

**STUDIES IN THE PHYSIOLOGY OF THE LIVER: I. TECHNIC
AND GENERAL EFFECTS OF REMOVAL.**

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THE relatively large size of the liver, its double blood supply, and its elaboration of an internal and an external secretion have contributed to make the organ a source of continual interest to the physiologist. Many problems concerning its function are not definitely understood or are still under debate. They have been investigated by the removal of the liver and a study of the effect on the organism. The usual method has been to modify the function of the organ by performing an Eck fistula and ligating the hepatic artery, leaving the organ in place, the animal being kept under an anesthetic throughout the period of observation. This method may be satisfactory for the investigation of some problems, but the autolysis and absorption of the remaining liver tissue is a serious complicating factor. For instance, cutting off the blood supply to one lobe of the liver of a dog by ligation usually makes the animal very sick within a short time and causes its death in less than twenty-four hours. Various lobes of the liver have been removed by repeated operations, but the remaining portion always regenerated so that a permanent deficiency of liver tissue was not produced. In one of my experiments the surgical removal of approximately 70 per cent. of the liver was followed by practically complete regeneration in the course of a few months. The same condition follows the functional removal of the liver tissue by ligating the ducts. I have been able to ligate the ducts that drain approximately 70 per cent. of the liver without producing any effect on the animal's general condition. The ligated portion of the organ has undergone biliary cirrhosis and the unligated portion regenerated to make up for the loss of functioning liver tissue. The complete removal of the organ has been complicated by its relation to the portal circulation and the vena cava.

The portal circulation can be taken care of easily by an Eck fistula, but the intimate relation of the liver to the vena cava in most species of animals is such that complete removal of the organ rarely can be accomplished without damage to the venous return from the extremities. If damage to the vena cava is avoided, liver tissue is always left. Usually the remaining tissue is without blood supply and undergoes autolysis, producing a definite toxic effect.

For the study of some problems in the laboratory it seemed desirable to know definitely the course of events following the removal of the liver under conditions complicated by no factors other than the

anesthetic used at operation. None of the methods previously described fitted our purpose. Accordingly the method herewith reported for the removal of the liver of the dog was developed. The success of the method depends on the fact that the portal capillaries offer more resistance than collateral venous channels and as a result collateral circulation develops through other venous channels.

Technic of Removal of the Liver. The operation is performed in three stages. Ether anesthesia and sterile technic are employed. In the first operation an anastomosis is made between the portal vein and vena cava in the manner followed in performing an Eck

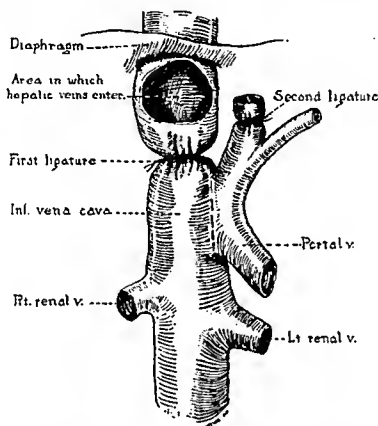


Diagram illustrating the steps in the technic of the removal of the liver. At the first operation the portal vein and vena cava are anastomosed along the dotted line and the first ligature is placed. At the second operation after the collateral circulation has been established the second ligature is placed. At the third operation the liver and the portion of the vena cava between the ligature and diaphragm are removed.

fistula, except that the vena cava is ligated instead of the portal vein. The ligature is applied just proximal to the entrance of the right lumbo-adrenal vein. This produces an increased pressure in both the vena cava below the ligature and in the portal system. Since the liver capillaries offer more resistance than that necessary to develop a collateral circulation through the azygos and internal mammary veins, in a short time most of the blood from the extremities will be passing through the latter route. The collateral circulation develops to such an extent that in three or four weeks after the first operation the second can be performed. The portal vein is ligated at the usual site in performing an Eck fistula, after which

all the blood from the posterior extremities and the portal system passes to the heart through the peripheral collateral circulation, see illustration. At the third operation the liver is removed completely by ligating the hepatic artery, the vena cava just below the diaphragm, and whatever small collateral veins have developed along the gastrohepatic omentum.

As in all experiments in which more than one operation is necessary, every experiment was not successful. In animals in which the diameter of the portal vein is narrow it is not always possible to ligate the cava without producing too much pressure in the portal system. Sometimes thrombosis occurs. In some animals the collateral circulation does not develop sufficiently to permit ligation of the portal vein. In a few cases a collateral circulation through thin-walled veins developed around the field of operation and resulted in unavoidable hemorrhage at the final operation.

The development of the collateral circulation has been interesting. In some animals, especially females, the superficial abdominal veins have returned most of the blood, anastomosing through the internal mammary veins. A very marked caput medusae developed in these cases. In other animals there was little dilatation of the peripheral veins, the collateral circulation developing through the deep vessels. In some animals a considerable collateral circulation developed through the capsular veins of the kidney. In one animal the vena cava thrombosed throughout its entire length from the ligature to below its bifurcation. The animal lived for several weeks with the blood from the kidneys returning through the capsular veins. In some animals the esophageal anastomosis was markedly developed.

The length of time between the different operations varied. In most instances it was at least a month and longer between the second and third operations.

Most of the animals remained in good condition throughout the entire period of observation and afforded us an opportunity to obtain some data with regard to the Eck fistula and the reverse Eck fistula. Few facts of value can be obtained concerning the reverse Eck fistula unless the collateral venous return has been occluded. Since the blood flow through the liver was but temporarily increased this probably explains why little of note had previously been observed in a study of the latter.

Every effort was made to perform the final operation as quickly as possible and to use a minimum of the anesthetic. The removal of the liver from the beginning of the anesthetic seldom required more than one hour, and the animal recovered almost completely from the anesthetic within another hour. Artificial heat was usually supplied until the animal fully recovered. This was not found to be essential, however. The widely dilated veins usually occasioned some hemorrhage, but only infrequently sufficient to constitute a

serious complication. Such data as a pulse-rate, respiration, and temperature were taken before and at various intervals after operation.

An excellent illustration of the mechanical function of the liver in offering resistance to the diaphragm was obtained in the first experiment in which the third stage was attempted. After the liver was removed the animal's respiration remained very shallow. Artificial respiration by manual means was instituted to assist recovery. To our surprise the animal died immediately after the artificial respiration was started. Necropsy showed that the thoracic compression had ballooned out the diaphragm at the former site of the liver, and, owing to the lack of resistance previously offered by the liver, a simple exchange of pressure between the thoracic and abdominal cavities resulted without any exchange of air in the lungs. In the subsequent operations insufflation was employed and no further trouble was encountered.

Results of Removal of the Liver. In general the course of events following removal of the liver has been quite constant in the different animals. It was anticipated that by carefully following the technique described it would be possible to keep a dog alive for a considerable length of time. This hope was not realized as all the animals in this series died within five to eleven hours after operation. But even though the length of life after operation was short we were able to observe the course of events subsequent to total loss of liver function and under conditions closely approximating normal.

The period of recovery of an animal from the anesthetic and from the immediate effects of the removal of the liver does not seem to differ from the period of recovery following other operations; in our series it varied from one hour to two hours. After the animal recovers from the anesthetic there is an interval which in this series of experiments varied from two to eight hours, during which the animal appears to be normal. It then becomes moribund and usually dies quickly, within one or two hours.

Before the animal develops the symptoms apparently of loss of liver function, its condition as to pulse, respiration or temperature is identical with that of an animal at a corresponding time following any other operation which has involved a similar period of time, amount of trauma, and anesthesia. During the period following the recovery from anesthesia the animal walks around, responds to call, drinks water and sometimes milk. To all appearances it is normal, except, of course, for the signs of a recent operation.

The onset of the moribund period is usually sudden and the first sign is muscular weakness. The animal prefers to lie down, and when standing it cannot hold itself erect or avoid swaying when walking. Usually within an hour after the first evidence of muscular weakness the animal is unable to rise, but lies quietly breathing, with muscles flaccid and relaxed.

The period during which the animal is quiet is usually short. It is soon noted that a loud noise or a jarring of the table upon which it lies produces a stiffening of the limbs. Muscular twitchings develop and later definite convulsions occur. The twitchings may involve only one muscle in a limb or a whole group of muscles. They are both tonic and clonic in character. Usually shortly after the muscular twitching has developed a very slight noise or a sharp slap produces a general convulsion. Some of the muscular spasms last one-half minute or more.

Often the animal exhibits movements similar to those employed when trotting; just before death it attempts to vomit and the slightest stimulation around the region of the head produces a snapping of the jaws as though at an imaginary foe. Death follows a convulsion, involving seemingly all the muscles of the body.

After the removal of the liver the pulse is more rapid than normal, but not more so than is usual, following other comparable operative procedures. After muscular weakness develops the pulse decreases but does not go below normal.

The respiration always becomes rapid and frequently of the Cheyne-Stokes type as the animal develops the moribund condition. Death is respiratory rather than cardiac; respiration in our animals has always stopped before the heart.

Contrary to expectations the temperature continues normal until the animal becomes comatose, when it may become subnormal. An interesting observation is that in some of the animals the temperature may go a degree above what it was previous to operation just before muscular weakness develops.

No findings at necropsy have as yet been noted which could be attributed to the loss of the liver.

In many respects the syndrome following the loss of liver function is typical of the syndrome following the total removal of the adrenal glands; the initial development of a muscular weakness is quite similar. On the other hand the muscular twitchings, and, particularly, the muscular spasms and the character of the respiration recall parathyroid tetany. The condition following removal of the liver, however, is, on the whole, a definite entity.

Since the preparation of an animal for the final operation of removal of the liver takes considerable time and there are some failures at the various stages, so far only a small series has been studied. This series, however, has shown conclusively that a definite and constant series of events occurs after complete removal of the liver tissue and a collection of data has been begun with regard to the changes which take place in the organism during the period the animal appears normal.

The data so far obtained do not justify many positive statements of the events after the removal of the liver or the cause of death.

There seems to be some change in metabolism whereby some intermediate toxic product is produced or some necessary element for metabolism is lacking. The process is probably of the same general nature, although of somewhat different characteristics than that following the removal of the adrenals or the parathyroids.

Special observations were recorded in a few cases:

1. One animal was transfused with blood and saline solution shortly after the first symptoms were noted. The usual course of the reaction did not seem to be affected by this procedure.

2. One animal was fed on a diet of liver for two weeks before the final operation. Except that the convulsions were more marked the results did not differ from those in other animals.

3. In two animals the carbon dioxide combining power of the plasma was estimated just before operation and again after the onset of the moribund condition. In both instances it was initially rather high and decreased slightly after operation, but not enough to account for any of the symptoms.

4. In one animal blood creatinin and in two animals urea determinations made before operation and during coma yielded normal values.

5. While careful estimates of the clotting time of the blood have not been made, gross observations have not revealed any difference. In one experiment blood removed just before death clotted in six minutes.

6. In two experiments in which observations were made bile appeared in the urine and in the plasma after operation; it was not present before operation.

7. In three animals the urine was tested for sugar after operation; sugar was found in one, but it disappeared before death.

8. In one experiment the blood sugar was estimated at various periods after operation. It progressively decreased to less than half its normal value.

Summary. A method is described for the total removal of the liver of a dog without complicating factors other than the anesthetic. This makes it possible to study the effect resulting solely from the loss of liver tissue. An animal from which the liver is removed by this technique recovers from the immediate effects of the operation and then presents a definite and characteristic syndrome, a sequence of events invariably ending in death. The length of life after removal of the liver in this series of experiments has been from five to eleven hours.