LIVER FUNCTION AND ANESTHESIA

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INTRODUCTION

The place occupied by the liver in the economy and daily function of
the body is unique. Anatomically, it is the largest; physiologically, its
diversified, ascribed functions are more numerous; clinically, its re-
serve and regenerative capacity are greater; and experimentally, in-
vestigation is more difficult than of any other organ in the body. While
in recent years many of its secrets have been divulged and methods for
accurately estimating its functions have been determined, the future
holds the key to its countless unsolved mysteries.

ANATOMY OF THE LIVER

The close relation of structure to function is well demonstrated in
the physiologic anatomy of the liver. Its size, double blood supply and
two types of functional cells with a remarkable power to regenerate
are the main characteristics pertinent to its function.

The percentage of blood contributed by the hepatic artery was found
to range from 12 to 30 (1), with an oxygen saturation of 85 per cent
(2), under a pressure of 90 to 100 mm. of mercury (7). According to
most investigations it contributes the major part of the oxygen supply
(3, 4) though this has been disputed (8). Ligation of the hepatic
artery causes necrosis of the liver cells and is incompatible with life
(5, 6).

The major blood supply to the liver is through the portal vein,
which carries 40 to 75 per cent of the blood (1) at an oxygen saturation
of 30 per cent and a pressure of 10 to 20 mm. of mercury (7). Ligation
of a branch of the portal vein causes atrophy of the liver cells (5, 6).
Ligation of the main portal vein is incompatible with life, owing to
shock and shunting of a large amount of blood in the intestinal tract
out of the general circulation (15). According to Grindlay and others
there is a reciprocal flow in the hepatic artery and portal vein which
may vary as much as 10 to 90 per cent in either vessel (4).

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The substance of the liver is composed of histologic units called lobules, held together by areolar tissue. The hepatic artery and portal vein, upon entering the liver substance, branch into the interlobular vessels at the periphery of the lobules, and these in turn give rise to the capillary-like vessels, the hepatic sinusoids. The principal cells of the liver are the polyhedral hepatic cells and the Kupffer cells, the latter belonging to the reticulo-endothelial system. Further histologic details may be found in a textbook of anatomy and histology.

The recent work of Wakinn and Mann (9, 10) is very interesting. They studied the circulation in the sinusoids and capillaries of frogs and rats by transillumination. The hepatic artery was found to supply the blood to the parenchyma by emptying directly into the sinusoids and into the branches of the portal vein just before the latter empty into the sinusoids, and by anastomotic branches between the hepatic artery and portal vein in the interlobular spaces. Stimulation of the hepatic plexus of nerves caused constriction of the sinusoids and arteriovenous anastomosis.

They also noted that inhalation of carbon tetrachloride produced immediate vasoconstriction of the sinusoids. If this agent was immediately removed, the circulation in the sinusoids returned to normal. If it was continued for one-half hour, liver injury resulted with maximum toxic effect in forty-eight hours. The liver became anaemic, and its vessels became obliterated by the pressure of the swollen hepatic cells. Repeated inhalations of carbon tetrachloride produced cirrhosis. In regenerating areas the blood vessels were extremely disorganized and the sinusoids in the area were supplied by arterial blood.

The remarkable proliferative powers of the liver cells were demonstrated in 1886 by Podwyssoszky (11). Chronic insufficiency in the liver is difficult to produce experimentally (12). Rous and McMaster (13) removed 65 to 70 per cent of hepatic tissue and in nine to twelve days the remaining lobes reached the size of the normal liver.

It is claimed that restoration of the liver after partial removal depends to a great extent on the flow of portal blood through the organ, the pressing stimulus being the portal blood itself (14).

Functions of the Liver

Those Concerned with Nutrition and Metabolism

Carbohydrate Metabolism.—Since the discovery of the glycogenic function of the liver by Claude Bernard in 1853, a study of the part played by the liver in carbohydrate metabolism has been greatly expanded. It takes up glucose from the blood and converts it into glycogen. As much as 20 to 25 per cent of the weight of the liver may be glycogen. The liver is the sole source of supply of glucose in the blood of the fasting organism (16).

The classical work of Mann (17, 18) and associates on the hepatectomized animals showed very clearly that the normal blood sugar cannot
be maintained without the liver. The animals die of hypoglycemia unless dextrose is administered. This was confirmed (20) by the fact that the known hyperglycemic agents such as epinephrine, ether, asphyxia and pituitary extracts have no influence whatever on the falling blood sugar level of the liverless dog (16, 21, 29).

Soskin called the liver the primitive regulator of the blood sugar, which can operate in the complete absence of insulin and the pituitary. The stimulus which elicits the hepatic response is the blood sugar itself—the so-called “homeostatic mechanism” (16).

There is evidence that the liver is able to convert a wide variety of substances, into glucose and glycogen, including carbohydrates such as fructose and galactose, proteins and fat. The use of isotopic carbon in the study of metabolism is yielding valuable information, the details of which are irrelevant to this discussion (26, 27, 16).

Hepatic gluconeogenesis is increased by the anterior pituitary hormone (22) and inhibited by insulin (16, 23). Epinephrine (23, 24) causes hyperglycemia, resulting in a sharp decrease, then rise of liver glycogen. In advanced hepatic disease hypoglycemia results (29, 30).

That the liver can convert lactic acid to glycogen and the muscle glucose to lactic acid is the basis for the Cori cycle. The removal of lactic acid by the liver is important in carbohydrate metabolism. By this cycle the muscle and liver glycogen become virtually interchangeable, which is clearly demonstrated by the action of epinephrine and in muscular action (23, 26).

Protein Metabolism.—That the liver is vitally concerned with protein metabolism was demonstrated by Mann (31, 32) and others from the results of hepatectomies in dogs. They showed conclusively that the process of deamination (33, 43), urea formation (36, 44, 45) and destruction of uric acid (18, 35) ceased after hepatectomy.

Part of the absorbed amino acids go to the formation of the plasma proteins, that is, albumin, globulin and fibrinogen. Experimental and clinical evidence (31, 37, 38) points to the liver as the chief site of the formation of these proteins, although small amounts of globulin may be formed by the reticulo-endothelial system. While proteins are not stored in the body as fats and carbohydrates are, the plasma proteins are a readily utilizable source in time of need. Fibrinogen is definitely formed in the liver (40). Clinically, in grave liver injury, blood proteins show lowered albumin and globulin with a reversal of albumin-globulin ratio (41).

The liver can also synthesize some of the amino acids. Alanine, tryosine, phenylalanine, histidine, glycine and others have been produced by liver in profusion experiments. The actual mechanism is not known (42).

In the process of deamination, the amino group is split off from the amino acid and the ammonia produced is combined with carbon dioxide to form urea (43). The remaining fatty acid residue may be
oxidized or transformed to glucose and glycogen or ketone bodies, a
process which probably takes place only in the liver (46).

The function of deamination in the liver is one of the last to fail in
disease. Definite impairment only occurred after removal of 90 per
cent of the liver (47). In fatal liver poisoning an increase has been
noted only shortly before death (48).

Fat Metabolism.—The striking deposition of fat in the liver under
various circumstances and its ability to form ketone bodies, and to
desaturate fatty acids are the main known factors which indicate it is
an important workhouse in the metabolism of fats. At present, how-
ever, relatively little is known about this field of metabolism and its
relation to the liver.

There are two main classes of lipid in the liver; one form is an
essential part of the cell structure of the gland, which is constant under
normal physiologic conditions. The other form is metabolic lipid
consisting of glycerides, phospholipins or cholesterol esters which may
vary greatly (49). Up to 60 per cent of the weight of the liver may
be fat (50) which produces impairment of its function. Although the
forces which attract the fat in such large quantities are more or less
obscure, relatively recent investigations have aided in the clarification
of variables such as diet, hormones and toxic substances. Accumula-
tion of fat in the liver will occur when the balance of fat income and
expenditure is upset (49).

The fat content of the liver increases after a meal. When no fat
is fed, that is, starvation, the liver may become full of fat which is
derived from carbohydrate and protein. In chloroform or phosphorus
poisoning the liver fat is deposited from fat depots as determined by
the use of radioactive carbon (51).

The phospholipids, especially lecithin, are important in that they are
the main means of fat transportation to the tissues. They are formed
mainly in the liver and after heptectomy there is a marked drop of
plasma phospholipids (52).

By the use of fatty acids earmarked with deuterium there is direct
evidence that the liver desaturates these substances (53). There is
also proof that the liver synthesizes fat from carbohydrate. Recently
it was found that 30 per cent of daily glucose supplement of the diet of
a well nourished animal is converted into fatty acids (34, 53). The
process requires vitamin B (54).

The formation of ketone bodies is an important step in the catabo-
lisim of fatty acids. It is generally agreed that the liver is the sole site
of ketone body formation (55) by the partial oxidation of fatty acids.

The metabolism of the sterols, of which cholesterol is the important
member, is not known. In the liver 60 to 80 per cent of cholesterol is
in the esterified form. The liver plays an important part in its
metabolism, possibly regulating its production and storage (56).
Liver Function and Anesthesia

Vitamin Metabolism and Storage.—The main role of the liver in relation to the vitamins appears to be that of storage (57). Vitamin A is stored mainly in the Kupffer cells and epithelial cells. The amounts depend on the blood level of vitamin A and on the functional state of the hepatic cells, being decreased in diseases such as cirrhosis. It is thought that conversion of carotene to vitamin A takes place in the liver (58).

The B-complex vitamins are also stored in the liver, especially vitamin B₁₂.

Vitamin K is dependent upon the secretion of bile for its absorption and it is necessary for the formation of prothrombin by the liver. Hypothrombinemia resulting from liver damage and removal is not altered by the administration of vitamin K, while that from diet or obstructive jaundice does respond to vitamin K and bile salts (58).

Vitamin D is stored mainly in the liver. Lack of bile salts prevents its absorption and liver injury its storage. Normal liver function is necessary to promote the antirachitic action of vitamin D (59).

Mineral Metabolism and Storage.—The liver stores minerals in varying amounts, the most important being iron and copper.

Iron is stored probably as haemosiderin until it is needed for the manufacture of haemoglobin by the reticulo-endothelial system, being salvaged from degenerating blood cells. It is eliminated in the bile although this may not be its only path of excretion (60).

The liver exerts an influence on both exogenous and endogenous iodine, some of which is excreted in the bile. Organic iodine is partly or completely broken down in the liver (61).

Those Concerned with Blood Formation and Maintenance

Embryonic Blood Formation.—Blood formation takes place in the fetal liver up to about the eighth month, after which time the function is taken over by the bone marrow. In severe anemia such as pernicious anemia the liver may regain part of this function.

Storage of Hematinic Principle.—This principle, which is necessary for normal blood formation, is stored in the liver. Impairment of this function occurs only in far advanced liver disease (62).

Production of Prothrombin.—Prothrombin, necessary for blood clotting, is definitely formed in the liver, as proved by its rapid decline after hepatectomy and damage by X-rays. Failure to synthesize prothrombin results in a prolonged clotting time, a condition which does not respond to vitamin K (63).

Production of Heparin.—Heparin, named as such because of its abundance in the liver, is produced by the mast cells of the body, the liver being one centre of production (64).

Regulation Blood Volume.—The liver regulates blood volume by storage of blood in the portal area, by the "valvular mechanism" and by its possible regulation of water balance.
Seventy-five per cent of the hepatic circulation is inactive under ordinary conditions with intermittent phases of activity. Some of the sinusoids may be full of motionless blood while others are empty (9). Experiments have shown (4) that there is considerable difference between the flow of blood to and from the liver, supporting the evidence that the liver is a site for the storage of blood.

Various workers have described thickened spiral bands of smooth muscle at the point where the hepatic venules open into the hepatic veins and where the hepatic vein opens into the inferior vena cava. These veins act as valves controlling the blood flow through the liver and they are affected by various drugs (39).

There is some evidence that the liver helps to regulate the transferring of water to the circulation and thus affects blood volume and water balance (65). It is suggested that the liver influences diuresis by destroying the antidiuretic substance of the anterior pituitary (66).

Production of Bile and Its Secretion

The secretion of bile by the liver is a continuous process, and was one of its earliest observed functions. Bile is a highly complex fluid containing, chiefly, the bile salts, sodium glycocholate and taurocholate, bile pigments bilirubin and biliverdin, cholesterol, lecithin, inorganic salts and water.

Jaundice occurs when the bile accumulates in the blood stream and in the tissues. There are three principal causes; obstruction of the bile ducts, depression of the liver cells and increased blood destruction. The excretory mechanism of the liver possesses a large reserve. Jaundice does not develop until 90 to 95 per cent of the ducts have been occluded (67).

The bile acids or sodium salts are formed by the conjugation of glycine and taurine with cholic acid, a process which takes place only in the liver. After complete removal of the liver, bile salts are not found in the blood or urine (68). Liver injury by chloroform results in a profound decrease in the concentration of bile salts (69). The bile salts are absorbed from the intestine into the blood stream and are reabsorbed by the liver for re-excretion. Only small amounts are lost in the feces.

The chief bile pigment, bilirubin, is excreted by the secretory cells of the liver, and passes into the intestine where it undergoes reduction to urobilinogen. A portion of it is reabsorbed, taken up by the liver and re-excreted into the bile (70). Minute amounts may be excreted in the urine where it is oxidized to urobilin. Bilirubin does not normally appear in the urine except when a biliary obstruction is present.

The change in bilirubin in its passage through the liver is the basis for the direct and indirect van den Bergh test. That which has passed through the liver gives a direct reaction, while that which has not passed through the liver gives an indirect reaction (71).
Lecithin is present in the liver bile in 0.02 to 0.05 per cent concentration. The cholesterol content is normally 0.04 to 0.16 per cent. The ratio of cholesterol to bile salts is 1 to 30. If this ratio falls, precipitation of cholesterol occurs.

**Power to Detoxify, Destroy and Excrete Substances**

The liver has been freely assigned a very definite function in its ability to detoxify, destroy and excrete a variety of substances. The various mechanisms may be grouped under chemical methods, excretion in the bile, storage and destruction in the liver cells and by the activity of the reticulo-endothelial system of which the liver forms a part. In many cases the actual mechanism is unknown or the substances may be excreted unchanged.

Some of the chemical methods include the processes of conjugation, oxidation, reduction hydrolysis, esterification and methylation. It has long been known that various toxic amines are detoxified in the liver. For example, indole is oxidized to indoxyl, conjugated with sulfuric acid and eliminated in the urine as indoxyl sulfuric acid or indican (72).

Many substances are detoxified in the liver some of which are worth mentioning. Acetylation of the sulfonamides to paraminobenzoic acid occurs in the liver (73). Procaine, cocaine and allied substances are destroyed by hydrolysis to paraminobenzoic acid (74). Morphine is detoxified by conjugation (75), atropine and scopolamine by partial hydrolysis (76). Nicotine (77) and strychnine (78) are also destroyed in the liver.

Some hormones are destroyed in the liver, including thyroxin (79), progesterone, testosterone, various estrogens (80) and epinephrine (81). Different substances are excreted through the bile, including some metals, estrogens and dyes, namely rose bengal and bromsulphthalein.

**Miscellaneous Functions**

*Heat Production.*—The liver, as a chemical factory of the body, is the source of approximately one-third of the heat of the entire organism. It has been shown that the temperature of the liver is reduced 1.3° to 3° upon simple laparotomy. Introduction of heat into the abdomen causes a coincident rise in the temperature of the liver and the brain. There is a 10 per cent decrease in chemical activity of the liver for every one degree fall in temperature (82).

*Anaphylaxis and Shock.*—Manwaring and associates (57) reported that exclusion of the liver from the circulation in a sensitized dog prevented the usual anaphylactic reaction when the antigen was administered. Later, histamine was found to be liberated from the liver in large amounts during shock (83).

The liver is also markedly damaged and profound changes take place during haemorrhagic shock from anoxia. The blood amino acid
is elevated, fibrinogen and prothrombin are reduced, blood keto acids, lactate and glucose become elevated (84). A 53 per cent decrease in portal blood flow has been produced with only moderate degree of shock and blood pressure fall. The inhalation of high oxygen concentration exerts a beneficial effect in shock (85).

It has recently been shown experimentally that the liver destroys the vasodepressor substance produced during shock. In the later irreversible stage of this syndrome, however, the anoxic liver loses this ability to destroy and starts manufacturing the vasodepressor substance, which further contributes to the shocked state (86).

LIVER FUNCTION TESTS

There are multiple tests for hepatic function, but only of recent years have they supplied reasonably accurate information. Each test measures only one function which may be impaired while other functions are unimpaired. The results must be correlated with the clinical picture. Boyce (87) stressed that one should get to know one or two tests and use them repeatedly rather than use many unfamiliar ones.

The function tests indicate diffuse and patchy disease when more than 80 per cent of the parenchyma is involved. By means of these tests, subclinical jaundice may be detected and they aid in classifying this symptom (88).

CLINICAL ASSOCIATIONS OF LIVER DYSFUNCTION

The state of the liver is just as important as the state of the heart, lungs or kidneys. Liver physiology is known to be disturbed in various extrahepatic conditions when no actual symptoms of hepatic disease are present. Graham (89) was the first to emphasize that hepatitis of some degree is an almost constant accompaniment of disease of the biliary tract. Many investigators in this field have repeatedly stressed the importance of the evaluation of liver function especially when there is associated jaundice (90). The patient with a damaged liver presents a risk for even the most trivial operation (15).

It is interesting to note a few of the clinical entities which have been found to have associated liver damage. In this category are acute and chronic infections (91), diabetes mellitus (104), severe burn injuries (95), intestinal obstruction (96) and advanced carcinoma involving the liver (92). Maclagan and Carter (93) observed significant functional changes in a variety of conditions including heart failure. In hyperthyroidism there is a degree of correlation between the severity of the disease, the basal metabolic rate and the degree of hepatic pathologic change (93, 94). In some cases of pregnancy, and more constantly in toxemia, there may be an impairment of liver function (97).

Heyd and others (98) have extensively described the so-called hepatorenal syndrome. In surgical cases, deaths from liver failure are
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often sudden and dramatic in patients who were supposedly good risks. There is a delay in recovery from the anaesthetic and within hours a semicomatose state ensues, coma hyperpyrexia and death occur within forty-eight to seventy-two hours. In other cases, especially with operations on the biliary tract, convalescence for four or five days is satisfactory when suddenly the patient passes into a coma and death. Often there is an associated renal failure.

There are several reports in the literature on the effect of surgical operations on liver function (91, 99, 100, 94, 141). The findings have been obtained by the use of various liver function tests preoperatively and postoperatively, the Quick hippuric acid and bromsulphthalein tests being the most common ones used. The extent and severity of the surgical procedure, duration of the surgical procedure, anaesthetic, age and nutrition of the patient are important contributing factors which are correlated with the degree of liver damage. Even patients with a normal liver and in supposedly good health showed transient hepatic insufficiency postoperatively.

The state of nutrition of the patient is a very important factor related to hepatic function. Patients coming for operation in a poor nutritional state from vomiting, diarrhea, poor diet or other causes, have a depleted protein and glycogen reserve (94). A study (19) of 215 surgical cases showed that the plasma proteins dropped markedly after operation. A definite relationship existed between the duration of the operation and the drop of plasma proteins. In operations lasting over two hours, all cases showed significant falls. Seventy-seven per cent of the patients who clinically needed preparation for operation had some impairment of liver function. During the postoperative course, these patients, in spite of intensive preoperative preparation with transfusions, showed a definite and prolonged drop in plasma proteins, whereas in those with normal liver function only 50 per cent had a drop in the plasma proteins. Depleted protein reserves may have a harmful effect on the structure of the liver itself. In starvation the liver may lose 40 per cent of its protein content (101). Regeneration of 40 to 60 per cent of the circulating plasma may be restored by the body when fasting, but is speeded up when a high protein diet (37) is given.

Various workers have investigated the effect of high carbohydrate, proteins and vitamins on liver function in different diseases, with anaesthetic agents and in surgery. Opie and Alford (102) in 1914–1915 first reported that a diet high in carbohydrate protected the liver cells against injury from chloroform, while a diet high in fat caused maximal susceptibility to liver damage (102, 103). Maise and Smith (105) and others (106, 113) found that both a high protein and a high carbohydrate diet were more effective, especially in the regeneration of the liver and in resistance to anoxia. Increasing fat storage and changes in the liver proportionately increase the mortality rate in surgery (107). It
has also been emphasized that sudden starvation in patients previously on a high carbohydrate diet should be avoided on account of the serious depletion of glycogen in the liver following sudden cessation of the carbohydrate diet (28).

The lipotropic action of choline (108) in decreasing fat deposition was one of the first factors discovered. The amino acid methionine, has a protective action from the injury of chloroform and production of fatty livers, while cystine may exaggerate the lipid content (109, 110). Anterior pituitary hormone and some estrogenic substances (57) may produce fatty livers.

**Effect of Anaesthetic Agents on Liver Function**

The effect of the anaesthetic agents depends on the kind and the quantity of the agent employed and on the extent of the hepatic damage that may already be present. Function tests show that even in patients with a normal liver and in supposedly good health, anaesthesia and surgical trauma may cause transient hepatic insufficiency. It has been shown that various anaesthetics cause, in different degrees, hyperglycemia, a lowering of the carbon dioxide-combining power, increased lactic acid, uric acid and organic phosphates, change of the nonprotein nitrogen and urea nitrogen, which are associated with liver function (15, 112).

The mechanism of hyperglycemia and glycogenolysis under anaesthesia is not definitely known. Up to 300 per cent increase of blood sugar has long been noted (111). Mann (113) stated that the ether hyperglycemia was entirely dependent on the liver and intact portal circulation, because it rarely occurred after heptectomy, and also that when the expected increase of blood sugar did not occur, hepatic degeneration frequently followed.

All the anaesthetics, even local, decrease liver glycogen to some extent, both during and for a period after the cessation of the anaesthesia. This decrease can be in part attributed to a direct action of the anaesthetic on the liver cells and to the liberation of epinephrine from the suprarenal glands. The rise is still obtained when both suprarenal glands have been removed and nerves to the liver have been cut (102, 114, 115).

Kniefel (117) advanced the theory that those anaesthetic agents which act principally on the cerebral cortex produce a rise of blood sugar through stimulation of the sympathethics and production of epinephrine. Also that the steps in the Cori cycle of conversion of liver glycogen to lactic acid is accelerated, while conversion of blood glucose to liver glycogen is inhibited. This theory has been supported and expanded by others (118, 134).

Recently it has been demonstrated that barbiturates decrease the hyperglycemia caused by agents such as ether which act principally on the cerebral cortex (119). These findings support the above theory.
Anoxia has a profound effect on the liver. It was first noted that in pernicious anaemia there was atrophy of the cells around the central veins of the hepatic lobules. Later, it was shown that if animals were kept in an atmosphere low in oxygen, a similar picture developed (120). The oxygen saturation of arterial blood is definitely decreased in liver disease; thus, it has been pointed out that the patient with a chronic hepatic lesion is poorly equipped to adjust to even minor degrees of anoxia (121).

Bourne and Rosenthal (122) found considerable impairment of liver function when gases were administered with asphyxia, thus increasing the toxicity of the anaesthetic. Goldschmidt and associates (123) showed that the use of oxygen with chloroform and divinyl ether markedly reduced the incidence of liver necrosis and led to the more rapid restoration of glycogen in the liver after anaesthesia. This protective action of oxygen compared favourably with that of a high carbohydrate diet prior to the period of anaesthesia. Improvement in the portal circulation as a result of adequate oxygen supply, may be a factor in this result.

The maintenance of an adequate blood pressure is an important protection against anoxia. It has been found that in 2 of 3 patients showing decrease in liver function postoperatively, a marked transient blood pressure fall had occurred (124).

Chloroform.—The evidence is now indisputable that “Chloroform poisoning is synonymous with chloroform anaesthesia” (122).

Casper was the first to suggest the possibility of death in the delayed action of chloroform. Langenback first demonstrated the fatty changes in the liver which may follow the administration of chloroform to man or beast. Later, a decrease in liver glycogen was noted, accompanied by an increase in blood sugar, and an increased excretion of nitrogen in the urine (11).

The first detailed pathologic changes occurring in chloroform poisoning were described by Fraenkel (11). Perhaps one of the most complete accounts is that given by Whipple and Sperry (125), who demonstrated that the central necrosis produced by chloroform is identical in dogs and man. Animals vary greatly in their susceptibility to the drug. Chloroform anaesthesia of only one-half hour duration produced changes in the liver which were demonstrable in six to twelve hours, reaching a maximum in forty-eight hours. When recovery ensued, the repair of this necrosis which in some cases involved more than half of every liver lobule, was restored to normal in two to three weeks. They also noted that pregnancy was no protection, but in fact chloroform in this instance caused severe liver necrosis and placental separation. These findings have since been confirmed (126, 62).

Whipple and Sperry (125) called the lesion of severe chloroform poisoning a condition of acute yellow atrophy. The liver is enlarged, pale and fatty. The lobules are distinct, with a deep red centre and
opaque yellow margin. Microscopically there is an extensive central necrosis which takes place chiefly around the central veins and expands centrifugally. This area may appear as a pink hyaline mass, which may be invaded by wandering cells. The peripheral cells are full of fat vacuoles, or the lobule may be very fatty. The bile ducts are unchanged. The injection of chloroform in the portal vein causes scattered peripheral necrosis, while injection into the hepatic artery causes mainly central necrosis. Perhaps the recent work of Wakim and Mann (9, 10) with carbon tetrachloride is an explanation of the type of lesion produced by this agent.

Various functional changes from chloroform poisoning have been demonstrated. The dye excretion, galactose and levulose tolerance are decreased and the nitrogen balance and protein metabolism are disturbed (127). Rosenthal and Bourne (122) found that one-half hour of chloroform anaesthesia produced transient bilirubinanaemia and urobilinuria that returned to normal in three days and the bromsulphthalein test returned to normal in eight days. Two hours of anaesthesia with this agent caused the icteric index to rise, and 100 per cent dye retention occurred for two days, taking six weeks to return to normal. The maximum injury occurred in the first twenty-four hours. The secretion of bile and bile salts is suppressed (25, 128). The bleeding tendency which occurs with chloroform owing to failure of synthesis of prothrombin never takes place when other agents are used with anaesthesia of one hour duration (129).

Ether.—Diethyl ether has various effects on the liver. As mentioned previously, it causes marked hyperglycemia and lowers the liver glycogen 15 to 20 per cent in five to six minutes, and more than 50 per cent after an hour of anaesthesia (114). It usually depresses the secretion of bile and bile salts, which has been shown by both laboratory and clinical investigation (113, 130). According to Rosenthal and Bourne (122), one-half hour of ether anaesthesia produced slight impairment, with return to normal in twenty-four hours. Others have obtained similar results, some cases taking one week to return to normal (94, 124, 141). The damage is intensified by oxygen lack and poor nutrition. Ether anaesthesia in dogs causes decrease in the oxygen saturation of arterial blood and an increase in oxygen saturation of venous blood, thus decreasing the arteriovenous difference and the amount of oxygen available to the tissues (131). Recently Armstrong (133) attempted to assess the effects of ether and trichlorethylene on the liver, using the cephalin flocculation test. Ether was found to cause a greater degree of damage.

Vinyl ether or divinyl oxide causes ketonemia and hyperglycemia (134). It does not significantly affect bile secretion (128). Repeated administration in dogs caused no alteration in the bromsulphthalein test unless accompanied by cyanosis (135). Liver necrosis, however, has been produced in dogs by this agent (136). Less damage results when
it is administered with oxygen (123). It has been used in obstetrical cases without any detectable liver damage (137). In a large series of one hour anaesthesia with vinethene and oxygen no hepatic damage was found (138).

Cyclopropane.—Cyclopropane causes no demonstrable damage to the liver. There is transient hyperglycemia (139) and no change or even a rise in bile salt secretion (128). Bourne (140) found that after long and repeated administration in the normal or chloroform damaged liver, no impairment was produced, as detected by the bromsulphthalein test. When it was administered to normal obstetrical patients and one who had eclampsia with liver damage, no changes in function were detected. These findings have been substantiated by others (130, 141).

Barbiturates.—The present relationship of the barbiturates to the liver is not completely settled. It has been generally accepted that the liver is necessary for the destruction of the short and ultra-short acting barbiturates but not in the metabolism of the long acting ones (142).

Sodium barbital is excreted by the kidneys. Nembutal is definitely destroyed by the liver as shown in various experiments (143, 144). There is evidence that evipsal is destroyed by the liver (144), but it is claimed that other tissues such as muscle and spleen may share in this action (145). From the experimental work of Masson and Beland (146) it is reported that the short acting barbiturates, namely nembutal, ipral, amyctal, seconal and others of this group, are mainly inactivated in the liver; while neonal, alurate, fenadorn, dial, pernosta and others of that group are detoxified in kidney and liver, and barbital and phenobarbital are excreted through the kidneys. Pentothal and other thiobarbiturates, they concluded, are detoxified in the body, but not necessarily in the liver and kidney. Others claimed that pentothal is destroyed in the tissues and blood (147). Recent reports (148), however, suggest the liver so efficiently detoxifies pentothal that very little functional tissue is required to detoxify the small dose used in man. It may be concluded that the liver is its main site of destruction but this may be assumed by the other tissues in case of liver failure.

There are few functional and anatomical changes in the liver following administration of the barbiturates. No impairment of function tests was found following administration of sodium amytal (149), pentothal (150), or evipsal (130) in human beings. There are various reports that repeated doses of barbiturates to animals cause no histologic changes (151). A few cases of hepatic damage in man have been reported (144). A slight rise in blood sugar, with a reduction of liver glycogen, occurs following the administration of barbiturates (114, 152).

Nitrous Oxide.—According to the majority of reports in the literature, nitrous oxide has no effect on the liver unless there is accompanying anoxia (122, 130). Coleman (91) reported, however, that 50 per cent of a series of patients receiving nitrous oxide-oxygen-ether and 31
per cent receiving nitrous oxide-oxygen showed functional impairment in twenty-four hours returning to normal by the eleventh to thirteenth postoperative day. Nitrous oxide has no effect on bile secretion (128) unless accompanied by anoxia and it causes only a slight rise in blood sugar (153).

Ethylene.—According to Rosenthal and Bourne (122) this agent produces no effect on the liver unless accompanied by asphyxia. Others (94) have found transient impairment of hippuric acid excretion in a series of cases, which returned to normal in two to seven days. Ethylene causes slight decrease in bile acid secretion (128). It also causes a rise in blood sugar (153).

Tribromethanol (Avertin).—Tribromethanol is detoxified in the liver by conjugation with glycuronic acid (154). It causes hyperglycemia and decreased secretion of bile acids.

Bourne and his associates have shown that after avertin anaesthesia in dogs a transient delayed excretion of bromsulphalein occurred. Repeated administration in dogs produces a mild parenchymatous degeneration of liver and kidneys. In the previously damaged liver, avertin caused a 5 to 30 per cent additional damage (155). Repeated administration to a patient over a long period caused no detectable liver damage (156). Others have found that patients receiving this agent showed liver damage twenty-four hours after operation which returned to normal in thirteen days (130).

Ethyl Chloride.—Since the general pharmacologic effects of this substance are similar to those of chloroform, but less intense, one would expect to find that it produces liver damage. Its actual effect on liver function has not been investigated by function tests. It is more toxic to the heart and is used only for short periods. Jaundice and fatty degeneration of the liver have been noted after repeated administrations (165).

Trichloroethylene.—This anaesthetic has been in extensive use only the last few years (157). Clinically, trichloroethylene is nontoxic to the liver, having been used successfully in short cases such as in obstetrics and in long neurosurgical cases (158, 160). After two or three hours of anaesthesia with this drug, no liver damage was produced in animals (159). Transient liver impairment has been demonstrated twenty-four hours after operation by the use of the cephalin flocculation test; a few cases of liver damage have been reported (133, 132). A transient increase of blood sugar occurs with this agent. Chlorinated compounds related to trichlorethylene are notoriously liable to damage the liver.

Local Anaesthetic Drugs.—Local anaesthetic drugs are destroyed chiefly in the liver. The synthetic group, such as procaine and allied compounds, are destroyed rapidly, while the destruction of cocaine and halocaine is much slower (163). Nupercaine elimination is also slow (74). Slight, if any, decrease in liver function occurs postoperatively
The use of local anaesthesia in liver disease is not without danger (163).

One might think that spinal anaesthesia had no effect on the liver. Boyce (94) and associates, however, found that those receiving spinal anaesthetics as compared with those receiving general anaesthetics showed the greater postoperative fall. Morrison (130) and others (124, 141) found that it placed the smallest toxic burden on the liver and produced the least evidence of dysfunction. All generally agree that spinal anaesthesia causes damage by a drop in blood pressure and by the effect of anoxia. It has been shown in dogs that spinal anaesthesia produces a stagnant anoxia, which is minimized by the use of vasoconstrictor drugs (116).

Curare.—The fate of curare in the body has been generally accepted to involve partial destruction in the liver and excretion by the kidneys. In heptatectomized animals no increased duration of action of the drug was noted (164).

SUMMARY AND CONCLUSIONS

The role of the liver in metabolism storage, excretion and detoxification are the most important of its many and varied functions.

Clinically, liver impairment may be found in hepatic, biliary tract and other extrahepatic diseases and following surgical operations.

The effects of anaesthetic agents on the liver have been reviewed; chloroform is the most toxic.

Anoxia is one very definite cause of hepatic damage.

It is of prime importance to consider the liver in all its manifestations.

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NOTICE OF MEETING

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The 1950 Convention of the Association of Military Surgeons of the United States will be held from November 9 to November 11, inclusive, at the Hotel Statler, New York City.

Appropriate to the times, the programs will deal with Civil Defense, the Defense Role of the Physician, Aviation Medicine, Rehabilitation, Military Medicine, Surgery, Sanitation, and discussions on the use of the newest therapeutic and prophylactic agents in emergency conditions.

It would appear that some of the items listed for the program for the above meeting would prove of interest to Anesthesiologists.

This information was received from Robert H. Kennedy, M.D., General Chairman, The Association of Military Surgeons of the United States. Additional information may be obtained from Col. Robert H. Kennedy (MC) AUS, 115 East 61st Street, New York 21, New York.