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IS THE LIVER AN INACCESSIBLE ORGAN?*

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The liver consists of 2 lobes, separated by the ligamentum falciforme. The right lobe is larger than the left, as it contains 2 additional parts: the quadrate lobe on the anterior side and the caudate lobe on the posterior side. All these hepatic lobes are characterized by an unusually abundant system of tubular structures. Not only are there arteries and veins but, in addition, the liver contains portal vessels which supply nutrients *from* the intestine and bile ducts which remove the bile *to* the intestine.

What is the role played by the hepatic cells in these tubular structures? It was once believed that the liver was composed of small clusters of hepatic cells: the lobules. The periphery of each of these lobules was believed to be enveloped in a reticulum of biliary capillaries, portal and arterial rami, while the centre contained a small vein. This point of view has changed, and it is now assumed that the liver has a diffuse structure. The organ consists of plates of hepatic tissue, each of which has a thickness of one cell. These plates are traversed by two tubular systems: the portal rami, arteries and bile ducts on the one hand, and the venous system on the other. Both systems are perpendicular to each other. The ultimate offshoots are woven round the hepatic cells, and they discharge their products—or receive them—via the space between the plates, the so-called vacuoles or sinuses.

The liver can be compared with a large building with innumerable rooms and cubicles, all of which are interconnected by windows and doors. Like the gas, water and electricity pipelines in a house, the tubes of the various hepatic systems are distributed from room to room, and from wall to wall. It is a good thing to involve these triumphs of modern technique in our comparison. They are based on physical or chemical formulae of human design. In the liver, too, the direction of flow in the tubular system—that is towards and away from the hepatic cells—is probably determined by such factors as pressure and tension. The liver can thus be regarded as an organ, which is governed, among other things, by the laws of hydrodynamics. This means that the organ can also be compared with a large system of irrigation in which 4 different types of fluid are involved, either to irrigate or to drain; a system which can only be maintained if the irrigating and draining canals can cope with their area by smoothly functioning pumping-stations, and if the correct pressure can be ensured by means of locks and sluices. This comparison, too, is a useful one. The heart can be regarded as a suction-station, and the digestive tract as a pumping-station. A conspicuous sluice is found in the papilla of Vater. All these comparisons make it clear that the minutely adjusted mechanism of the liver *must* be upset in the presence of, say, insufficiency of the right cardiac ventricle, which causes retardation of the flow in the hepatic veins. The comparisons also clearly show how much the liver must be disturbed when an extrahepatic cause impairs the flow in the portal system (extrahepatic portal hypertension) or when—for whatever reason—the removal of bile towards the intestine is impeded. Invariably the hepatic cells are forced to function under abnormal conditions.

CHANGES WITHIN THE LIVER

All this refers to pathological conditions of extrahepatic origin. It is equally obvious, however, that pathological changes within the liver must interfere with satisfactory function. We are referring to inflammations of the hepatic tissue (hepatitis) or of the small biliary capillaries (cholangitis). In such cases oedema and cellular infiltrates will constitute dams which threaten to upset the equilibrium of the system of irrigation. Reactions are inevitable—in an attempt at correction on the one hand and to be regarded as irreparable loss of cells on the other.

This also holds true for a hepatic affection not hitherto mentioned: the notorious cirrhosis. This disease is characterized, among other things, by progressive proliferation of connective tissue. This connective tissue will soon disturb the capillary flow and, gradually, asphyxiate the hepatic cells themselves. Both mechanisms are clearly defined in the clinical course. For it is cirrhosis of the liver which provides so pertinent an example of the interrelationship between intrahepatic and extrahepatic pressure. Among all the causes of portal hypertension, the intrahepatic aetiology based on cirrhosis of the liver is most frequently encountered. We know that such a liver, after a more or less prolonged period of insufficiency, becomes completely decomposed and leads

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to a fatal issue. A survey of this series—venous or biliary congestion of the liver, hepatitis, cholangitis, extrahepatic or intrahepatic portal hypertension—immediately shows that they are pathological conditions which can be therapeutically influenced.

It is possible to improve the condition of the liver by stimulating the poorly functioning heart or by controlling the disturbance in the drainage of bile (obstruction by concretion or stricture). Today it is certainly possible to control the inflammation of the bile ducts with the aid of antibiotics. Moreover, the hepatic cells that tend to become insufficient, can be assisted—even in a disease such as cirrhosis —by supplying the constituents which the affected liver cell requires. Liver extract, certain liver diets and transfusion of albumins are useful in this respect.

THE ACCESSIBILITY OF THE LIVER

It is not primarily this pathology of the liver, therefore, which we have in mind when we express doubt about the inaccessibility of the liver. There is also an entirely different pathology and, in fact, in this respect there is nothing to distinguish the liver from other organs. When enumerating these pathological conditions, therefore, it is better to adhere to the normal classification. In the liver, too, distinction is made between congenital and acquired anomalies, and the latter can be divided into inflammations and neoplasms. The inflammations are either acute or chronic, and either specific or aspecific. The neoplasms are either malignant or benign, either of primary hepatic origin or of a secondary, metastatic nature. Thus the list of diffuse affections can be supplemented with a list of a number of more circumscribed anomalies: abscess of the liver, hepatic cysts, haemangiocavernoma, teratoma, the so-called hepatoma, hepatic concretions, primary carcinoma of the liver and, especially, invasion of the liver by a carcinoma of the gall-bladder or the stomach. It is these conditions which have so far emphasized the inaccessibility of the liver.

In the past, liver abscesses were drained, and liver cysts scooped out. It will be observed, however, that the operating surgeon in such cases attempted with special care to confine his work to the affected tissue, leaving the hepatic tissue itself untouched as much as possible. In the past few years case reports have been published on wedge resections, or even partial hepatectomies, performed with the object of attaining a radical cure of a cancer of one of the adjacent organs. These operations, however, were exceptions, and the impression is gained that the operating surgeon was surprised by the fact that the patient survived them. And why this surprise? Man has but one liver. Total extirpation, therefore, was not feasible. Partial resection, however, also seemed unjustifiable. The liver is a very large organ indeed, but should not this volume be regarded as necessary for the multitude of important demands made on it? In view of the fact that the liver is the largest of all organs, in animals as well as in man, it is obvious that Nature must have had its reasons for providing such a large liver. If this is so, can artificial reduction of this volume then be justified? Yet another aspect has to be considered: however insufficient our understanding of the hepatic structure may have been, our preceptors were only too well aware of the ease with which surgical intervention in this highly vascular organ could give rise to a fatal haemorrhage, and they knew how readily an incision into the bile ducts could cause a fatal infection. They had had experience with these complications in cases in which it was the fighter's knife rather than the surgeon's lancet that injured the liver, or in which a lesion of the hepatic tissue resulted from contact with a waggon-wheel or other obtuse objects. Briefly, operations on the liver were considered a feat, the performance of which was not, or hardly, permissible for two reasons: no part of the human liver is dispensable and the intervention itself is too hazardous.

THE INDISPENSABILITY OF LIVER TISSUE

A few years ago, at one of the staff meetings in our hospital, a liver was demonstrated which was nearly completely filled by large carcinomatous nodes which had not been clinically noticeable. The question arose how this absence of symptoms could have been possible in view of the fact that so much tissue was functionally impaired. Animals were known to have overcome extirpation of large portions of the liver without any ill effects. It had to be admitted, however, that it is very difficult to demonstrate signs of disfunction or to estimate the functional capacity of the remaining part of the liver in animals. Even such a simple indication as jaundice is only established with difficulty in hairy test animals.

We ourselves had previously elaborated an exact method of determining the total quantity *and* the type of bilirubin in the blood. It was therefore decided to use this method in an attempt to establish the effects of inhibition of the function of bilirubin excretion in large parts of the liver.

This could have been done by resecting parts of the liver. It seemed technically simpler, however, merely to obstruct the bile drainage. The experimental animal selected was the rabbit, as this involved a minimal expense. Our choice proved to be a fortunate one, for the liver in these animals could be divided into a large, trilobate main liver and a small so-called accessory liver. Both had their own hepatic duct, and the rabbit was therefore extremely well suited to our experiments. By ligating the hepatic duct of the main liver we were able to deprive 75% of the hepatic tissue of its bile drainage. Not only did the rabbits tolerate this intervention but chemically they showed no trace of jaundice. This experiment demonstrated that rabbits have been endowed by nature with a liver which might well have been considerably smaller. In other words, the cells of the rabbit liver possess a reserve power so considerable that a relatively small number of these cells are capable of counter-balancing the loss of a great many other cells. This, then, was the *reserve capacity* of the liver.

REGENERATION OF LIVER TISSUE

Our experiments meanwhile yielded a second—and unexpected—result, which could be attributed to the fact that we had preferred ligation of bile ducts to resection of parts of the liver. Not only was the obstructed part of the liver found to become atrophic but, at the same time, the unobstructed part was found to start growing—to such an extent that at the end of our experiments—regardless of whether it was after a month or a year—the total hepatic weight was found to have remained the same. This observation proved that the liver has regenerative powers, and also that these powers had been released by this technique.

We were fascinated by this reserve capacity and regenerative power, and attempted to establish whether both could be regarded as intrinsic properties of the hepatic cell. For this purpose we performed our experiments on animals previously starved. The liver showed a splendid response, with unmistakable reserve capacity and regenerative power. In addition we were able to demonstrate the same properties when the liver was not deprived of its bile drainage but injured in some other way. Reserve capacity and regenerative power could both be released by ligating a branch of the portal vein.

These experiments seemed to warrant the following conclusions:

1. The liver possesses a considerable reserve capacity.
2. The liver is capable of regeneration under various conditions.
3. This regeneration becomes manifest as soon as one part of the liver is placed under relatively more favourable conditions than the other part.

In advancing these hypotheses we had to bear in mind that they were tenable exclusively for our experimental animal, the rabbit. We therefore repeated the experiments with an animal which seemed to us to be somewhat closer to man, viz. the pig. The result was identical; reserve capacity and regenerative power were again demonstrable.

It now remained to be established whether the human liver, too, possessed these properties. From our own material and from the literature, we collected a number of observations which afforded conclusive proof of the existence of such properties. Invariably these cases involved patients who did not complain of hepatic symptoms, or did so only immediately before death, but in whom this organ—as a result of obstruction of a bile duct or a portal branch—showed unmistakable atrophy of a lobe, associated with striking hypertrophy of the unobstructed part of the liver. In all these patients Nature performed the experiments we had made in our rabbits with identical results. The regenerative power could be read at a glance from the illustrations accompanying the reports; and in the patients good condition during life showed that, during the period preceding the hypertrophy, there had been a sufficient reserve capacity.

In the course of a study of the literature we found a report on a meeting of the anatomical Society of Great Britain and Ireland, which contained a very important communication. This concerned the liver of an otherwise completely healthy Chinese who committed suicide by hanging himself in a Hong Kong prison. This man's medical history included an abscess on the right side of the liver during childhood. The abscess had caused complete destruction of the right lobe but was subsequently healed by perforation via the pleural cavity. The speaker described an atrophy of the right lobe but also recognized the left-sided hypertrophy. He concluded his address as follows:

'It is theoretically possible to tie the vessels of one side at the gate of the liver, leaving the other side to do the work. That one-half of the liver can hypertrophy, so as to perform the function of the whole, is attested by pathological study. I commend this subject to all those who are working at the surgery of the liver, and I believe that if, in the hands of future observers, the statements I have made receive closer investigation, the surgery of the liver will be advanced a step.'

That was in 1899! The name of this investigator (Cantlie) should be mentioned here to his honour. And we ourselves—some 60 years later—can observe that it is indeed justifiable to reduce the volume of the human liver by surgical means whenever this can be expected to contribute towards controlling pathological conditions. The only question which remains is whether the risk entailed by such an operation should prevent us from performing it.

THE PRACTICABILITY OF SURGERY OF THE LIVER

We find ourselves in a period when it is 'fashionable' to inject all hollow organs with some contrast medium, after which a possible anomaly can be demonstrated with the aid of X-rays. Thus, we are familiar with X-ray examination of ventricles, joints, bronchi, the urinary system, the digestive tract, heart, large vessels, etc. Some 10 years ago the large bile-ducts were added to this series. Operative cholangiography provides us with important data on the contents of the bile-ducts. The method has been advocated especially by investigators in Sweden. It was in this country, too, that attention was drawn to a feature which was revealed partly by cholangiography. This method makes it possible to visualize not only the common duct and the 2 hepatic ducts, but also the network of intrahepatic remifications. It was found that the bile-ducts in the liver are distributed in such a way that the organ can be considered composed of 2 parts. This recalled the 2 lobes of the anatomists. However, the lobes which were defined cholangiographically showed no correspondence whatever with the anatomically described lobes. The left half extended much farther to the right, and included both the caudate and the quadrate lobe. In fact the division between right and left was localized in a plane traversing the gall-bladder and the vena cava.

The exact position of this plane was subsequently determined by injecting the 4 tubular systems of the liver, separately or combined, with an indurating plastic substance, after which the liver parenchyma could be removed by maceration. It was found that the bile ducts are invariably accompanied by portal and arterial branches (as assumed by Glisson as early as 1654), and that each of the 3 has a typical, constant course. This course enables us not only to make a division into two lobes but even into a number of segments. The hepatic veins, on the other hand, show a completely independent but equally typical course. Recalling the fact, established in comparative anatomy, that the majority of mammals have a liver composed of several lobes it is clear that the human liver, too, can have a multiple anlage, the the fully grown organ being a result of fusion. This means that the human liver contains at least one plane—but in fact several planes—in which it is possible to make incisions without causing leakage of blood or bile. It is this fact which constitutes the basis of hemihepatectomy—an intervention first devised by French surgeons. A thoraco-abdominal incision is made, so that the liver can be mobilized towards the thoracic cavity after severance of the diaphragm. The suitable branches of the hepatic artery, portal vein and common bile duct are then ligated at the hilus. Theoretically, this should be followed by ligation of the hepatic vein on the posterior side of the liver. This vein, however, is often too short and sometimes runs an entirely intraphepatic course. It is for this reason that the liver is first divided, while this blood vessel is left alone until the very last.

Recalling the 2 lists of hepatic affections, and the fact that the more diffuse affections can be controlled by more general measures with an extrahepatic site of action, it now becomes evident that it is also possible to control localized intrahepatic anomalies. By means of hemihepatectomy we can remove ruptured or inflamed parts of the liver, hepatic concretions, cysts and benign tumours. And perhaps we can even use this technique in operations for malignant tumours.

CIRRHOSIS

One disease has remained undiscussed so far. I refer to cirrhosis of the liver. It has been pointed out that it is possible to keep patients suffering from cirrhosis in relatively good condition for some considerable time by medication and especially by dietetic measures. Essential cirrhosis of the liver, at least as we know it in the Netherlands, is a progressive and intractable process. We have therefore considered whether the reserve capacity and especially the regenerative power of the liver can be utilized in these cases too. A study of the anatomical substratum of cirrhosis of the liver shows that there is an excess of connective tissue which threatens to supersede the hepatic tissue. The sequelae are bound to be the more serious the more severely the parenchyma is suppressed. Would it be possible, then, to assist the hepatic cells in the fight against this proliferating connective tissue? Would it be possible to stimulate the regenerative power of the still unaffected hepatic cells? This question, too was approached on the basis of an experimental investigation.

The test arrangement chosen was obvious. We had to determine whether the cirrhotic liver, too, might possess a reserve capacity sufficient to tolerate ligation of a hepatic duct or portal vein. And above all we had to determine whether this artifice would stimulate even a cirrhotic liver to hypertrophy. Cirrhosis of the liver was produced in our rabbits by injecting carbon tetrachloride. A number of animals died as a result of the injection. Those that survived were subsequently submitted to ligation of the hepatic duct of the main liver.

Again a number of animals died but the mortality was not higher than that due to the carbon tetrachloride itself. This proved that the reserve capacity of the livers rendered cirrhotic was not inferior to that of the normal rabbit liver. The next point was the hypertrophy. Autopsy on our animals after 3-6 months revealed that the unaffected accessory liver had hypertrophied in an entirely analogous way. The worst thing which could be said was that the rate of regeneration was somewhat slower. And a particularly encouraging fact was that the hypertrophied lobe showed considerably more favourable microscopic features that did the initial cirrhosis.

Could this encouraging observation also apply to human cirrhosis? In such a case the carbon tetrachloride cirrhosis of our rabbits will have to be considered similar to that of human cirrhosis of the liver. This seemed rather dangerous. Cirrhosis caused by carbon tetrachloride is the result of a chemical intoxication, and this cirrhosis is known to be immediately arrested when administration of the noxious agent is discontinued. One of the most characteristic features of human cirrhosis, however, is its progressive nature. On the other hand, the clinical picture of this cirrhosis has taught us that jaundice does not generally occur until the terminal stage is reached. This means that relatively few cells suffice to ensure hepatic function—at least as far as bile production is concerned. The question is whether this should be considered an indication of reserve capacity?

Furthermore, the histological features are of importance. Every pathological anatomist knows that cirrhotic specimens, apart from diffuse proliferation of connective tissue and cellular atrophy, show parts in which the hepatic cells are not only apparently completely normal but sometimes even appear to be newly formed. Can this not be regarded as an expression of the regenerative power which is required so urgently?

It seemed to us that we could rely on the human cirrhotic liver to behave like the rabbit liver. In principle, therefore, we decided to make an attempt to exert a favourable influence on human cirrhosis of the liver by ligating a hepatic duct in a suitable case. A suitable case! This meant that we were to employ this technique on a patient in whose case it was firmly established that no other type of therapy could succeed for any considerable period of time. Such a suitable patient was found in 1954 in a man of 73, who was suffering from a very severe form of cirrhosis. More than 3 years ago this man underwent a ligation of the right hepatic duct. His clinical tolerance to the intervention was good and this fact—combined with the laboratory data obtained during the first post-operative period—showed that we had rightly relied on the reserve capacity.

In the course of subsequent months the patient's condition gradually improved and, to our great satisfaction, he developed a swelling in the left upper abdominal region which could only be interpreted as a new liver.

CONCLUSIONS

In view of this development we decided to communicate our method to a small circle of colleagues. As a result, there are now 4 successful surgical cases of this type in our country. This is a very small number. We should also mention that 5 other cirrhotic patients had this operation—performed by ourselves or by other surgeons—in the course of this same period. They all died. In no case, however, could the death be ascribed to insufficient reserve capacity or to failure to regenerate. The fate of these patients merely showed that there are still many pitfalls in the field of determination of indications and that of the technical performance.

We consider that the useful effect of this method—if indications are determined with accuracy—has been proved. Further experiences will have to show the exact value at which this therapy should be estimated.