobules of different animals, and at the same time indicated how they were separated from one another by prolongations of Glisson's capsule carrying the blood vessels. Laennec (1802), the pioneer in the study of hepatic cirrhosis, was naturally interested in Glisson's capsule and its ramifications within the liver, and in trying to interpret the old views of the physiology of digestion he suggested that Glisson's capsule might yield to allow the portal blood vessels to carry an increased supply of blood during the course of digestion. It is curious to notice how later physiological knowledge concerning the nervous control of the portal vessels, subsequently referred to, bears on this old hypothesis of Laennec.

Kiernan and Beale differ widely in their views concerning Glisson's capsule and its intrahepatic distribution; and because of problems which inevitably arise in connexion with hepatic cirrhosis it is essential to state briefly their opposing opinions. Kiernan describes the portal canals of the liver as containing

"the hepatic ducts, the portal veins, the hepatic arteries and the vaginal branches of all these vessels with the nerves and absorbents, enveloped in a sheath of cellular tissue first described by Glisson and called Glisson's capsule."

He affirms further that "Glisson's capsule is not mere cellular tissue; it is to the liver what the pia mater is to the brain." He describes it as finally entering the hepatic lobules and, with the multitude of vascular capillaries, expanding over the secreting biliary ducts. Kiernan was clearly a most accurate observer, and some of his statements, if true, are of such obvious importance, in view of modern work, that their accuracy must be retested. He states, for example, that in the smaller portal canals (not the larger ones) Glisson's capsule is confined to one side, enveloping the artery and bile duct only, while the portal vein lies free from the capsule in direct lateral contact with the interlobular spaces. Kiernan also refers to the extreme vascularity of the walls of the bile ducts, their blood supply being obtained from the hepatic artery. He claimed that these vascular capillaries surrounding the bile ducts return into branches of the portal vein, and not into branches of the hepatic vein. He also put forward the suggestion, which has never been adequately

followed up, that because of their extraordinarily rich blood supply we may almost assume that the bile ducts serve some other function beside that of the conveyance of bile. It was known to Kiernan that many of the larger bile ducts contain in their lining membrane "muciparous follicles," or collections of goblet cells, and these observations must raise questions in our mind concerning the possible functional activities of what has become known to surgeons and pathologists as "white bile."

Beale's opinions, as has been indicated, are somewhat different, and he attaches far less importance to Glisson's capsule. His views, as given on page 60 of his book, *The Liver* (1889), are as follows:

"Facts, however, as I shall endeavour to show, render it necessary to regard this structure from a different standpoint, for in the liver of young small animals not a vestige of this Glisson's capsule can be demonstrated between the lobules, and it is more probable that the capsule itself results from degenerative changes in the superficial lobules at a very early stage of development than that it is specially developed or a distinct tissue for a particular purpose."

It is curious to note here that the embryological studies of Toldt and Zuckerkandl (1876) prove the actual occurrence of such a degeneration in the embryo. Beale also disagrees with Kiernan's observation that Glisson's capsule in the smaller portal canals surrounds only the bile duct and artery. He admits the presence of fibrous tissue between the lobules in the liver of the pig, and also that in old age fibrous tissue tends to appear between the lobules of the human liver, but he is completely opposed to the view which "many authorities have entertained" that Glisson's capsule is developed "as a special structure and discharges a special office."

THE SPLEEN

In my Lettsomian Lectures, "The spleen: its structure, functions, and diseases," delivered last year before the Medical Society of London, I set forth my individual views concerning the minute anatomy of this organ. Since these lectures have been published in the *Lancet* and in the Medical Society's *Transactions*, it would be redundant to recapitulate them now. It is universally agreed that the structure of the spleen is extraordinarily difficult to interpret, and there is still wide divergence of opinion concerning some of the fundamental points of splenic structure. The Malpighian bodies or follicles are universally accepted as potential lymphatic glands, present in some animals but not in others, present sometimes at one period of life and not at another. The spleen pulp is composed, so far as its fixed tissue elements are concerned, of the meshwork of splenic reticulum on which lie vast numbers of reticulo-endothelial cells. There remain the pulp spaces between the reticular meshwork, containing red and white blood corpuscles of all varieties. The chief controversy has been, and still is, concerned with the peculiar vascular arrangements within the spleen, but here again splenic structure and splenic function are so closely interwoven that this matter is considered separately for clearness.

The liver and spleen contrast markedly in their vascular arrangements. Blood is conveyed to the spleen by a relatively very large artery, and returns through a very large and tortuous vein, without valves, to join the valveless portal vein. All splenic blood must pass through the liver before reaching the heart. The liver is unique in that much the greater part of the blood flowing into it, in the "arterial" sense of other organs, is already venous and comes by the portal vein. The hepatic artery is very small in relation to the size of the liver, and as Heyd, Killian, and MacNeal (1924) remind us, almost two-thirds of the blood of this small arterial trunk is deflected away

from the liver through the gastro-duodenal, cystic, and gastric branches of the hepatic artery. The anatomy and physiological control of the blood supply of the two organs may now be considered separately and in detail.

VASCULAR CIRCULATION THROUGH THE LIVER

The double blood supply of the liver has been aptly described by Herrick (1907) as a large-volume circulation with a low pressure (the portal vein) and a small-volume circulation with a high pressure (the hepatic artery). These two afferent vessels have a common channel of exit by the hepatic veins into the inferior vena cava.

Normal Blood Pressure in the Two Circulations

The blood pressure in the hepatic artery is identical with the general arterial blood pressure, is subject to the same variations, and in man is presumably 120 mm. Hg or more. The portal venous pressure is subject to very great variations due to nervous control, as recent physiological experiments, to be described later, have shown. The pressure in the portal vein has never been directly estimated in man, but in the dog varies on an average from 6 to 10 mm. Hg. As the arterial blood pressure in man and in the dog is not very different, it seems probable that the normal pressure in the human portal vein is also of the same order as in the dog. An important problem, to be discussed subsequently, is where and how the two very dissimilar blood pressures in the hepatic artery and portal vein are equalized before the efferent hepatic veins are reached.

Amounts of Blood Carried to the Liver by Hepatic Artery and Portal Vein

In both vessels the inflow is subject to great variations due to nervous control, but it is important to have a general view of the relative and absolute amount of blood flowing into the liver by the two circulations.

Our earliest information on the quantitative relations of the portal flow and hepatic artery flow is due to Burton-Opitz (1908-14), who in experiments carried out on dogs by a stromuhr method found that the hepatic artery contributes from 24 to 44 per cent. of the blood entering the liver. Macleod and Pearce (1914) confirmed these observations, and stated that

"as a general rule we are probably safe in concluding that from 26 to 32 per cent. of the blood which flows through the liver is derived from the hepatic artery."

Barcroft and Shore (1912), in their experiments on cats, estimated the hepatic artery inflow as 39 per cent. of the total.

Quite recently this problem has been reinvestigated by Grab, Janssen, and Rein (1929), who have used a new and very perfect thermo-stromuhr method in which the blood vessels remain undamaged and unopened. With the technique employed they were able to measure readily in dogs, at one and the same time, the amount of blood flowing through the thoracic vena cava, the abdominal vena cava (between liver and kidneys), the portal vein, and the hepatic artery. In five experiments they were able to show that the inflow through the hepatic artery in the dog is from 12 to 22 per cent. of the total inflow to the liver. Dale, Bauer, Poulsson, and Richards (1932) have very recently published an account of experiments in which the livers of various animals were artificially transfused outside of the animal body—these experiments are referred to later in connexion with the nervous control of the hepatic circulation. They showed, incidentally, in transfusion experiments that the hepatic artery contributed in the dog about 25 to 30 per cent. of the inflow to the liver, in the cat about the same amount, but in the goat only about 15 to 25 per cent.

The actual amount of blood carried to the liver by the two circulations has also been estimated experimentally, and results of considerable importance have been obtained. The early work is again by Burton-Opitz (1908-14), who used his stromuhr method in dogs. We need not do more than take his average figures from a number of experiments: the average total blood flow through a dog's liver of about 500 grams is, according to his results, about 420 c.cm. per minute. This proportion is exceeded only by the brain, the kidney, and the thyroid, this last organ receiving the most of all. Grab, Janssen, and Rein (1929), using their very accurate thermo-stromuhr method, have also calculated the blood flow entering the liver of a dog. Their figures are given in rather a different way, and with a different end in view; but in an experiment which is comparable with those of Burton-Opitz they estimated the blood flowing into a dog's liver of 494 grams as 65 c.cm. per minute for the hepatic artery and 340 c.cm. for the portal vein, or a total inflow of just over 400 c.cm. per minute.

Amounts of Blood Coming from Abdominal Organs to Form Portal Venous Inflow

This is an important matter, but the experimental difficulties are considerable. Burton-Opitz is again our chief source of information, and in a series of experiments he obtained the following results; in cubic centimetres per second the figures are: total portal inflow to the liver, 4.92; flow from intestines, 2.74; flow from stomach, 1.23; and flow from spleen, 0.95.

It is thus evident that by far the greatest part of the portal blood comes from the intestines, while the spleen, according to these experimental results, contributes less than one-fifth of the total. The experiments recorded were carried out in dogs, in which animals the ratio of the weight of the spleen to that of the liver is about 1 to 5, or 1 to 6. In man the ratio of spleen weight to liver weight is not very different, so that with all the reservation which must always apply in such circumstances, it seems possible that the human spleen also contributes one-fifth or less of the total portal blood which enters the liver.

The two parts of the intrahepatic circulation having so far been dealt with separately, it is now essential to consider in what ways the portal and hepatic streams of blood may influence one another. This is obviously a most important problem, involving as it does the whole dynamics of the intrahepatic circulation. It is a matter which must directly affect our interpretations of disease in organs such as the liver and spleen, which are situated at the upper end of the portal venous system.

In the discussion of this problem anatomical and physiological considerations are frequently blended in a way which makes it impossible to separate them.

How and Where within the Liver do the Widely Differing Pressures in Hepatic Artery and Portal Vein come to a Common Level?

This very obvious question has attracted attention for many years, but even now its solution is not entirely complete. The anatomical side of the problem has been approached directly by histological methods, and indirectly in a variety of experiments. Some of the latter have been simple transfusions either of human livers removed in the post-mortem room or of livers freshly removed from animals. Some of these transfusion experiments have also been applied to diseased as well as to normal livers (Herrick, 1907), and the results are in consequence important for us. Other experiments have quite recently been carried out with the primary object of investigating the nervous control of different parts of the hepatic

circulation, and these are referred to in a separate section.

It has been known for a long time (Herrick, 1907) that when fluid is injected into a liver through the hepatic artery as much returns by the portal vein as passes on into the efferent hepatic vein. Recently Cameron and Mayes (1930) have reinvestigated this matter by improved methods, using as their injection fluid either milk or lipiodol. The milk stains easily with Sudan III in formalin-fixed frozen sections, while the distribution of lipiodol is clearly seen by the use of x rays. In these experiments it was found that, during continuous perfusion of milk through the hepatic artery, a considerable portion of the milk returns by the portal vein as well as flowing out by the hepatic vein. Almost all the lipiodol injected returned by the portal vein, very little passing on to the hepatic vein. From their observations Cameron and Mayes concluded that, owing to some very close communication between the branches of the hepatic artery and portal vein within the portal canals, it is "easier for fluids to pass from one to the other than from the vessels in the portal canals through the intra-lobular sinusoids to the hepatic veins." A search was made for anastomoses of a direct arterio-venous kind between branches of the artery and vein in the portal canals, but none were found. It has been known since the work of Kiernan and Beale, however, that there is an enormously rich plexus of capillaries surrounding the bile ducts in the portal canals, and this would seem to be the likeliest place for the joining together of the blood from the hepatic artery and portal vein before the actual hepatic lobule is entered at all. The matter unfortunately cannot be taken as definitely settled, and recent work by Olds and Stafford (1930) throws the problem again into the melting-pot. These writers claim that the greater part of the blood from the hepatic artery is emptied into the sinusoids within the lobule, and that the free communication between the arterial and portal venous blood occurs in the plexus of sinusoids within the lobules.

Herrick's perfusion experiments on cirrhotic livers obtained in the post-mortem room gave results strongly in favour of a free communication between branches of the hepatic artery and portal vein in the portal canals. He claimed that in portal cirrhosis this communication is far more extensive than in the normal liver; and that through the dilated intercommunicating capillaries the arterial pressure can, in portal cirrhosis, be transferred to the venous side, causing an increase of portal blood pressure.

Gad's Hypothesis

Some of the very old work on this problem is worth referring to simply for its historical interest. It was done long before vasomotor nerves, or the possibility of nervous control of the circulation, was thought of. The problem, as it presented itself to the old investigators, was how, and to what extent, the one circulation through the liver might influence the other. The first published work appears to be that of Betz (1863), who worked in Ludwig's laboratory on this question. The next publication, to which all writers in the past have devoted great attention but which few can have read because of its rarity, is the inaugural dissertation of Johannes Gad, published in Berlin in 1873, and entitled *Studien über Beziehungen des Blutstroms in der Pfortader zum Blutstrom in der Leberarterie*. Mr. Powell, the librarian of the Royal Society of Medicine, has been fortunate in obtaining a copy of Gad's dissertation, which is now available in the library of that society. Gad was then a young physiologist with pronounced mathematical leanings, and a part of his dissertation deals with the theoretical laws governing the flowing together of two enclosed streams of fluid. The part of his thesis which interests us, although now chiefly

for historical reasons, is the hypothesis he put forward that the arterial and portal venous communications in the portal canal probably meet at an acute angle, leaving a wedge-shaped valve between them at their junction.

Gad's hypothesis is represented in the accompanying figure, and it would explain on purely mechanical grounds

H.A., hepatic artery ;
P.V., portal vein.

a number of points which agree with the results of experiments. From the figure it will be seen that any pressure in the portal vein sufficient to close the valve would shut off all fluid coming by the hepatic artery, whereas if pressure be increased on the arterial side the wedge-shaped valve is insufficient to close the wide portal vein. This hypothesis, as has been stated, fits in well with the observations of Herrick and a number of other observers, including Cameron and Mayes, who have carried out perfusion experiments in livers cut off from nervous control.

The conclusion may be stated that alterations of total inflow or blood pressure within the hepatic artery can, quite apart from nervous control, influence the flow and blood pressure in the portal vein.

Nervous Control of Hepatic Circulation

This certainly must have fundamental effects on both liver and spleen, and, while this section deals with its influence on the liver, its importance to the spleen will be considered subsequently. It seems quite obvious that changes in the blood pressure, in the amount of inflow of arterial and portal blood, and in the outflow from the hepatic veins, must be of notable importance in disease. Moreover, nervous influences or definite alterations in structure must, possibly at different times and at different stages, be the chief factors at work in the production of the increased portal blood pressure, which I believe to be one of the most important aetiological factors in combined diseases of the liver and spleen.

The earliest work on the nervous control of the hepatic circulation was done by von Basch (1875), and by Bayliss and Starling (1894), who showed that stimulation of the splanchnic nerves resulted in a rise of the portal venous pressure. Bayliss and Starling concluded that this must be due to a constriction of the portal circulation at the liver, and this view was also supported by François-Franck and Hallion (1896), who made the additional observation that the volume of the liver diminishes after splanchnic stimulation, even when the hepatic artery has been clamped. The diminution in volume could therefore not be due to any changes in the hepatic artery inflow, but only to constriction of the portal venous system within the liver. Many experiments on this problem were also made by Burton-Opitz (1911 onwards), using his stromuhr method, but his results were on the whole inconclusive.

A new method of approach to the problem had meantime developed by the introduction of adrenaline into physiology by Oliver and Schäfer (1894-5), and the demonstration by Elliott (1905) that this substance could be used as an accurate test of the activity of sympathetic nerves. Edmunds (1915) investigated the effects of injections of adrenaline on the portal circulation, but his results were at the time difficult to interpret. Sometimes

the liver volume diminished, but at other times it increased—even in experiments on the same animal species. Bainbridge and Trevan (1917) made similar experiments in dogs, and found the liver volume always increased, while Clark (1928), on the other hand, declared that the volume of the liver was diminished by adrenaline injections. These opposing results were to a considerable extent cleared up by Griffith and Emery (1931), who showed that in experiments in which the blood pressure of the animal remained high and the circulation good the effect of adrenaline or of splanchnic nerve stimulation was always a diminution in the volume of the liver. On the contrary, in animals in which the circulation was failing and the blood pressure low (that is, in a condition closely resembling shock) the only effect, following both procedures, was an increase of liver volume. McMichael (1932), working in Aberdeen and at University College Hospital, has confirmed the results of Griffith and Emery, and has further shown that in an animal in the state of experimental shock, with low general blood pressure, the splanchnic arterioles and portal venules in the liver are already fully constricted and cannot be influenced directly by adrenaline. In an animal of this kind adrenaline injection causes a rise of arterial pressure, almost entirely as a result of arterial constriction in the limbs, but when this rise of arterial pressure is at its height the previously constricted splanchnic vessels suddenly dilate, allowing a greater inflow to the liver and an increase in hepatic volume.

The evidence now seems complete that stimulation of the splanchnic nerves, or injection of adrenaline, each cause constriction of the branches of the portal vein before they have entered the hepatic lobules. The main effect of splanchnic stimulation is thus a damming back of blood in the portal vein, which in turn leads to a temporary diminution of the volume of the liver. Another factor influencing the intrahepatic circulation has also been engaging attention. It has been shown by Mautner and Pick (1915, 1922, 1929) that there is a mechanism acted upon by histamine and its derivatives which controls the outflow of blood from the hepatic vein by a powerful constricting action. This mechanism has recently been investigated very fully by Bauer, Dale, Poulsson, and Richards (1932), whose paper was published in the *Journal of Physiology* only a few weeks ago. In their work they demonstrate what they have termed a "sluice mechanism" controlling the outflow of blood from the liver, closed or contracted by histamine, and opened either by adrenaline or by sympathetic nerve impulses.

It appears that this sluice mechanism is not present in the liver of all animals, but only in those in which there is an adequate supply of plain muscle fibres in the walls of the hepatic veins. A history of our knowledge of this anatomical point is given by Dale and his colleagues, and it seems clear from the work of Arey and Simonds (1920) that in the hepatic veins of the dog (the animal used in most experiments of this kind) there is a large amount of unstriated muscle fibres in the vessel walls; whereas in some other animals, such as the cat, muscle fibres are apparently absent. In man, according to Elias and Feller (1926), there appears to be a considerable development of plain muscle in the hepatic veins, so that the existence of a sluice mechanism seems probable enough.

This very complicated nervous control of the circulation within the liver has an important bearing on the so-called "blood-depot" function of the organ, referred to in a subsequent section. It seems certain that so complicated a mechanism must also be deranged in a variety of circulatory and hepatic diseases, but here physiological knowledge has gone far beyond the possibility of its immediate usefulness in clinical medicine.

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CLINICAL COMPARISON OF ERGOTOXINE AND ERGOTAMINE

A REPORT TO THE THERAPEUTIC TRIALS COMMITTEE OF
THE MEDICAL RESEARCH COUNCIL*

BY

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The subject of ergot, the method of its preparation and the nature of its active principles, has been the source of more discussion during recent years than probably any other matter in pharmacology. Even now, twenty-six years after the discovery of the active alkaloid ergotoxine, and fourteen years after the isolation of the closely related alkaloid ergotamine, there remains an uncertainty not only with regard to the clinical action of these alkaloids, but also with regard to the part played by other constituents present in the crude ergot, or formed during its manufacture into medicinal preparations. The matter is one which interests pharmacologists and clinicians alike, for the urgent and sometimes desperate emergencies of

obstetric practice demand the use of therapeutic agents whose mode of action is understood, and whose reliability is thoroughly proved.

CHOICE OF METHOD

Since ergot is now no longer used before delivery of the foetus it is difficult to get objective evidence of its action: clinical observations such as the timing of the duration of the red lochia¹ or the measuring of the rate of involution of the uterus² have been shown to be unreliable. A more direct method is called for, such as a recording of the actual uterine contractions. In 1927 Bourne and Burn² published the results of an investigation of the action of oxytocic drugs administered during labour. By means of a bag passed between the foetal membranes and the uterine wall and connected with tubing to a manometer, they were able to make tracings of the variations of intrauterine pressure; the tracings thus obtained showed very clearly the effect of drugs on the uterine activity. The work dealt chiefly with the action of pituitary extract and its dosage, but included three experiments with ergotamine.

The usefulness of this method of investigating the uterine action is limited by certain serious disadvantages. It is sometimes difficult to introduce a bag above the foetal head, and this usually requires an anaesthetic. The patient is frequently very restless during labour, which makes for obvious difficulties, and causes false and erratic recordings. Again, the duration of the experiment is limited by the termination of labour. Lastly, many oxytocic drugs are used, not during labour, but in the puerperium. This is the case with the ergot group, and it is therefore of more interest to record their action at this time than it is during parturition. For these reasons I resolved to modify the method and to try the effect of introducing a bag into the uterus in the late puerperium. As in the previous experiments the bag was connected with tubing to a mercury manometer, and this in turn was fitted with a float by means of which variations of intrauterine pressure were recorded on a slowly moving drum. Before use, the bag and tubing (previously sterilized by boiling) were filled with water to a pressure equivalent to 2.5 cm. of mercury and introduced into the uterus with full antiseptic precautions. The early trials were encouraging, and showed that this apparatus could record the normal contractions of the uterus which take place every ten to twenty minutes, and that the physiological variations such as occur with the act of suckling could also be clearly shown. The seventh day of the puerperium proved to be the most satisfactory, although the sixth and eighth days are almost as good.

At the request of the Therapeutic Trials Committee of the Medical Research Council an investigation was made of the clinical effects of ergotoxine ethanesulphonate; in the experiments to be recorded this alkaloid was contrasted with ergotamine tartrate (femergin or gynergen).

HISTORICAL CONSIDERATIONS

The history of these alkaloids is of interest, for they have been the source of much dispute amongst pharmacologists. A very fair statement of the position is given in a letter by Sir H. H. Dale³ to the *Lancet*. The history is briefly this. In 1906 Carr and Barger isolated an active alkaloid, ergotoxine, the pharmacological effects of which were fully studied by them and by other British workers, notably by Dale. Unfortunately, appeals to clinicians to test the action of this pure substance met with little response, and to this day no adequate clinical trial has been reported. In the meantime, in 1918, Professor A. Stoll, working in the Sandoz laboratories, isolated a new alkaloid—ergotamine—which was found to be very active. This substance was eagerly tried out by German and Swiss clinicians, and ample evidence was soon accumulated to prove its worth: under the

* The ergotoxine ethanesulphonate used in these tests was submitted to the Therapeutic Trials Committee by Messrs. Burroughs Wellcome and Co.