THE COMPLEXITY OF LIVER DISEASE—SURGICAL STEPS TOWARD SOLUTION*

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by
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IN SELECTING A subject for discussion to-day, my mind constantly turned to one or another aspect of liver disease, a field in which my associates and I have long been interested and in which the contributions of British workers have been substantial. It represents, therefore, a common ground for inquiry. For purposes of clarification, I have divided my subject into four major related categories, the circulation of the liver, portal hypertension, ascites, and ammonia metabolism. Each, obviously, will be presented with brevity but in the hope of defining and resolving, in as far as possible, the salient recent problems in surgical physiology and practice.

THE CIRCULATION

It is appropriate that I should begin my discussion with some comments on the hepatic circulation, for the abnormalities of liver disease are largely circulatory, and modification of the vasculature has formed the foundation on which recent therapy rests. The structure of the liver parenchyma is the essence of simplicity, yet its vasculature is both complex and unique. The dual afferent blood supply consisting of the hepatic artery and portal vein distinguishes the liver from all other organs.

Physiologic anatomy

A description of the morphology of the hepatic circulation is not relevant to my discussion. Rather, I wish to emphasise the functional anatomy of the hepatic vasculature as it relates to disease and to surgical treatment. In this regard, the collateral circulation of the liver is important. We all have observed the numerous collateral connections of the portal vein to the systemic circulation, dramatically demonstrated in patients with portal hypertension. Less well appreciated, are the many communications of the branches of the hepatic artery with each other and with vessels of other systems, there being greater than twenty possible routes of collateral blood supply to the liver (Michels, 1953 ; Segall, 1923).

Within the normal liver anastomoses between the three vascular systems have been demonstrated in animals (Wakim, *et al.*, 1942 ; Andrews, *et al.*, 1953 ; Knisely, *et al.*, 1948 ; Prinzmetal, *et al.*, 1948) and it has been suggested that similar intrahepatic shunts are present in man (Berman, *et al.*, 1953 ; Herrick, 1907 ; Mall, 1906). Studies of hepatic

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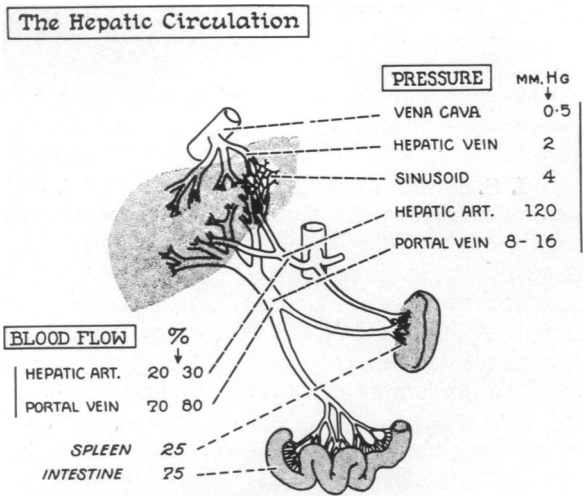

Fig. 1. Pressures in the various components of the hepatic circulation and the amount of blood contributed by each component.

morphology and of blood flow in man, however, have failed to show intravascular communications (Elias, 1949 ; Mann, *et al.*, 1953) and it is my belief that in the normal liver either they do not exist, or if present, are of little functional importance.

The pressure relationships of the hepatic artery and portal vein attest further to the unique nature of the circulation (Fig. 1). The pressure in the small hepatic artery is that of the peripheral arterial vessels, while in the large portal vein it is but eight to sixteen mm. of mercury. In the sinusoids where the two systems join, the pressure is only three to four mm. Thus, somewhere within the hepatic parenchyma, the high pressure, small volume arterial system is brought to equilibrium with the low pressure, large volume venous system. It is certain that the elasticity of the liver is one factor to account for the equalisation of pressures. Moreover, the hepatic arterioles must be capable of maintaining an enormous frictional resistance in order to reduce the high arterial pressure! It is probable that nervous regulation of the blood vessels is primarily responsible for these adjustments, although mechanical influences have been postulated.

As early as 1911, Burton-Opitz measured the amount of blood flowing through the liver of the dog by means of a thermostromuhr. Because of the inaccessibility of the hepatic vasculature in man, it was not until 1945, when Bradley and his associates developed the indirect brom-sulphalein method, that measurement of hepatic blood flow in the human was accomplished. Other methods based on the urea output (Lipscomb, *et al.*, 1947 ; Myers, 1947), the plasma clearance rate of dyes (Simpson,

et al., 1954), and the disappearance rate of colloidal radioactive materials (Dobson, *et al.*, 1953; Vetter, *et al.*, 1953) have subsequently been developed and have furnished valuable information.

In animals, the hepatic artery contributes approximately twenty to thirty per cent. of the blood flowing through the liver, and the portal vein the remaining seventy to eighty per cent. (Fig. 1). About one-fifth of the blood carried by the portal vein comes from the spleen and the remainder comes from the intestinal tract. It is presumed that these figures apply to humans, although measurements have not been made in man. The mean hepatic blood flow in normal man has been found to be 1,310 to 1,800cc. per minute. This represents about twenty-five per cent. of the cardiac output. Undoubtedly, the flow of blood varies according to the needs of the liver and of the body as a whole. For example, during exercise blood flow through the liver falls sharply, while the cardiac output and circulation to other vital organs such as the brain, heart and muscles increases greatly. As a result of its ability to effect rapid and striking alterations in its blood flow, the liver is an important organ in maintaining circulatory homeostasis.

The circulation in cirrhosis

Since the classic descriptions of Laennec (1826) and of Charcot (1877), the striking transformation of the hepatic vasculature in cirrhosis has aroused the interest of pathologists and clinicians alike. As a result of the widespread parenchymal destruction and overgrowth of fibrous tissue, the tiny radicals of the portal and hepatic veins are twisted, curled and distorted beyond belief (Fig. 2). The small branches of the hepatic artery

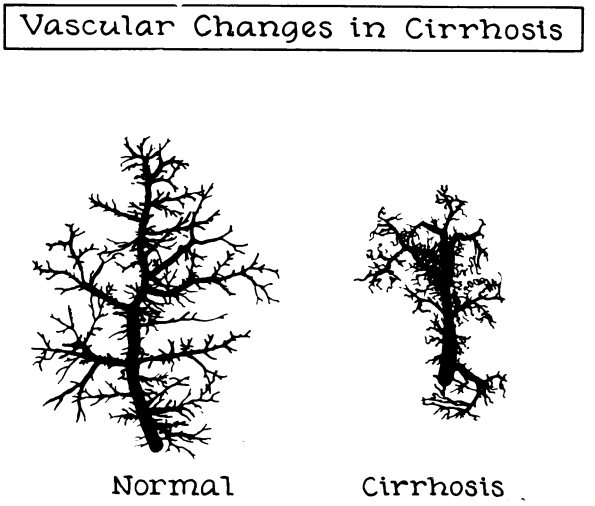

Fig. 2. Drawings of casts of branches of the portal vein from a normal liver and from a liver with cirrhosis. Note the attenuation and distortion of the vessels from the diseased organ.

are similarly affected, although, like arteries elsewhere, they resist modification for a longer period of time. Consequently, in cirrhosis the liver becomes dependent upon the hepatic artery for the major portion of its blood supply. The regeneration of the hepatic parenchyma, under these circumstances, occurs in a soil so unfavourable for growth that areas of newly formed cells become in large part divorced from their portal blood supply. Regeneration is attempted because of the irresistible urge of this organ to regenerate.

As a consequence of the disruption of hepatic integrity in cirrhosis, extensive communications develop between the branches of the hepatic artery and portal vein, and between the tributaries of the portal vein and hepatic vein (Mann, *et al.*, 1953 ; Popper, *et al.*, 1952). These intrahepatic shunts, in cirrhosis, in combination with the well-known extra-hepatic porto-systemic connections, divert a large portion of the portal blood past the hepatic parenchyma and into the systemic circulation. Thus, the vasculature of the liver in cirrhosis consists of multiple internal and external Eck fistulae. The disturbance created by these abnormal communications affects the hepatic cell which in its struggle for survival is deprived of its fair share of portal blood. It is of course well known by surgeons that the hepatic parenchymal cells are sensitive to periods of oxygen deprivation.

The cirrhotic process is a dynamic one and the vascular alterations necessarily vary with the stage of the disease. Upon this concept rests the explanation for the apparently contradictory results of the classic perfusion experiments of Herrick, of McIndoe, and of Dock. In 1907, Herrick perfused normal and cirrhotic human livers and concluded that in cirrhosis the total vascular bed, and particularly the hepatic arterial supply was increased. Further, he provided evidence of arteriovenous communications within the cirrhotic liver, and suggested that as a result of these, the pressure in the arterial system had a profound effect upon the portal venous pressure. McIndoe, in 1928, performed similar perfusion experiments and provided further evidence for the existence of abnormal vascular connections in the cirrhotic organ. However, he disputed Herrick's contention that the vascular bed is enlarged in cirrhosis, since, in studies of vascular casts of cirrhotic livers he found a marked diminution in all three systems comprising the hepatic vascular tree. In 1942, Dock repeated the experiments of his distinguished predecessors. Although in most of the cirrhotic livers the entire vascular bed was reduced, he found several in which the portal venous and hepatic arterial beds were normal or increased. Thus, Dock's studies indicated that the contradictory findings of Herrick and McIndoe were probably genuine phenomena. In addition Dock again demonstrated the influence of hepatic arterial pressure upon portal venous pressure in cirrhosis.

Recently, Madden and his associates (1954) have resolved the controversy regarding the vasculature in cirrhosis by correlating the clinical findings in cirrhotic patients with the post-mortem appearance of

casts of their hepatic vasculatures. They have demonstrated that in cirrhosis with irreversible ascites, there is an increase in both the arterial and portal venous beds, and a decrease in the hepatic venous bed. In contrast, in cirrhosis without ascites, or with reversible ascites, there is a decrease in all systems, particularly in the venous beds. Thus, it seems probable that the vascular network in cirrhosis varies with the progress of the disease.

Therapy involving the circulation

During the past decade the surgical therapy of liver disease has largely concerned the hepatic circulation. The effects of compromise of the hepatic blood supply, therefore, merit the surgeon's serious consideration.

Ligation of the portal vein in the rabbit and the dog results in death, not from hepatic vascular insufficiency, but from splanchnic stasis and loss of an adequate circulating blood volume. The monkey and man, however, tolerate ligation of the portal vein because of numerous collateral porto-systemic connections which allow a sufficient quantity of splanchnic blood to enter the general circulation (Child, *et al.*, 1952). We have succeeded in ligating the portal vein in man without producing fatal effects in radical operations for cancer of the pancreas and duodenum, as have others. Certain it is, that this procedure should remain in the realm of emergency and radical cancer surgery, for a number of instances of death from portal vein ligation have been recorded. Nevertheless, it is apparent that man has a reasonable chance of surviving ligation of this vessel.

The immediate effects of portal vein ligation in both man and animals are a severe, transient elevation of portal pressure, and a fifty per cent. reduction of hepatic blood flow. Ascites and splenomegaly do not occur. The portal pressure returns to normal within several days, and the hepatic blood flow increases gradually as collateral vessels develop which by-pass the site of obstruction. Attempts to produce persistent portal hypertension by ligation or partial occlusion of the portal vein have failed, and I share with others the belief that the aetiology of portal hypertension in man cannot be explained solely on the basis of portal obstruction.

Interest in the consequences of diversion of portal blood has been particularly keen of late because of the use of venous shunts in the therapy of portal hypertension. In animals, the liver becomes pale, atrophic and fatty following an Eck fistula, its ability to manufacture essential proteins is impaired, and it does not regenerate when a part of it is excised (Mann, *et al.*, 1931). Recently, it has been shown that regeneration does not depend upon a specific factor in portal blood, but upon an adequate blood supply (Child, *et al.*, 1953 ; Fisher, *et al.*, 1954). Although effective in preventing bleeding and prolonging life in humans, animal experiments suggest that diversion of portal blood may actually have, in part, a deleterious effect upon the diseased organ.

The consequences of hepatic artery deprivation depend largely upon the site of ligation. There are no deleterious effects of ligation anywhere proximal to the gastroduodenal branch. However, ligation of the hepatic artery distal to its last branch in dogs, cats, and rabbits is followed by liver necrosis and death in most, but not all, of the animals. It can be shown by injecting the aorta with dyes, plastics and radiopaque material that the animals, which survive, do so as a result of a sufficient collateral blood supply (Grindley, *et al.*, 1951 ; Jefferson, *et al.*, 1952). Most prominent among the collateral vessels are the phrenic arteries. Further proof of the importance of a collateral vasculature resides in the demonstration that ligation and excision of the entire hepatic arterial trunk can be accomplished without ill effects if performed in stages between which the auxiliary network is given the opportunity to enlarge (Huggins, *et al.*, 1937).

In 1949, Markowitz, Rappaport and Scott made the exciting discovery that the mortality rate in dogs from ligation of the hepatic artery distal to its last branch was greatly reduced by the administration of penicillin. The following year, we demonstrated that chlortetracycline was equally capable of preventing liver necrosis and death following arterial deprivation (Grant, *et al.*, 1950 ; Fitts, 1952). It has been proven that the protective action of antibiotics is a result of inhibition of bacterial growth. I wish to emphasise, however, that the primary, though not necessarily the fatal lesion following hepatic artery ligation is an ischaemic necrosis of the hepatic parenchyma, the development of which depends upon the adequacy or inadequacy of the collateral arterial network. A significant number of animals die following hepatic artery ligation, despite treatment with antibiotics. The livers of these animals often are found to be sterile (Fraser, *et al.*, 1951). Roentgenograms performed after injection of radiopaque material into the aorta demonstrate the absence of a collateral blood supply (Grindley, *et al.*, 1951). On the other hand, animals which survive ligation of the hepatic artery, with or without antibiotics, are found to have a collateral circulation adequate to nourish the liver despite exclusion of the main arterial trunk.

The liver of the normal dog contains bacteria, prominent among which is a bacillus identical with clostridium perfringens (Markowitz, *et al.*, 1951). The foul necrosis which follows fatal hepatic artery ligation is associated with the presence of millions of these bacilli, as well as gram positive cocci and gram negative rods. Further, lecithinase, the alphatoxin of the Welch bacillus, has been extracted from the peritoneal fluid of dogs dying from arterial deprivation. This evidence has been interpreted as indicating that the gas bacillus is the prime factor responsible for liver necrosis and death. Recently, in an excellent study of this matter, Schatten (1954) has demonstrated that neomycin, an antibiotic which has little effect on clostridia, and which is not absorbed into the systemic circulation, is as effective in preventing liver damage as the other antibiotics. Moreover, he has indicated convincingly that the clostridia found in the

necrotic liver of the dog are essentially saprophytes. Finally, Schatten has further shown that the organisms primarily responsible for the fulminating hepatic infection are gram positive cocci which arise in the gastrointestinal tract, rather than in the liver. The fact that various antibiotics afford protection against hepatic artery ligation does not alter this concept, for it appears that penicillin and aureomycin exert their influences upon the bacteria once they have reached the liver, while neomycin, by sterilising the intestine, prevents bacteria from reaching the liver.

The results of experiments in animals have, I fear, been applied to man in the absence of sound supporting evidence. Studies in our laboratory indicate that the liver of man is sterile. The effectiveness of the broad spectrum antibiotics in the treatment of liver disease has never been established convincingly. Although it is possible that bacteria may play a role in the production of liver necrosis following arterial deprivation in man, there is little to suggest that the process is similar to that which occurs in the dog.

Until recently ligation of the hepatic artery in man has been regarded as a drastic procedure. Of over 100 cases of hepatic artery aneurysm which we have reviewed, only six were cured by ligation or excision and many died as a result of attempted extirpation (Grant, *et al.*, 1950). Similarly, we have reviewed reports of some fifty cases of accidental ligation of the hepatic artery, sixty per cent. of which died as a result of the ligation. The weight of many years of experience has given the surgeon good cause for regarding the arterial supply to the liver with ominous respect. However, several years ago intense interest was centred on the use of ligation of the hepatic, splenic, and left gastric arteries as treatment for cirrhosis with portal hypertension. The rationale for arterial ligation is based upon the vascular abnormalities which occur in this disease. I have mentioned the numerous arteriovenous shunts which develop in cirrhosis, and the influence of blood flow in the arterial system upon pressure and flow in the venous system. It is presumed that ligation of the hepatic and splenic arteries, and the consequent reduction of arterial pressure, will both lower the portal venous pressure and allow portal blood to enter the sinusoid against less resistance. Moreover, it is believed that ligation of the splenic artery, will reduce the contribution of the spleen to the volume of blood in the portal system (Berman, *et al.*, 1951 ; Rienhoff, *et al.*, 1953).

In the dog, ligation of the hepatic and splenic arteries produces an immediate but transient decrease of the portal pressure. However, it has been our experience that the portal pressure returns to pre-ligation levels within one to three months after operation (Baret, *et al.*, 1955). In humans with cirrhosis, the immediate response of the portal pressure to arterial ligation is similar to that which occurs in animals (Berman, *et al.*, 1952 ; Altemeier, *et al.*, 1955). Whether or not the pressure reduction is persistent has not been determined. The effect of the procedure on ascites, bleeding

HEPATIC AND SPLENIC ARTERY LIGATION IN CIRRHOSIS

	Number of Cases	Deaths		Survivors	
		Operative	Total (one year)	Ascites improved	Bleeding absent
		%	%	%	%
Berman *et al.*	23	30	70	50	20
Reinhoff-Woods.. ..	21	29	33	100	40
Madden	8	62·5	87·5	0	0
Witter-First	3	33	33		100
Jennings-Blanchard ..	7	43	71	50	100
Miller-Owen	3	67	67	0	0
McFadzean-Cook ..	7	14	14	100	100
Altmeier	18	11	50	100	50
	90	30	53	74·5	50

Fig. 3. The effects of hepatic and splenic artery ligation in cirrhosis.

from oesophageal varices, and longevity, and the mortality rate of the operation are shown in the combined statistics of Figure 3. If hepatic and splenic artery ligation is of any value at all, it is in the cirrhotic patient with ascites alone. The results in patients with haemorrhage from oesophageal varices are disappointing. Moreover, the mortality rate in the best of hands is inordinately high.

In view of the extreme anatomical variability of the hepatic artery, it is difficult to conceive how one can predict the therapeutic effects of a standard ligation with reasonable certainty. Moreover, I seriously question the safety of any procedure in which the anatomical variations are so little subject to surgical control. Our experience with arterial ligation has been limited, but our results have been poor, and we are no longer employing this form of therapy.

PORTAL HYPERTENSION

Perhaps the most widely appreciated clinical example of circulatory derangement in liver disease is portal hypertension, which is the second topic of my discussion. Since McIndoe in 1928 forecast the employment of the Eck fistula in decompression of the portal system, and Whipple and Blakemore established its practicality in 1945, much has been learned about portal hypertension, its sequellae and its surgical management. Although the aetiology of portal hypertension remains as cloudy in areas as it was thirty years ago, certain obstructive factors have been identified, including the liver fibrosis and architectural distortion of the cirrhotic, the mutual influence between the portal and arterial pressures, and the extrahepatic portal blockade whether a fibrosis secondary to thrombosis, a cavernous transformation or a neoplastic lesion. For purposes of broad discussion these may be classified as intrahepatic or extrahepatic block. Why one person should develop extensive, hazardous collateral channels to divert the semi-stagnant portal flow and others not, remains a mystery, as much so as arterial hypertension in the systemic sense.

In any account of portal hypertension, it is important to define exactly what is meant clinically by this term. The commonly accepted standard of normalcy for portal pressure ranges upward to 26 cm. of saline, measured from the level of the portal vein itself. This has been confirmed in the human by serial determinations employing an indwelling plastic catheter both during and following different operative procedures. Various drugs and postural changes have failed to alter these values significantly. It has been affiirmed that oesophageal varix bleeding is associated with pressures over 30 cm. of saline. No one, however, has been able to correlate the pressure measurements within the portal system with the bleeding phenomenon to a point of acceptable predictability, and this seems unlikely in view of the factors noted by Taylor (1954) in his experimental work. He found that coughing could bring even normal pressures to a level of 55 cm. and the reverse Valsalva manoeuvre effectively raised portal pressure by 160 cm.

Portal hypertension remains, however, more than just a number of measurements. It represents a grave threat to life in two important areas. First and foremost is the danger of uncontrolled haemorrhage with exsanguination, and secondly are the serious consequences of large amounts of blood in the gastrointestinal tract in the face of liver deficiency, both stemming from rupture of oesophageal varices.

Diagnosis and evaluation

Numerous clinical and laboratory methods are available to establish the diagnosis of portal hypertension pre-operatively. Among these are the determination of portal circulation time (Newman, *et al.*, 1949), measurement of splenic pulp pressure by percutaneous puncture (Taylor, *et al.*, 1955), estimation of oesophageal varix pressure by puncture through the oesophagoscope (Palmer, 1951), measurement of wedged hepatic vein pressure (Myers, *et al.*, 1951), actual observation of bleeding varices by oesophagoscopy and roentgenography to demonstrate varices.

The usual clinical criterion for shunt procedures has been one episode of massive gastrointestinal bleeding from oesophageal varices. In view of the serious nature of these operative procedures in bygone days, only the more desperate, poorer risk patients could be justifiably subjected to surgical manoeuvres. However, with the advent of large blood banks, better anaesthesia, better instruments and more accurate diagnostic studies, the operation of portal decompression is being offered to a wider segment of the patients in need. Our definitive surgical approach for the patient afflicted with portal hypertension has been and remains the decompressive shunt, portacaval or splenorenal. Numerous large series of cases have been reported with mortality rates within reasonable limits. Exemplifying this are the experiences of Blakemore (1951), Linton (1951), Child (1955), Jahnke (1953) and my own group with operative mortality rates ranging from 6·7 per cent. to 16·2 per cent. Even more impressive is the fact that the recent operative undertakings have shown lower and

lower mortality figures. Important in producing this reduction have been the enormous improvements in pre-operative and operative management of these patients as shown by Patek (1948), by Habif (1953), and by Ebeling (1956) who employed low sodium regimens, adequate diet, vitamins, rest, blood transfusions and the intravenous administration of serum albumin for restoration of blood volume and restitution of depleted proteins. The work of Ephraim Shorr, Jacob Fine, and ourselves, pointing out the danger of liver anoxia has led to added stress on avoidance of anoxia during the operative procedure itself. Important too has been the achievement of control of infection with antibiotics and control of haemorrhage with freshly prepared banked blood. One additional and extremely valuable technical advance has been the introduction of splenoportography, originally devised by Abeatici and Campi in 1951. More recently Rousselot (1953), Cooper (1953), and O'Sullivan (1955) have clarified the roentgen patterns obtained by percutaneous splenic injection of the radio opaque substance, and have established this procedure as being of paramount value in determining the correct approach to operation. Its safety has also been affirmed.

Basically, the general criteria clearly elucidated by Linton (1951) still apply in the selection of suitable patients for shunts. These are that jaundice should be minimal or absent, that ascites should not be a feature of the disease, that the serum albumin should be maintained at or above 3 grammes per cent., that hepatic coma should not have been present, that the prothrombin time should be capable of attaining normal or near normal values and that the bromsulphalein test should show no more than 20 per cent. retention after 45 minutes. In recent years a certain degree of relaxation of these standards has been evident when it was felt to be in the best interests of the individual patient.

Patency of shunts

The fact that the shunts remain open is beyond dispute. Numerous tests have been devised to determine patency in the post-operative period, all showing excellent results. Among these have been the portal circulation time (Newman, *et al.*, 1949), the wedged hepatic vein pressure (Myers, *et al.*, 1951), the percutaneous splenoportogram (Rousselot, *et al.*, 1953), the bile acid concentrations (Akita, *et al.*, 1954), the oesophageal vein pressures (Palmer, 1951) and ammonia metabolism following oral ingestion of various drugs. Perhaps the most conclusive of all tests, as far as the patient is concerned, has been the absence of haematemesis following shunting. Most large series reveal that only one in ten or more patients experienced this untoward reaction. Child in his 56 cases has not had a single episode of post-operative gastrointestinal bleeding. The exact mechanism for the cessation of variceal haemorrhage following portal decompression remains as much a matter of conjecture as the aetiology of portal hypertension itself. On the basis of work by the Minnesota group (Wagenknecht, *et al.*, 1953) who found oesophagitis and ulceration of the

oesophageal mucosa in almost 50 per cent. of patients with bleeding varices, it would appear that the lowering of portal pressure affected the oesophagogastric junctional area sufficiently to improve function and decrease acid peptic regurgitation, ulceration and haemorrhage.

Circulatory effects of shunts

The circulatory effects of the shunting procedures have been determined by many groups using the techniques enumerated previously. Bradley and his associates in a study of 12 patients noted a fall in estimated hepatic blood flow of about one-third, with quantitative values averaging 1266 cc. per minute pre-operatively and 845 cc. per minute post-operatively. In addition, the hepatic arteriovenous oxygen difference increased significantly without affecting hepatic oxygen consumption. One may attribute the fall in flow to the diversion of blood through the shunt, and the increased arteriovenous oxygen difference to slower perfusion of the liver with augmented extraction of oxygen. This has been confirmed by Nardi and co-workers using radio-colloidal chromic phosphate, who in addition found it to hold true for splenorenal as well as portacaval decompressions (Nardi, 1955). It is interesting to note that the patient in Nardi's series who had the greatest drop in estimated hepatic blood flow died in hepatic coma with toxic levels of blood ammonia, and similarly the only two patients in Bradley's series who suffered from mental deterioration had the greatest reductions in flow, suggesting that too large or too efficient a shunt may be detrimental.

Effects of shunts on liver function

One of the most controversial points in this field has been the effects of venous shunting on liver function. Numerous authors have tersely commented that while the patient's bleeding may be controlled by operation, the liver remained permanently damaged and the patient could look forward only to progressive liver failure and eventual death, perhaps hastened by operative trauma. Recently, reports have appeared which dispel this clinical forecast of gloom. McPherson of Edinburgh in 1954, in a well planned series showed that despite diversion of the portal stream, there was no detectable deterioration of liver function as measured by the standard tests in the immediate and late post-operative periods. Additional support is found in the comprehensive review by Ellis, Linton and Jones (1956) who studied 125 shunt patients for from one to ten years. Of this group, 81 per cent. were alive one year following operation, 50 per cent. were alive five years after operation and two of three patients were alive ten years after surgery. Eighty-two per cent. were either fully active or reasonably active with only minor limitations. Liver function studies revealed little significant decrease in liver status and a number of patients had improved liver function. In addition, these patients had suffered few episodes of haematemesis and a reasonable percentage had had clinical improvement which was not as apparent before operation even in the face of prolonged medical management. These changes included an

improved feeling of well-being and strength, improved appearance, and restoration of normal skin colour, musculature and weight without the formation of ascites or oedema.

Problems

No question exists in the minds of those interested in portal hypertension as to the advisability of undertaking shunting operations on individuals who have bled previously as the result of extrahepatic block or for those who have haemorrhaged and have intrahepatic blockade. The primary problems which tax clinical ingenuity are those in which a patient presents himself at the time of massive haemorrhage as a consequence of his portal hypertension, and secondly those in which the surgeon is consulted to evaluate a patient with varices who has never bled. The first of these problems has been partially resolved with the advent of large blood banks and the introduction of the oesophageal tamponade balloon in its many modifications. Our experience, however, has been that most patients are incompletely controlled by these means or relapse promptly following the release of intra-oesophageal pressure. Accordingly, it has been my strong belief that prompt operative intervention is indicated. In the exceptional patient whose liver status and general condition are satisfactory, a definitive shunting procedure may be carried out with a reasonable mortality rate. In the overwhelming majority of these patients, however, I have found it wise to employ a local approach on the bleeding site. Many unique ideas have evolved in this regard including Crile's (1953) suggestion of trans-oesophageal ligation of the varices, Phemister's (1947) and Baronofsky's (1949) thought of oesophago-gastrectomy, Som and Garlock's (1947) approach of mediastinal packing and Crafoord and Frenckner's (1939) innovation of injecting sclerosing agents into the varices. Others have employed splenectomy, ligation of coronary veins, and ligation of the vessels coursing from the celiac axis. In our hands and in the hands of many others the technique of trans-oesophageal ligation has been extremely satisfactory from the standpoint of minimal trauma to the patient and stoppage of the haemorrhage. With the extra time afforded by this means, patients can be stabilized and prepared for venous shunting on an elective basis. In opposing this viewpoint, Child (1955) reported eight cases of so-called " emergency portocaval shunting " with an immediate operative mortality of thirty-eight per cent. Others have had similar experience. Just as pancreaticoduodenectomy and cervical oesophageal diverticulectomy were originally devised as two-stage procedures and later, when techniques, pre-operative and post-operative care and basic physiologic understanding of the problems improved, excisions at a single stage became feasible and popular, so it is likely that the " emergency portocaval shunt " will take its place in our armamentarium ; but the time is not upon us now.

As to the second problem, that of patients with varices which have never bled, a maze of statistical data can be produced to support either

the conservative or radical stand. Most impressive to me have been the multiple, recently appearing, reports from major clinics establishing the mortality of the first episode of bleeding at 60 to 76 per cent. (Child, 1955 ; Nachlas, *et al.*, 1955, Welch, *et al.*, 1956) whether from exsanguination or from hepatic coma resulting from the haemorrhage. The question is often asked, " How many with oesophageal varices never bleed ? " This question has not been answered. It seems reasonable to assume that all or almost all patients with varices as the result of cirrhosis will eventually bleed if they do not succumb to their liver disease first. If this were not the case, every sizeable clinic would have a substantial number of cirrhotics with established varices being followed, and no one has presented a group of these patients with long follow-up and freedom from haemorrhage. Why not practice effective preventative medicine in this justifiable situation ?

It would be unfair to conclude this discussion of portal hypertension without some mention of the medical aspects. Despite the good results of surgical therapy it is to be noted that the mortality of cirrhosis and allied liver disease has been greatly decreased by dietotherapy and skilful care as witnessed by Patek's reduction of fatal outcome by 30 per cent. over a six year period. Certainly there is no substitute for careful evaluation of these patients before operation as it is well known that gastritis, duodenal ulcers, hiatal herniae and oesophagitis may produce the haemorrhage initially attributed to oesophageal varices. Finally, it is important to establish as accurately as possible the site of portal block as well as the type of liver disease present in order to evaluate critically standards for and results of therapy. In the past eleven years, we have come a long way in the surgical attack on portal hypertension.

ASCITES

Ascites, my third topic of discussion, is perhaps the most perplexing problem of liver disease. The mechanisms responsible for the formation of ascitic fluid are indeed complex, and the development of a rational approach to the therapy of this manifestation continues to test our acumen.

Pathogenesis

Ascitic fluid is a transudate, containing electrolytes and metabolites in concentrations similar to those of plasma, and protein in a somewhat lower concentration. Sixty years ago, the great English physiologist Starling (1895) proposed that the interchange of fluid across membranes is controlled by the hydrostatic and osmotic pressures on each side of the membrane. Since in cirrhosis with ascites the serum protein osmotic pressure is often low and the portal venous pressure is elevated, Starling's hypothesis has served as a likely explanation for the transudation of ascitic fluid (Fig. 4). Recent observations have implicated other factors which seem of greater importance.

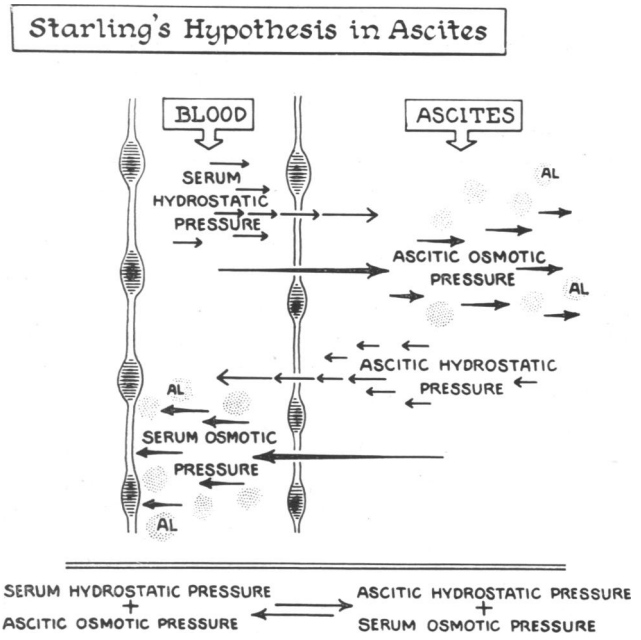

Fig. 4. Starling's hypothesis as applied to the formation of ascitic fluid.

It is well known that the concentration of serum albumin is frequently low in patients with liver disease and ascites, and it is believed that the serum osmotic pressure is reduced accordingly for the liver alone, synthesises this important substance. Numerous investigators suggest that there is a " critical level " of the serum osmotic pressure, below which ascites occurs. That no such " critical level " exists has become apparent with the finding of normal or slightly elevated pressures in many ascitic patients (Giges, *et al.*, 1954). Further, patients under treatment frequently lose their ascites many months before an elevation of the serum albumin concentration is detected (Ralli, *et al.*, 1945 ; Davidson, *et al.*, 1950). Moreover, the serum albumin concentration and osmotic pressure can be brought to normal levels by the intravenous administration of human serum albumin without effecting a significant decrease in the rate of ascites formation (Patek, *et al.*, 1954). It has been demonstrated convincingly that the serum albumin concentration does not correlate with the rate of ascites formation. Radioactive tracer experiments in humans with cirrhosis indicate that albumin passes freely into and out of both the plasma and ascitic fluid in a dynamic state of interchange, and it is believed that the osmotic effectiveness of infused albumin is limited by its failure to remain within the vascular compartment (Tyor, 1954). Thus, it appears likely that the role of the serum proteins in the aetiology of ascites is at most a minor one.

Among the many recent additions to our knowledge, those regarding the role of the sodium ion in the pathogenesis of ascites are outstanding. The dramatic therapeutic response to restriction of dietary sodium intake has served to emphasise the influence which this ion exerts on the formation of ascites. There is a virtual absence of sodium in the urine of patients with cirrhosis and ascites. Moreover, the serum sodium concentration is often low, a misleading finding, since actually these patients have an excessive amount of salt hidden in the extravascular accumulations of fluid. Although increased renal tubular reabsorption has been found to be responsible for the low urinary sodium concentration (Epstein, *et al.*, 1950; Farnsworth, *et al.*, 1948), several bits of evidence suggest that sodium retention is a generalised rather than a purely renal phenomenon (Eisenmenger, 1952). While the exact mechanisms governing its role remain to be elucidated, there is little doubt of the importance of the sodium ion as playing a real part in the genesis of ascites.

The possibility that hormones influence fluid and sodium retention in cirrhosis is a matter of speculation. Patients with ascites present obvious abnormalities in the metabolism of water, manifested by a subnormal volume of concentrated urine. Several investigators have found an antidiuretic substance in the urine of these patients, which they believe is in part responsible for the accumulation of fluid (Ralli, *et al.*, 1945; Hall, *et al.*, 1949). Other studies have failed to demonstrate this substance with any consistency or in significant amounts (Van Dyke, *et al.*, 1950). Another finding of interest is a diminished concentration of sodium and an increased ratio of potassium to sodium in the sweat and saliva of cirrhotic patients with ascites. Since it is known that this ratio varies directly with the degree of adrenal cortical activity and since this same electrolyte pattern is seen following the administration of desoxycorticosterone acetate (Frawley, *et al.*, 1951), it has been suggested that the formation of ascites may in some way be related to adrenal cortical hyperactivity. In the ascitic dog, bilateral adrenalectomy effects a prompt disappearance of ascites (Davis, *et al.*, 1953), and the same procedure, albeit a drastic one, has been employed with similar results in man (Marson, 1954).

Thus far I have mentioned only the metabolic factors attending the formation of ascitic fluid, namely, the serum proteins, the sodium ion and the hormones. To these, I wish to add a discussion of mechanical influences. From the time of Eck, the concept that ascites is due to portal hypertension has remained popular, despite a bulk of evidence to the contrary. Let us examine this evidence. Ligation of the portal vein in animals and in man, while producing severe, although transient portal hypertension, does not produce ascites. Furthermore, patients with normal livers who have portal hypertension as a result of extrahepatic obstruction of the portal vein, rarely develop ascites. In addition, numerous cirrhotics with severe portal hypertension and associated oesophageal varices are never troubled with ascites. Moreover, it is not uncommon for ascites

to appear for the first time following a portacaval shunt which is known to have reduced the portal pressure to a normal level. Conversely, patients with both ascites and oesophageal varices may respond to restriction of dietary sodium with absorption of the ascites and yet go on to bleed from their varices, indicating that portal hypertension has not been reduced. We have repeatedly failed to find a correlation between the degree of portal pressure elevation and the presence or absence of ascites.

Evidence is rapidly accumulating to establish that obstruction of the hepatic venous outflow tract, rather than blockage of the portal venous inflow tract, is responsible for ascites. The most consistent method of producing ascites in animals is that of partially constricting the hepatic veins or inferior vena cava above the liver. When the vena cava is constricted below the liver, ascites does not occur. Following constriction of the thoracic inferior vena cava in the dog, fluid is seen to drip continuously from the liver surface, indicating that experimentally produced ascitic fluid enters the serous space directly from the liver, rather than from the splanchnic bed (Hyatt, *et al.*, 1954). If this same liver is transferred into the pleural cavity, hydrothorax rather than abdominal ascites results (Freeman, 1953 ; Mallet-Guy, *et al.*, 1954). In the Budd-Chiari syndrome, a condition characterised by thrombosis of the hepatic veins, acute and massive ascites is the most striking clinical manifestation. The most crucial evidence implicating obstruction of the hepatic veins in the pathogenesis of ascites comes from recent studies of casts of the hepatic vasculature (Madden, *et al.*, 1954) which demonstrate that in cirrhosis with irreversible ascites there is an increase in both the portal venous and hepatic arterial beds, the inflow tracts, and a decrease in the hepatic venous bed, the outflow tract. Histologic sections of these same livers reveal an extensive obliterative fibrosis of the hepatic veins, an obvious cause for the refractoriness of these cases to treatment. In contrast, in cirrhosis without ascites or with reversible ascites, casts show a deficit in all of the vascular systems and histologic studies show that obliterative fibrosis of the hepatic veins while present, is not as extensive as in cirrhosis with irreversible ascites. It is believed that when ascites is reversible, the obstruction to the outflow tract is not permanent and that it will respond to proper medical treatment.

Although it is apparent that ascitic fluid transudes directly from the liver, the exact site where fluid traverses the barrier has not been established. Interesting in this respect are studies of the hepatic lymphatics. Frequently, at the operating table, the hilar lymphatics in cases of cirrhosis are seen to be many times larger than normal, and in animals with ascites from vena cava constriction the flow in the hepatic lymph vessels has been found to be greatly increased (Nix, *et al.*, 1951). Contrariwise, the flow in the intestinal lymphatics under these circumstances is normal. Hyatt and Smith (1954) collected the fluid which drips from the liver surface in experimental ascites and found it to be similar to lymph obtained directly

from the hilar lymphatic vessels. It is possible that the gateway to the peritoneal cavity is the hepatic lymph vessel which, unable to resist the elevated pressure transmitted from the obstructed hepatic veins, allows fluid to escape through its walls.

I trust that the evidence which I have presented serves to emphasise that no single mechanism is responsible for ascites. Rather, the formation of ascitic fluid represents the complex interplay of a number of processes which, although imperfectly understood, are now rapidly being clarified.

Medical treatment

The treatment of ascites has suffered from the enthusiasm which accompanies uncertainty. Few other manifestations of disease have been subjected to so many and varied methods of therapy. I would be remiss indeed if I did not emphasise that the bulk of patients with cirrhosis and ascites are best treated by medical rather than surgical measures. Yet, the methods of treatment merge so often that it becomes essential for the surgeon to understand the medical treatment of this condition.

Certain general principles relating to hepatic damage and repair merit restatement. In 1939, my associates and I established that a diet rich in carbohydrate and protein protects the liver from injury by toxins (Goldschmidt, *et al.*, 1939 ; Ravdin, *et al.*, 1950). Numerous clinical trials have shown that the high carbohydrate, high protein diet containing a moderate amount of fat and added vitamins and lipotropic substances forms the basis for the modern therapy of liver disease. To this, a programme of bed rest and abstinence from alcohol should be appended.

The single most important factor in the medical therapy of ascites is the rigid restriction of sodium intake. On a diet containing 500 to 1,200 milligrams of sodium per day, a large number of patients with ascites will in time experience a diuresis with consequent resorption of fluid. Of late, ionic exchange resins have been used to allow a larger intake of salt, and thereby a more palatable diet. A number of patients derive significant benefit from these agents. However, in our experience, ionic exchange resins are poorly tolerated by many patients with liver disease, and complications such as acidosis, hypokalemia and ammonia intoxication are not infrequent.

The use of intravenous salt poor albumin in the management of ascites, while sometimes effective in promoting diuresis, is usually of temporary value only. The most significant benefit derived from this agent is an improvement in general nutrition. Mercurial diuretics are efficacious in a limited number of patients who retain the ability to excrete sodium, and even then their effect is short lasting. Finally, I wish to mention paracentesis, only to emphasise that ascitic fluid contains large quantities of protein and electrolytes which are lost to the body once removed. While paracentesis is sometimes imperative to relieve

discomfort, it should be required less often with the intelligent use of diet and ancillary measures.

Surgical treatment

Despite impressive advances in the medical management of cirrhosis and ascites, a significant number of patients do not respond to treatment, either because of inability or unwillingness to follow the rigid tenets of the medical regimen, or because of the duration and extent of their disease. It is this group of patients, many of whom are in the stage of hepatic decompensation, to which the surgeon all too frequently falls heir.

The treatment of ascites represents one of the least brilliant chapters in surgical history. The great variety of suggested surgical procedures indicates more clearly than statistics the unsatisfactory results obtained from any particular one. Numerous reports of satisfactory results are based on incomplete follow-up, incorrect interpretation and erroneous diagnosis. The surgical methods of therapy may be divided into three groups, namely those which attempt to establish a collateral circulation, those which propose to modify the portal venous flow, and those which are directed at promoting drainage of ascitic fluid.

Procedures which attempt to establish a collateral porto-systemic circulation are predicated on the assumption that portal hypertension is responsible for ascites. Since it is unlikely that this premise is correct, these operations are doomed to failure. The most popular of these procedures is the omentopexy of Morrison and Talma (Drummond, *et al.*, 1896), which consists of suturing the omentum to the parietal peritoneum or in subsequent modifications to the soft tissues of the anterior abdominal wall. Placing the spleen in the abdominal wall and moving the testicle into the peritoneal cavity have been advocated (Henrikson, 1936). Finally, excision of the parietal peritoneum in the hope that the omentum would adhere to the raw surface has been practised (Otto, 1941). Each of these procedures has achieved sporadic success, but there is little to indicate that they have had any lasting beneficial influence on ascites or life span.

The operations in the second group, those which modify the portal blood flow, are also based on the unlikely supposition that the cause of ascites is portal hypertension. Both Moynihan and Mayo advocated ligation of the inferior mesenteric vein, and later splenectomy to reduce the portal flow (Henrikson, 1936). Resection of seven to twelve feet of small bowel has been proposed with the same goal in mind (Fuller, *et al.*, 1937). In recent times, ligation of the hepatic, splenic and left gastric arteries has been performed with but a modicum of success and a high mortality rate. Lastly, portocaval anastomosis has met with little success when employed as treatment for ascites. I am unable to recommend any of these procedures.

Techniques which promote drainage of ascitic fluid and comprise the third group have as a major shortcoming the inability to resist becoming

blocked. Of historical interest are several bizarre and rather heroic operations such as anastomosis of the renal pelvis to the peritoneum, and drainage of ascitic fluid directly into the bladder. The procedure with which we have had the greatest experience is that which involves the use of a button to drain the ascitic fluid into the subcutaneous tissues. Almost all of our buttons have become plugged by omentum or adjacent bowel within a short period of time. Moreover, the cavity in the subcutaneous tissues surrounding the button soon develops a thick fibrous wall which is incapable of absorbing fluid. Another technique which fails almost from the start is that of attaching one end of the divided saphenous vein to an opening in the peritoneal cavity (Routte, 1910). The rectus wick operation, which consists of suturing the detached superior end of the rectus muscle to the posterior peritoneum is similar to the others (Crowe, 1953). Recently an intriguing technique has been described whereby ascites is effectively absorbed by the mucosa of an isolated segment of ileum which has been opened and exposed to the free peritoneal cavity (Neumann, *et al.*, 1956). Although experience with this method is confined to animal experiments, the encouraging results suggest that clinical trials are warranted.

The many unanswered questions regarding pathogenesis and the failure of surgical treatment have encouraged two of my young associates to study the problems of ascites in our experimental laboratory. Proceeding on the assumption that ascites is due to obstruction of the hepatic veins, they have investigated methods of developing collateral circulation on the outflow rather than on the inflow side of the hepatic vasculature. One of these methods involves anastomosis of the spleen to the liver. In normal dogs with splenohepatic anastomoses, my colleagues have shown that a significant amount of hepatic blood passes from the liver to the spleen across the anastomosis. In addition, some blood passes from the liver into the systemic circulation through collateral connections which develop between the liver and the diaphragm as a result of the operative manipulations in this region. In a small group of dogs with ascites produced by vena cava occlusion, splenohepatic anastomosis has effectively prevented accumulation of fluid.

It is hoped that across the splenohepatic anastomosis communications will develop between the inflow tract of the liver and the vasculature of the spleen which by-pass the obstructed hepatic veins and thereby relieve intrahepatic venous hypertension. Admittedly, the rationale of this procedure requires clarification. However, it is conceivable that the expansibility of the spleen, which was so brilliantly pointed out by the elder Barcroft, in its new position may assume sufficient importance as a reservoir and decompression chamber to reduce the pressure within the system. On the other hand, it is possible that the incidental collateral connections between the liver and diaphragm are responsible for the encouraging early results.

The studies which I have described are not yet complete and the early results require confirmation. They represent but a small portion of the current inquiries into the nature and management of ascites. I am confident that these broad efforts, in surgical laboratories throughout the world, will result in solutions to the problems of cirrhosis and ascites in the near future.

AMMONIA METABOLISM

Finally, I should like to consider in this quartet of inquiries into the complexities of liver disease the problem of ammonia intoxication and hepatic coma. One has only to see these patients with bizarre behaviour, disorientation, characteristic flapping tremor reminiscent of the beating of a bird's wings, cogwheel rigidity, clonus, ataxia, excessive salivation, and later stupor, coma, convulsions and sometimes death, to share an interest in this intriguing circumstance. It is important for me to note that many of the significant contributions in this field have been made by British surgeons and physiologists, working not only alone, but also hand in hand with American colleagues.

Natural history and development

Since Pavlov and his associates in 1893 described the occurrence of meat intoxication in the Eck fistula dog, the sequence of events leading to present-day knowledge has been fascinating. Research workers began to suspect that ammonia intoxication might be the cause of neurologic symptoms in patients with cirrhosis. Soon, experiments were presented describing elevated levels of blood ammonia in association with meat intoxication (Monguio, *et al.*, 1934). At about the same time, a classic series of papers appeared demonstrating the induction of central nervous system abnormalities by the administration of ammonium chloride in patients with cirrhosis (Van Coulaert, *et al.*, 1932). A few years later it was shown that urea synthesis in these patients was entirely normal and that the occurrence of ammonia intoxication was most likely due to the development of collateral channels between the portal and systemic venous systems (Kirk, 1936). More recently the electroencephalographic changes in this entity have been detailed with the demonstration of a diffuse cerebral abnormality (Bickford, *et al.*, 1955) and this has been related to the characteristic histologic findings in the brain, namely, profuse proliferation and hyperplasia in the cerebral cortex, basal ganglia, red, pontine, and dentate nuclei and the purkinje layer of the cerebellum (Riddell, 1955). In 1954, this toxic capacity of nitrogenous substances to produce neurologic sequellae was appreciated more fully by the report of episodic stupor and confusion following portacaval shunting (McDermott, *et al.*, 1954). It was noted shortly thereafter that 10 per cent. of patients undergoing shunting procedures suffer from this complication some time in their post-operative course, and further, that multiple natural precipitating agents could be demonstrated including haemorrhage, infection, paracentesis, and even narcotics. In some of these communications it has

been apparent that the investigators were disturbed by the inexact correlation between the peripheral blood ammonia levels and the mental status of the patients. The question presents itself as to whether all cases of encephalopathy in liver disease are examples of ammonia overloading. Obviously this would be an over-simplification. Although it is true that the etiology of hepatic coma has long been confused and confusing, the hypothesis of ammonia intoxication provides a rational basis for discussion of this problem and its treatment.

Body metabolism of ammonia

The metabolism of ammonia has been extensively investigated in animals, but until very recently no comparable studies in man were available. In 1954, McDermott, Adams and Riddell, working with patients, were able to confirm these animal experiments. Exhaustive work in clarifying many of the difficulties involved in the chemical determination of circulating blood ammonia (Conway, *et al.*, 1950) along with the clarification of ammonia levels in the cerebrospinal fluid (McDermott, *et al.*, 1955) and the permeability of the blood brain barrier, were the vital steps in providing accuracy and authority in recent data.

In studying the metabolism of a toxic substance such as ammonia, one is concerned with two primary aspects of its homeostasis, namely, the sources by which it is introduced into body metabolism, and the mechanisms whereby it is removed from the body, thereby preventing accumulation to toxic levels. Three sources exist whereby ammonia is presented for metabolism. The first and probably the most important is absorption of the ammonia which is formed in the gastrointestinal tract by the action of amino-acid oxidase and urease derived from bacteria. The fact that the ammonia which is formed in the bowel is absorbed into the circulation has been repeatedly demonstrated by comparing portal venous blood ammonia and peripheral blood ammonia and noting considerably greater concentrations in the former. A second source is the kidney, probably from glutamine stores, and a third is through the process of deamination in protein metabolism (Krebs, 1952). Elimination is accomplished by synthesis to urea or uric acid in the liver through the ornithine cycle (Krebs, 1952). In addition, the processes of transamination and deamination by which ammonia is transported and stored in the body are important in guarding the patient from sudden toxic accumulations.

Cellular metabolism of ammonia

Though a knowledge of the general body metabolism of ammonia is essential to an understanding of this problem, full appreciation of its vital role in the creation of pathologic change comes only through a familiarity with its utilisation at the cellular level. Numerous studies have been carried out pointing up a definite arteriovenous difference across the brain in patients with hepatic coma, leading to the conclusion that free ammonia is converted by the brain through chemical reactions to a bound form which is not detectable by our present methods. Of the

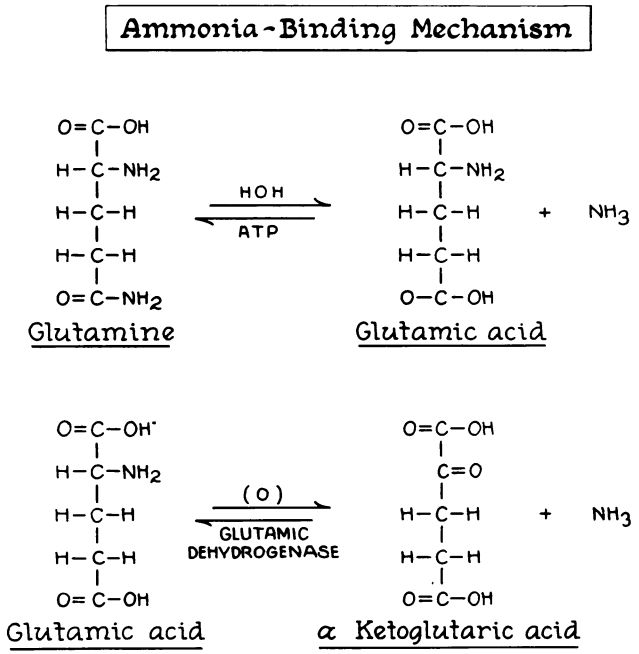

Fig. 5. The " Ammonia-binding mechanism."

multiple reactions involving ammonia, two appear to be significant in the brain, namely, glutamine synthesis, and the reductive amination of alpha ketoglutarate, commonly referred to as the " ammonia-binding mechanism " (Weil Malherbe, 1952) (Fig. 5).

The synthesis of glutamine from glutamic acid requires ATP, an oxidation enzyme, the removal of which from an oxidizing system not only does not inhibit the system but rather stimulates it to further oxidative activity, and glutamate, which is formed from alpha ketoglutaric acid. To elucidate this more clearly, we must refer to the Krebs cycle (Fig. 6) which is the final oxidative pathway in the brain. This cycle possesses the following features pertinent to this discussion : It is regenerative, it requires only minimal concentrations of any member at any time, and it possesses as an essential member, alpha ketoglutaric acid. It seems clear that any process which would tend to remove alpha ketoglutarate from the chain would also diminish the formation of succeeding members (Bessman, *et al.*, 1955). Since a major portion of the oxidative phosphorylation of the brain is derived from the Krebs cycle, oxygen utilisation and the formation of high energy phosphate will be reduced in proportion to the diminution of ketoglutarate available for the cycle. This, indeed, fits the experimental data revealing a decreased cerebral oxygen consumption and depression of cerebral metabolism

in hepatic coma (Wechsler, *et al.*, 1954). The finding of some increase in the glutamate leaving the brain while ammonia is entering is further corroborative evidence (Bessman, *et al.*, 1954). While many uphold the theory that the toxic action of ammonia is the removal of ketoglutarate from the Krebs cycle, some evidence has been presented indicating that under appropriate circumstances allowance is made for replacement by the transamination process converting glutamate to alpha ketoglutarate under enzymatic regulation (Weil Malherbe, 1952).

It is not generally appreciated that the administration of methionine to patients with advanced liver disease may be followed by the development of hepatic coma without elevation of blood or cerebrospinal fluid ammonia levels. This toxic action of methionine is thought to be due to the amino groups present in the molecule. Methionine sulfoxide has been shown to be a glutamic acid antimetabolite in laboratory studies and accordingly may interfere with the ammonia-binding mechanism, of which glutamate is an integral component. Protection against the toxicity of methionine has been afforded by the oral ingestion of chlortetracycline (Sherlock, *et al.*, 1954).

The integrity of the intracellular ammonia-binding mechanism is probably of more importance than the blood ammonia level *per se*. An elevated blood ammonia concentration may well be tolerated by individuals with liver disease whose ammonia-binding mechanism is functioning efficiently, but disturbances of this function may lead to the development of coma in the face of relatively normal blood ammonia values.

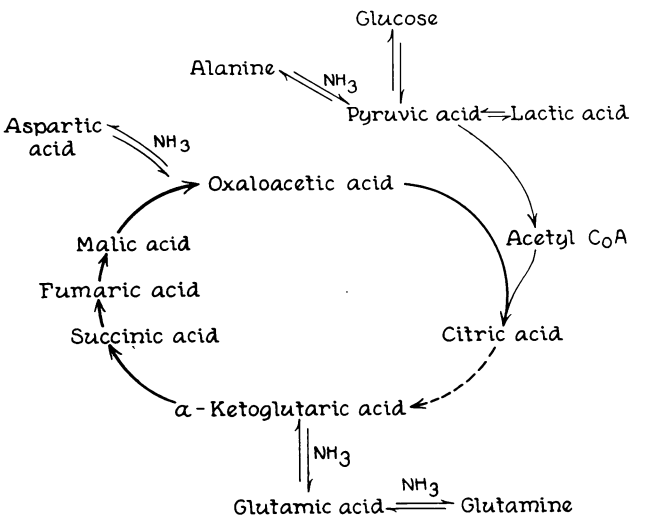

Fig. 6. The Krebs cycle, demonstrating sites of ammonia uptake and utilization.

Experimental and clinical studies supporting the ammonia intoxication theory of hepatic coma are plentiful. Varied agents have been employed to produce abnormal blood ammonia concentrations in animals with liver disease, including many high protein foods, blood given by gavage, urea, ammonia containing cation-exchange resins, ammonium containing compounds, and urease (Gabuzda, *et al.*, 1952 ; Phillips, *et al.*, 1952 ; Riddell, *et al.*, 1954). With each agent a degree of correlation could be demonstrated between elevation of blood ammonia and central nervous system symptoms. Although a definite lag period was noted in the correlation curves, results have been consistent enough to suggest a cause and effect relationship. More recent studies on patients following venous shunting procedures have served to strengthen this opinion.

Therapy of ammonia intoxication

The present day therapy of ammonia intoxication is based on this quasi physiologic interpretation of the evidence as set forth to-day. Two primary goals can be stressed, elimination of the sources of ammonia, and support of the natural mechanism by which the body removes this substance. Entailed in the elimination of the sources of ammonia is the restriction of nitrogenous intake, the administration of antibiotics to reduce the urease activity of the gastro-intestinal micro-organisms, and the prevention or control of alimentary tract bleeding, a very obvious source of ammonia, by oesophageal tamponade (Sengstaken, *et al.*, 1950), direct or indirect surgical means and by purgation and ionic exchange resins. In order to assist the body in disposing of abnormally high amounts of circulating ammonia, one should employ high carbohydrate feedings since it has been demonstrated that in the presence of adequate glucose, brain slices are able to synthesize glutamine from glutamic acid rapidly and bring about the disappearance of ammonia (Krebs, 1935 ; Weil Malherbe, 1950). On this same basis, the use of glutamic acid was introduced into therapy in 1953 (Walshe, 1953). Multiple reports now fill the literature reviewing hundreds of cases where it was employed, with divergent claims expressed. From these studies it seems apparent that glutamic acid has a definite role in the treatment of those patients who have compensated liver disease with acute symptoms of encephalopathy precipitated by a variety of exogenous factors, and of those patients with mild chronic neurologic difficulties associated with their liver disease (McDermott, *et al.*, 1955). Glutamic acid obviously cannot be expected to restore or replace the failing liver. The same can be said concerning succinic acid and probably alpha ketoglutaric acid which have already been given preliminary trials. One new agent, thioctic acid, or the pyruvate oxidation factor, does appear to warrant continued investigation. This biocatalyst is important to the oxidation of keto acids and in the transference of pyruvic acid into the Krebs cycle. It can be given intramuscularly in combination with thiamine, and has resulted in a favourable response in a majority of those patients with impending or full-blown

hepatic coma. Only a fuller understanding of the basic biochemical disturbances can lead us to a more rational programme of therapy.

From all these clinical and laboratory data, it is apparent that great strides have been made in probing the pathogenesis of hepatic coma. Unquestionably the available data incriminates some defect in the metabolism of nitrogen as an aetiologic abnormality in this state. The fact that blood ammonia levels frequently fail to correlate absolutely with the mental status of patients possessing liver disease may mean merely that our present method of measuring blood ammonia is not of sufficient accuracy or specificity, or it may be that it reflects only the extracellular concentrations of this substance and not the intracellular levels which are presumably more clearly related to ammonia toxicity. Further, the encephalopathy may be the result of an excess of some derivative of ammonia such as glutamine, which is known to be present in high concentrations in the brains of hepatectomized dogs and has been found in the urine of patients with hepatic coma. In an organ mediating as many complex pathways as does the liver, it is extremely unlikely that any single cause underlies all cases of hepatic coma, and it may well be that the relation of blood ammonia to liver coma is analogous to the blood urea level in clinical uraemia. Only additional experimentation will finally clarify the aetiology of this syndrome. With the rapid steps already taken, there is great expectation of a swift solution.

CONCLUSION

I have touched only briefly upon four areas of investigation associated with the liver and its diseases. Each of these fields of inquiry has by itself occupied the attention of many workers over many years. I have tried to emphasise the physiologic basis of the clinical phenomena attending hepatic injury. Perhaps my objectives have been too ambitious, for in attempting to translate the great mass of data of the recent past, I have relied heavily on the prospects of the future. With an eye to these prospects, I would close with the words of my friend Vannevar Bush. "A fascinating future surely lies before us, provided we can escape certain perils, and the most heartening potentialities lie in the field of medicine, and in the sciences adjacent to it. The time is coming when the practice of medicine will rest securely upon a firm scientific foundation, upon a systematic understanding of the life processes in all of their complexity, and no longer upon the insecure and shifting basis which partially supports it to-day."

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RESTORATION AND REBUILDING OF THE COLLEGE

The Opening of the Nuffield College

THE NUFFIELD COLLEGE of Surgical Sciences is at last in use. The students already in residence in the old building moved into their new quarters on 16th January, to be followed soon afterwards by others in sufficient numbers to fill the house. The administrative offices and Department of Anaesthetics came into use a few days earlier.

At the time of writing a few minor items of finishings remain to be completed by the builders inside the College, and the forecourt will not be completed for about another month.

By the time this article appears in print the refectory facilities in the Nuffield College will be in full swing and it will be possible for Fellows of the College and others to join the resident postgraduate students for lunch or informal dinner, and to make use of the lounge and bar which will be open every evening.

The official opening of the Nuffield College is to be performed on the afternoon of Friday, 5th April 1957, by Lieutenant-General The Lord Freyberg, V.C., and Viscount Nuffield himself will also be present.

Invitations to the ceremony will be issued later on. Many Fellows are accustomed to receiving notices of functions at the College, and it is suggested that others may like to send their names to the Secretary for inclusion in the invitation list, for they will be most welcome to attend, accommodation permitting.

Phase IIIa

Meanwhile steady progress is being made with phase IIIa at the back of the College. The steel framework is complete and floor slabs are being cast and the girders encased in concrete, this work being still at basement and ground floor level.