Review

Anesthesia and the Liver

David M. Little, Jr., M.D., and Howard J. Wetstone, M.D.

"A boy four years of age was admitted to the Paddington-green Children's Hospital on Sept. 6th, 1889, under the care of Mr. Stanley Boyd, suffering from double talipes equino-varus with contraction of some of the thigh extensors. There was also wasting of the left arm. The deformities were due to infantile paralysis occurring at the age of four months. In other respects he seemed on admission to be in perfect health. On Sept. 7th, at 4 P.M., under chloroform, Mr. Boyd divided the tendo Achilles and also the tendons of the flexor longus pollicis in each foot. Tight bands under the arch of each foot were also divided in several places, and finally the contracted tendons below the superior iliac spines on each side were severed. The punctures were dressed with carbolic gauze, and the feet put up in normal position by means of plaster-of-Paris bandages. Cloths soaked in carbolic acid (1 in 20) had been applied to the feet for about two hours before the operation, which lasted about an hour. The chloroform was taken well, but the patient vomited brown, bilious-looking fluid once or twice. He came completely round without appearing to be unduly collapsed and in the evening seemed to be well and lively and cried for food. The temperature after the operation was 97°F., at 9 P.M. it was 99°, but at 5 A.M. on the 8th he suddenly began to vomit. The house surgeon was sent for and found him unconscious; his pulse was very weak, and his breathing shallow and irregular. He was very restless, constantly shrieking shrilly and grating his teeth. Twenty minims of ether were injected, after which the pulse seemed to improve, but the vomiting remained incessant. The vomit was generally of a dark-brown colour, somewhat resembling beef-tea, and answering to Gmelin's test for bile, but it was sometimes light or slightly yellowish. Four ounces of urine were drawn off by catheter (none having been passed since the operation); it contained neither albumen nor carbolic acid. At 1 P.M. a small quantity of urine was again drawn off; this also contained no carbolic acid, but some albumen was present; in both samples the sulphates were normal. The child's condition changed but little all day, except that the breathing became of a more sobbing character, with convulsive movements of the lower jaw, and for the last hour or so of life it was of a sighing or moaning type. Consciousness was never regained. At 7:30 P.M. the dressings were changed for salicylic wool, on the chance that carbolic acid poisoning might be the cause of the symptoms, but no improvement took place, and the child gradually sank and died at 11:20 P.M., thirty hours after the operation. The temperature at 9 P.M. was 101°.

"*Necropsy.*—The body was well nourished. The lungs were congested, but otherwise quite normal. The heart, somewhat pale, was in diastole. The right auricle was full of dark clot. The liver was small; it weighed fourteen and a half ounces; it was of a pale buff colour, studded by minute purple dots. On section it was of similar appearance and felt greasy to the touch. Oily fluid remained on the surface of the knife after gently scraping. Under the microscope little else beside oil globules and debris of liver cells could be seen in a fresh scraping. The kidneys were normal. The spleen was small and pale. The brain was normal.

"*Microscopical examination of the liver.*—Thin sections of the liver on being placed in a 1 per cent solution of osmic acid, became in a few moments of a deep mahogany brown, which deepened into coal black within a few hours. By transmitted light they presented a variegated appearance, due to the much deeper staining of the circumferential portions of the lobules as compared with the more central parts. About two-thirds of the external portions of the lobules were of an intense black, whilst the colour gradually faded to a pale drab in the immediate neighbourhood of the intra-lobular veins. The cells of the periphery of the lobules were globular and distended, but towards the centre they were of normal shape, and looked granular from containing innumerable droplets of oil. The nuclei of all the cells stained deeply with logwood. The connective tissue cells were normal and showed no signs of fatty degeneration. The condition then was one of intense fatty infiltration, apparently unaccompanied by fatty degeneration."[1]

This quotation is from Guthrie's article entitled, "On Some Fatal After-effects of Chloroform On Children," in the January 27, 1894, issue of the *Lancet*. It was the first detailed description of a liver death following anesthesia in the English literature, although there

Received from the Department of Anesthesiology and the Department of Medicine, Hartford Hospital, Hartford, Connecticut.

are earlier references to delayed chloroform toxicity by the Germans.[2,3] Guthrie's report recorded ten cases, nine of which were fatal, and all in children. It soon became evident, however, that the condition could occur with equal facility in adults and, further, that unpleasant effects upon the liver after anesthesia were not limited to chloroform. Indeed, over the past seventy years, considerable attention has been accorded investigation of the effects of anesthesia upon the liver, and during the past twenty years or so there has also been interest in the effects of liver function on anesthesia. The present review, therefore, will consider briefly some pertinent knowledge of liver structure and function, of the effects of anesthetic drugs and techniques upon liver structure and function, of the effects of the liver upon anesthesia, and of the anesthetic management of patients with various forms of liver disease.

The Liver

The past decade or so has seen a vast amount of investigation into the fundamental physiology of the liver and its diseases, and much of this information is of import to the anesthesiologist. It is patently impossible to cover all of this material, but certain aspects of the liver's anatomy and histology will be considered, as well as some recent concepts of liver function and function tests.

Anatomy

Although the arrangement of the hepatic parenchymal cells in terms of the central (draining) veins appears to be hexagonal, in fact, the basic physiologic unit is arranged about vessels bringing blood into the liver.[4,5] Thus, the *simple liver acinus* has as its central axis a terminal branch of the portal vein and an hepatic arteriole. In addition, a bile ductule leaves the acinus in this axis and lymph vessels and nerves are also to be found in this core which appears as a triangular *portal field* under the microscope. Wrapped around the axis there are three-dimensional zones of tissue which are distinguished empirically by their relative distance from the center. As might be expected the blood supply of the innermost zone is generally richer in oxygen and nutrients than that of the middle or outermost zones. Each zone occupies two or more of the so-called hexagonal fields.

Even under normal conditions the hepatic cells of each zone demonstrate quantitative differences in the distribution of the various enzyme systems within them[6] suggesting that their function is not nearly so uniform as previously believed. When events occur such as to decrease the hepatic blood supply, the cells of the outermost zone will be compromised first of all and regenerate last of all when normal blood flow is restored. The actual pattern of injury or fibrosis seen depends upon the plane of the cut section, and if interpreted in terms of the hexagonal field, leads to such irrelevant terms as "paracentral" or "pericentral." In reality, the *physiologic* zones effected by disease processes are the subsections of the simple acinus. Three or more of the simple acini join together as a *complex acinus*, three or four of which relate anatomically to form the *acinar agglomerate*.

The healthy liver is like an organ in a perfusion system in that the *external* system, rather than intrahepatic factors, is the major determinant of the rate of blood flow through it.[7] The regulation of circulation in the liver depends more upon modification of blood flow distribution *within* that organ than on changes in *total* resistance to the perfusion. The extraordinary degree of branching of the portal venous tree and the existence of side as well as terminal branches contribute to this control of distribution.[8] This complicated portal tree empties into the sinusoidal bed which is a labyrinth of interconnected passageways whose walls consist of a continuous system of sheets and beams of liver cells.[9,10] A complicated series of inlet and outlet sphincters, venous and arteriolar constrictions, and bulging Kupffer cells further control the intrahepatic distribution of blood whose flow ". . . through each territory of hepatic parenchyma, no matter how small, is controlled by specific mechanisms located at strategic points."[11] It is, therefore, not surprising that measures of total blood flow through the liver are not reliable indices of the actual circulatory status of that organ.[7]

The normal resting value for hepatic blood flow in man ranges from 1.5–1.8 liters per minute, of which 20–40 per cent is arterial.[12] General anesthesia is said to reduce this flow.[13,14] However, hepatic blood flow was not found to be affected by thiopental-nitrous oxide anesthesia[15] or with pentobarbital anesthesia.[16–18] This has led Fischer to conclude that hypotension and hypoxia, rather than the anesthetic agent *per se*, is the factor in anesthesia affecting total hepatic blood flow.[19]

The normal hepatic oxygen consumption is one-third of the total for the entire body or about 40 ml. per minute per square meter of body surface. Under mildly hypoxic conditions the hepatic arteries participate in the resultant generalized systemic vasodilatation, but in the presence of severe hypoxia they undergo vasoconstriction. Also, despite the increase in cardiac output in hypoxia, the hepatic fraction of one-fourth the total output may decrease. Thus, conditions which can cause hypoxia (pulmonary disease, heart failure, anesthesia or shock) may be the last straw for a liver already suffering from circulatory embarrassment, or even for a normal liver if the hypoxia is severe enough.

The intrahepatic causes of liver circulatory distress may vary from inflammation (hepatitis) to the obstructions causing portal hypertension (above, within or below the liver). In the normal liver, shifting from the resting to the upright posture generally results in a fall in hepatic blood flow[12,20] due to an increase in vascular resistance of the liver that is not seen following sympathectomy.[21] This factor is of considerable importance in the management of liver conditions in which cellular injury is combined with total flow reduced to hypoxic levels.

The damaged liver cell is particularly vulnerable to hypoxia which if present can result in a "vicious circle."[7] In addition, animal experiments have shown that during regeneration the peak of the mitotic wave is associated with a 50 per cent higher oxygen consumption than in resting cells.[22] It is thus evident that the injured liver requires more oxygen than normal resting hepatic tissue. For these reasons bed rest is essential in the management of serious, acute and chronic disorders of the liver.

Portal venous blood arrives at the liver loaded with absorbed nutrients, at 60–75 per cent oxygen saturation (more than systemic veins) and under only 8–10 mm. of mercury pressure delivered through an aperture, the portal vein, ranging from ¾ to 1½ cm. in diameter. On the other hand the arterial blood enters the liver through the 3 mm. diameter hepatic artery under a 100 mm. of mercury head of pressure at 95 per cent oxygen saturation.[12] The average venous flow rate is 9 mm. per second as opposed to 17 cm. per second in the artery. In the liver's simple acini the terminal portal venule blood mixes with the hepatic arteriolar blood in the sinusoidal spaces and by direct A-V connections. The wedged "occluded" hepatic vein pressure determined by catheterization is 5–6 mm. of mercury under normal conditions.[23] The percutaneous intrasplenic pressure is 8 mm. of mercury.[24]

The large volume of portal venous blood flows slowly into the liver with slight increases during respiratory movements. The high-pressure spurts of hepatic arterial blood drive through the sinusoids containing the semi-stagnant portal venous blood, pushing it along in the manner of "rivulets moving through the delta of a swampy river." The aforementioned intricate mechanism of constrictions and valves controls the overall distribution of flow. The liver normally adapts well to wide fluctuations in its total blood supplies. This is fortunate since its total chemical function depends upon the volume of blood reaching the hepatic cells. Interruption of flow and/or oxygen supply will result, however, in failure of major detoxification systems by default in the disease-compromised liver.

For example, when portal blood bypasses the liver as in the surgical Eck fistula created to treat portal hypertension,[25] or the intrahepatic "Eck" fistula of severe cirrhosis,[26] the ingestion of protein material or presence of blood in the intestinal tract may result in "exogenous" hepatic coma.[27,28] The cirrhotic stasis in the small intestine permits the growth of urea-splitting organisms in this area[29] which convert protein material to toxic substances such as ammonia. The use of protein restriction[30,31] and broad spectrum antibiotics[27,32] tend to prevent this from occurring.

Histology

In recent years it has been possible to break the light barrier of the conventional microscope and explore the liver cell by means of electron microscopy.[33] In addition, improved methods of histochemistry and immunochemistry have permitted correlation of the visible with the functional, and a brief outline of the liver cell structure and some of its functions that may be utilized as clinical tests of its status is in order.

The more-or-less rectangular hepatic cell has straight borders where two cells approximate each other. However, where a cell margin lies along a tissue space or bile canaliculus, numerous finger-like projections (microvilli) project into these spaces suggesting the absorptive and excretive functions of the selective membrane. A host of enzymes lie within the cell differing quantitatively according to the distance of the cell from its source of blood supply. Within the cytoplasm of the cell lie the rod-shaped mitochondria with their double-membranes, the inner of which invaginates to form grooves or cristae within this structure. Both membranes control the interchange of such substances as potassium, water or sucrose. In addition, the inner membrane contains the electron-transport system which releases energy from the materials of the Krebs cycle. The mitochondria are oriented along lines connecting the sinusoidal and canalicular surfaces of the cells.[34]

Stretched out through the cytoplasm a host of wavy lines may be seen constituting the microsomal fraction of the particulate matter of the cytoplasm. These are seen to consist of single-membranous string-like structures known as the endoplasmic reticulum or ergastoplasm. Under light microscopy these account for the basophilic stipling of cells. Along these strings in varying amounts are tiny granules of ribonucleoprotein (Palade granules). The strings themselves contain nucleoproteins, cholesterol and detoxifying and metabolic enzymes.

Lying alongside the much larger mitochondria are found small, oval packets of material containing hydrolytic enzymes and other substances. These lysosomes are usually near the bile canaliculus side of the cell, as are the collection of vesicles and particles called the Golgi zone. The rest of the cytoplasm between the microsomes, mitochondria and other organelles consists of hyaloplasm or "cell sap." This contains enzymes of metabolism, glycogen, RNA, NAD, transaminases, and the like.[34]

The hepatic cell nucleus has a membrane closely associated with the endoplasmic reticulum, thus permitting the genetic DNA material to influence the RNA, both of the nucleolar and Palade granule. The other characteristic cell of the liver is the sometimes stellate reticuloendothelial Kupffer cell which lines sinusoids and may exhibit ameboid projections. Its function is phagocytic and to act as a filter of particulate matter.

The cellular basis for hepatic disease has been well stated by Popper and Schaffner.[35] In summary, the liver cell may react pathologically in the following general ways: by alteration of the sinusoidal part of the cell wall; by changes in the bile canaliculus with decrease in microvilli: by injury to the mitochondria; by injury to the microsomes which are the sites of specific functions for the liver and which "mirror specific injuries of the liver cells" forming ". . . the basis of most of the hepatic function tests"; by damage to the lysosomes; by infiltration of foreign material; and by lesions of a multi-organelle nature.[35] Secondary effects of injury to the liver cells include the hepatocellular epithelial response which can produce regeneration or lead to neoplastic lesions; reactions of ductular cells or mesenchyma; and mesenchymal reactions such as phagocytosis, fibrogenesis and the formation of gamma globulin and antibodies. A tertiary response of the liver to injury of great importance is the condition of variable scarring known as cirrhosis of the liver. In addition to the infectious and vascular diseases which may effect the liver, there are a large number of known hepatotoxins some of which constitute drugs or therapeutic substances used in man. For a complete list of such hepatotoxins the reader is referred to Table 1 in the article by Rouiller.[36]

Function and Function Tests

The major role of the liver in the metabolism of carbohydrates, proteins and lipids is

far beyond the scope of this review. However, of particular interest is the existence of glucose-6-phosphatase which permits the release, on demand, of free glucose to the blood stream. This is not feasible in muscles (where this enzyme is absent), which cannot effect the final step in the breakdown of stored glycogen to glucose. An alternate pathway of carbohydrate metabolism, the pentose shunt, is very active in the liver. This permits the production of five-carbon components of nucleic acid as well as acting as a major energy source.

Among the liver's roles in the anabolism, catabolism and interrelationship of basic foodstuffs and body materials is its function as a major organ in the catabolism of steroid hormones. Although often by nonspecific mechanisms this is shared by other organs, the generous blood supply and size of the liver as well as, in certain cases, its possession of specific enzymes make its role in steroid hormone metabolism of some considerable importance. When liver function is impaired there is a generalized slower rate of hormone production and turnover. That "estrogenic" effects seen in patients with chronic liver disease are due to disruption of this mechanism has long been suspected but is not yet confirmed.[37] However, it is known that human fetal liver, as well as lung, kidney, adrenal and skeletal muscle, can conjugate estrogens.

The liver is involved in the storage or metabolism of a number of vitamin materials. As examples are the fact that the liver is the main site of storage of vitamin A, can manufacture it from a precursor (beta-carotene) and can convert it to the aldehyde by the use of liver alcohol dehydrogenases. The liver also stores two forms of vitamin D (D_2 and D_3), is involved in B complex metabolism and stores vitamin K_1 which is synthesized by the bacteria of the gut and absorbed with the bile. The liver does not, however, store menadione or vitamin K_3.

Certain hepatic and biliary disorders are associated with clotting defects and hemorrhage due to the liver's role in the coagulation of the blood. In obstructive jaundice the absence of bile in the intestine leads to failure to absorb vitamin K which is essential if the liver is to manufacture certain procoagulants such as Factor II (prothrombin), Factor VII (serum prothrombin conversion accelerator) and Factor X (Stuart Factor).[38] On the other hand, after severe liver damage the supply of vitamin K may be adequate but the hepatic cells will no longer be able to synthesize either these factors or Factor V (accelerator globulin), whose production is not dependent upon vitamin K. The parenteral administration of vitamin K and its effect on the *prothrombin test* may distinguish these two types of situations. In obstructive jaundice (without severe cellular damage) the prothrombin test will improve since Factor V is being made satisfactorily; whereas, in severe cellular damage, the exogenous vitamin K will have no effect on the prothrombin test. Other clotting abnormalities seen in liver disease include fibrinolysis, the presence of antithrombins, and the occurrence of thrombocytopenia or thrombasthenia.

Perhaps of greatest current interest in the assessment of function of the liver are those tests which reflect its roles in the detoxification, modification and synthesis of various compounds through the aid of its elaborate enzyme systems. Most, if not all, of those enzymes which are unique to the function of the liver have a pattern of development in the mammal which is quite characteristic.[39] This is especially evident with regard to enzymes effecting bio-transformation of foreign drugs.[40] These enzymes lie in the lipid-rich microsomes which originate from the endoplasmic reticulum of liver cells where lipid-soluble foreign substances can have ready access. In aquatic animals with gills, these organs, which are lipid in nature, can excrete such lipid-soluble compounds[41] but their livers lack detoxifying enzymes. However, in higher forms such as mammals, the liver of necessity contains such enzymes. Likewise, during the development these enzymes are absent in the embryo but develop at, or shortly after, birth. An example is glucuronide formation which is governed by the glucuronyl transferase system. Its delayed appearance at birth accounts for the high toxicity in the newborn of such substances as chloramphenicol,[42,43] progesterone or novobiocin.[44,45,46] In certain hereditary disorders the enzyme never appears. In other cases the failure to conjugate

material may not mean inhibition or absence of the enzyme but merely competition for excretion by the liver cells as in the unconjugated hyperbilirubinemia seen following cholecystographic contrast media such as Orabilix, Telepaque or Cholografin.[47]

The liver has a number of functions which revolve around the hematopoietic system. Some of these are related to its most prominent excretory function which is the elaboration of up to one liter of bile daily.[48] This bile contains 10–15 Gm. of bile salts which act as a detergent in emulsifying certain fatty materials in the gut, an action essential to the digestion and absorption of certain fats and lipoids, particularly, as already has been noted, the precursors of vitamin K. The bile acids originate from cholesterol which the liver excretes as it does other conjugated metabolic products such as thyroxin, other hormones and bilirubin. Hemoglobin catabolism ends in the production of bile pigments although the original compound may also be metabolized by alternate pathways and bilirubin may be formed from sources other than the hemoglobin of erythrocytes. This may explain why hydrocortisone-type corticosteroids can lower *serum bilirubin* levels. The liver is also capable of inducing a change in the structure of the hemoglobin molecule which prevents this material from causing renal vasoconstriction.[49]

The most important function of the liver with respect to catabolism of hemoglobin involves the fact that the open-chain degradation product of the heme portion of hemoglobin, unconjugated bilirubin, is a relatively nonpolar material which is insoluble in water. For this reason it reacts very slowly (indirectly) with Ehrlich's reagent unless alcohol is added to bring it into solution. In addition, this indirect bilirubin dissolves readily in lipoid material, such as brain, which can lead to kernicterus if it is present in high amounts as in Rh incompatibility in infants. The unconjugated material ordinarily does not enter the urine.

The liver possesses an enzyme system (glucuronyl transferase) which can conjugate *indirect bilirubin* with two glucuronic acid molecules. The newly formed diglucuronide of bilirubin is a much more polar material which dissolves in water and reacts promptly (directly) with Ehrlich's reagent. This direct bilirubin is poorly soluble in lipoid material and can enter the urine.[50-55]

The relatively slow development of the glucuronyl transferase enzyme system after birth produces a relative deficiency of this enzyme which leads to physiologic jaundice of the newborn.[56] Hereditary defects in this enzyme system result in characteristic syndromes in the human as well as the well-known Gunn rat disorder. The defect is related to extremely high levels of indirect bilirubin and a very high incidence of kernicterus when it occurs in infancy in the Crigler-Najjar syndrome;[57] it is also seen in adults in Gilbert's Disease.[58-61] The latter situation may be confused with liver or biliary tract disease in the adult and often leads to unnecessary gallbladder surgery. The same may also occur in certain poorly understood bilirubin excretory disorders such as the Dubin-Johnson syndrome[62] in which the elevated bilirubin is both conjugated and unconjugated.

Ordinarily the *ratio of indirect to direct bilirubin* is so variable in disease that it is not useful in distinguishing hemolytic from hepatic causes of bilirubin elevation. Whatever testing methods are used to detect this pigment must, of course, exclude other materials which discolor serum.

Another consequence of the liver's role in the metabolism of the heme materials is its storage of iron, and, indeed, plasma iron may be elevated in such situations as acute infectious hepatitis.[63]

After the delivery of the bile pigment into the intestine its metabolism by intestinal bacteria and reabsorption of the catabolic products leads to the appearance of urobilinogen in the urine. The amount of this material in a twenty-four hour sample of urine may be detected readily by the use of Ehrlich's aldehyde reagent. When the flow of bile to the gut is interrupted by obstructive phenomenon or when the bacteria are destroyed by antibiotics this urine urobilinogen decreases or disappears. Conversely, when excess bile pigment enters the gut as in hemolysis or when the liver does a poor job in excreting

reabsorbed material the urine urobilinogen may increase.[64]

Although *alkaline phosphatase* is an enzyme, its major usefulness in evaluation of liver function depends upon excretory processes in the liver. It is elevated in such bone disorders as active rickets, hyperparathyroidism and Paget's disease, as well as in situations which produce intrahepatic obstruction (the early phases of inflammation as in hepatitis or chlorpromazine hepatosis) or in obstruction of the extrahepatic biliary system. It has also been noted to be elevated in diffuse infiltrative lesions of the liver such as cancer, lymphoma or sarcoidosis. In the complex situation of cirrhosis this test, along with most of the other major tests of liver function, may or may not be abnormal. In fact, the pattern of liver function tests in patients with cirrhosis is a somewhat haphazard one. It should be noted that the values for alkaline phosphatase tests vary considerably with the numerous test methods.[65,66] In general, interpretation of this test is best done in combination with the level of total bilirubin, particularly in distinguishing extrahepatic obstructive phenomena from those of acute infectious hepatitis.

Still another test partially dependent upon the liver's excretory processes is the *Bromsulphthalein (BSP) test* which depends upon the delivery of a given load of a highly soluble dye, its binding to serum albumin, and its transfer from blood to the hepatic cell where it is conjugated and excreted into the bile. Excretion takes place at a rate of about one-third that of its uptake from the plasma.[67] Alkalinizing the blood sample collected at a fixed time after the dye is given results in the color reaction measured in the laboratory.[68] The normal retention of less than 5 per cent of a dose of 5 mg./kg. in forty-five minutes may be doubled (8–10 per cent) due to artifacts in the test. In addition, the exquisite sensitivity to such extrahepatic factors as physical strain and hypoxia[69] tends to limit its usefulness, and, in fact, the inhalation of 10 per cent oxygen may significantly effect the results.[70] The administration of *Norethandrolone* (Nilevar) may also increase retention of the dye.[71] Abnormal retention of BSP in the presence of other normal liver function tests and normal histology may reflect subcellular lesions[72] but is of doubtful clinical value.

Despite the many reported changes in serum non-enzymatic proteins detected by *paper electrophoresis* in liver disease[73] none of the patterns is reliable enough to be useful diagnostically or prognostically. There is a general tendency toward a poor prognosis in cirrhosis with low serum albumin,[74] a general correlation with very high gamma globulin, and poor prognosis in infectious hepatitis; and, an early change in certain globulins in hepatitis. The low albumin may also be detected by one of a number of conventional chemical methods.[75]

An indirect appraisal of non-enzymatic protein relationships is afforded by the *cephalin-cholesterol flocculation test*.[76,77,78] This semi-quantitative procedure becomes positive when albumin concentration is low, altered in composition, or inhibited by elevated gamma globulin. The results are non-specific, do not measure liver function, and are often normal in decompensated cirrhosis, and abnormal in compensated cirrhosis or in patients with no liver disease at all.[74] However, it is almost universally positive in viral or toxic hepatitis[74] but rarely positive in hepatoses such as seen after chlorpromazine administration.[79] The other tests based on flocculation or turbidity also tend to be non-specific in nature.

The liver plays a role in the over-all metabolism of the body's *cholesterol*. Mechanical failures of excretion of this substance can result in an elevated serum total cholesterol in such situations as obstructive jaundice or biliary cirrhosis. Values are also found to be high in nephrosis or uncontrolled diabetes and low in serious parenchymal damage of the liver, but are generally of little value in the evaluation of liver disease. More important from the point of view of liver function is the role of the liver in esterifying the free cholesterol. If the cholesterol-ester test is performed carefully and painstakingly it will produce results most useful in following the variations of the liver's involvement in infectious hepatitis[74] although it is somewhat more complicated and expensive than the serum cholinestrase test, which will be discussed later.

Of great interest in recent years have been certain serum enzymes that are characterized by their appearance in elevated amounts when conditions causing a loss of cellular energy effect the permeability of the membranes of their cells of origin. Their elevation is therefore "fortuitous"[80] and does not directly reflect "dynamic" or functional capacity of any body organ. This phenomenon has been demonstrated *in vitro* with liver slices[81] or cells,[82] occurs *in vivo* after severe muscular exercise,[83] and is noted in disease conditions causing cellular injury or death.

Among the enzymes which behave in this manner are two *transaminases,* glutamic oxaloacetic (GO-T) and glutamic pyruvic (GP-T).[84] Despite the original inferences that GO-T was specific for myocardial injury and GP-T for liver disease, it is known that both may be increased in injuries to heart or liver as well as other organs. If clinical judgment indicates that the liver is the site of disease, elevated transaminases may serve an adjunctive diagnostic value. However, elevations of these two enzymes do not measure liver function specifically, but merely reflect the process of active injury.[80,85] Indeed, they may be quite normal in advanced cirrhosis if the liver is in a non-inflammatory phase of the illness.

In general, the same situation is true for *lactic dehydrogenase* (LDH) in which the fall in $NADH_2$ is measured as pyruvate reduced to lactate.[86] The usefulness of organ-specific isozyme patterns of LDH in liver and other disease is currently undergoing clinical evaluation. Additional enzymes which may be elevated fortuitously in serum following hepatic cell injury but are relatively non-specific in nature include, among others, phosphohexose isomerase,[87] aldolase,[88] malic dehydrogenase and serum leucine aminopeptidase.

Serum cholinesterase is an example of a functional or dynamic enzyme which is produced solely by the liver and whose changes in serum may reflect total functional capacity of that organ. Serum levels of this enzyme are of prognostic value in viral hepatitis and are a reliable index of over-all involvement of the liver in cirrhosis.[74,89] Values of this test tend to delineate with high accuracy benign from malignant causes of obstructive jaundice.[90,91] The test may give low results during normal pregnancy[92] or in the presence of certain organic phosphate poisons. Of unique interest is the fact that this serum enzyme may also be depressed in carcinoma probably due to the presence of an inhibitor produced by tumor tissue.[80,89,93,94] A qualitative, genetically-determined abnormality of this enzyme which has some bearing on the use of muscle relaxant drugs in anesthesia is discussed later in this review.

Values for certain standard liver function tests during the various trimesters of pregnancy and at the time of labor indicate essentially normal function of the maternal liver during pregnancy whereas values for the newborn infant taken from placental vein serum reveal some striking differences from the maternal state.[92]

Effects of Anesthesia Upon the Liver

The drugs employed in the administration of anesthesia are protoplasmic poisons, albeit generally reversible poisons, and anesthesia is capable of affecting a number of the hepatic functions enumerated above. Furthermore, the magnitude of the effect of anesthesia upon the liver may, at times, be of a sufficient degree of severity to produce profound morphological changes. Many of the early investigations of liver function during or following anesthesia utilized a single hepatic function test[95]; it has come to be recognized within recent years, however, that a single test under such circumstances is not adequate for a liver profile, and more recent studies have employed a battery of liver tests to determine a number of functions simultaneously. Many of the earlier studies also were carried out in laboratory animals, and the factor of species difference must always be borne in mind in the interpolation of these data to man[96]; today, there is a salutary trend toward performing such investigations directly in man. Finally, it must be emphasized that there can be a very real difference between the effects of anesthesia upon the normal liver and the effect of anesthesia upon the diseased liver, and that the results of studies of liver function that pertain to the one do not necessarily apply to the other.

Anesthetic Drugs

Almost all of the drugs employed to produce anesthesia have some effect upon the liver, but the more potent drugs, not unreasonably, have the most profound effects.

The most dangerous of the anesthetic drugs from the viewpoint of liver injury is unquestionably *chloroform*, which has produced liver dysfunction over a wide range including a great many reported cases of fatal toxic hepatitis.[97-99] The fact that chloroform also is a halogenated hydrocarbon and closely related chemically to carbon tetrachloride has led to its classification as a true hepatotoxin by a number of authorities.[100,101]

In the laboratory animal, even brief periods of exposure to chloroform can produce both immediate and delayed toxic effects as measured by decreased bromsulphalein dye excretion, elevated icteric index, bilirubinemia, and urobilinogenuria.[102] Marked hyperglycemia is produced, with a concomitant decrease in liver glycogen, and there is a great increase in the urinary excretion of nitrogen reflecting a rapid breakdown of protein.[103,104] The formation of bile and bile salts is reduced,[105] and the synthesis of prothrombin is suppressed[106] to the extent that a bleeding tendency results.[107]

Prolonged or repeated exposure will lead to much more severe derangements of function or even to extensive necrosis and fatty degeneration of the liver. In acute yellow atrophy resulting from fatal chloroform poisoning in the dog, the liver is large, swollen and fatty looking; and on cut surface the lobulation is very distinct, each lobule having a dark red, clean-cut center and an opaque, yellowish, swollen margin. Microscopically there is extensive central necrosis, about three-fifths of all of the liver cells being dead and appearing as a pink-staining hyaline mass. Fatty degeneration and vacuolization may be slight or extreme, but it is most intense in the boundary zone between the central necrosis and the intact liver cells about the portal spaces. There is hemorrhage into the parenchyma, and infiltration of polymorphonuclear cells and monocytes.[108,109] The incidence of toxic hepatic necrosis is considerably influenced by nutrition,[110] infection,[111] pregnancy,[112] and a host of other factors which will be considered separately in some detail.

The equivalent pathological entity in the human is "delayed chloroform poisoning." This syndrome generally begins about one to three days following chloroform anesthesia and is characterized by lethargy, drowsiness, fever, nausea, vomiting that becomes copious, jaundice, coma, convulsions, and ultimately death by the third to tenth day from its onset.[113-115] Laboratory studies prior to death reveal leukocytosis, hypoglycemia, azotemia, and marked evidence of liver damage. Autopsy shows a hepatocellular necrosis that is usually centrilobular in distribution, with varying fractions of the lobule destroyed, but often a small rim of intact cells around the portal areas. The necrotic cells break up into hyalinized fragments and undergo lysis, while the intact cells peripherally show marked fatty infiltration. A varying degree of inflammatory reaction is present, indicated by polymorphonuclear leukocytes and phagocytic cells.

The adverse hepatic effects of chloroform, and particularly the occurrence of fatal massive hepatic necrosis, have led to its abandonment as an anesthetic in many areas of the world.[116-118] However, there is a small but vocal opposition that insists that the dangers of chloroform have been magnified and distorted to an unreasonable degree.[119,120] They believe that much of chloroform's reputation as a dangerous drug is based on older studies that are invalid because of inadequate control of the conditions surrounding the anesthetic administration[121]; and that when the drug is employed with modern anesthetic techniques[122,123] it causes no more postoperative liver dysfunction than other anesthetic agents[124,125] and, in fact, is indistinguishable from other agents by double blind study.[126] It is worth pointing out, however, that even its use with today's techniques and attention to the details of administration continues to produce instances of fatal delayed chloroform poisoning.[127,128]

Ether (diethyl ether) also has a profound effect upon liver function and histology although these effects are less profound than those produced by chloroform.

Marked hyperglycemia is produced in the

experimental animal with a concurrent reduction in the glycogen content of the liver,[129-135] presumably due to adrenal-sympathetic activity,[136-138] the same mechanism invoked by chloroform and other anesthetic drugs which cause glycogenolysis. Bile secretion is actually stimulated during light anesthesia with ether,[139] but depressed by higher concentrations.[140-142] Mild to severe functional impairment as measured by hepatic function tests is noted in laboratory animals following ether anesthesia[143-145] and histological changes can be produced which vary from slight fatty infiltration to a frank central necrosis which is very similar to that produced by chloroform.[146,147] In general, however, injury to the liver in laboratory animals appears to be somewhat less from ether than from chloroform, and its production requires a higher relative concentration of drug, longer duration of administration, and the influence of other factors that tend to set the stage for the appearance of necrosis following anesthesia.

Alterations in blood sugar, liver glycogen, and carbohydrate metabolism during ether anesthesia in man have also long been recognized,[148,149] but the mechanisms may be somewhat different than in laboratory animals. There is suggestive evidence that in man ether may not only increase hepatic glycogenolysis but also may interfere with cellular transfer of glucose thereby impeding the phosphorylation and subsequent metabolism of glucose.[150] Bromsulphalein retention and other functional derangements have been reported in man also,[151-153] and studies employing a battery of hepatic function tests reveal a degree of liver injury varying from that produced by cyclopropane, halothane, or spinal, to, in one series at least, that produced by chloroform.[154-157] At times the liver insult is sufficiently severe to cause massive hepatic necrosis,[158,159] although as will be seen subsequently there is reason to doubt that ether is a true hepatotoxin but rather that in such instances other factors are at play.

Divinyl ether (divinyl oxide or Vinethene) causes hyperglycemia and ketonemia in laboratory animals,[133,160] but does not affect bile secretion significantly[139] or increase bromsulphalein retention under normal circumstances.[161,162] These comparatively benign findings, however, must be considered in the light of the fact that central zonal necrosis can be produced routinely in the dog[163] and after relatively short exposures to the drug. Indeed, in the dog, divinyl ether acts like a more toxic agent to the liver than chloroform.[163] In man, the few studies of hepatic function that have been performed show little derangement of liver activity[164]; but at least three postmortem examinations in humans have been reported which showed liver damage[163] and there is little doubt that central necrosis can occur.[165] An undoubted case of liver impairment (as demonstrated by changes in cephalin-cholesterol reaction, prothrombin time and the icteric index) which survived has also been reported.[166] As with other agents producing severe liver damage, there are a number of factors including the duration of anesthesia, nutritional status and the like, which are of importance in the development of necrosis.

Ethyl vinyl ether is not hepatotoxic to dogs even if sixty minutes of deep anesthesia is administered repeatedly,[167] nor is there evidence of hepatotoxicity as measured by either a single liver function test[168] or a battery of such tests performed postoperatively.[169] It must be added, however, that neither the investigational studies nor the clinical trials of this drug have been extensive, and its capacity for liver damage really is not known on the basis of available data.

The fluorinated analoque of ethyl vinyl ether, *trifluorethylvinyl ether* (Fluroxene, Fluoromar) has had both considerably more laboratory investigation and more clinical usage than the parent drug, but still an insufficient study to determine the extent of toxicity which the drug can produce in the liver. Animal studies of chronic toxicity have failed to show hepatic toxicity,[170] but liver function tests in patients have shown slight to moderate retention of bromsulphalein dye[171] and some increases in the levels of serum glutamic oxalacetic transaminase.[172]

Since *tribromoethanol* is a halogenated hydrocarbon, its effects upon the liver were suspect from the time of its first introduction into clinical anesthetic practice.[173] In dogs, it was found to produce slight but transient bromsulphalein dye retention,[174] but even re-

peated administrations caused only mild parenchymatous degeneration of the liver.[175] In the rabbit[176] and cat,[177] on the other hand, central necrosis of the liver has been described following the administration of Avertin (tribromoethanol in amylene hydrate).

In man, Avertin produces hyperglycemia and glycogenolysis,[178] but does not seem to affect functional integrity to any significant degree.[142, 153, 179] However, Andersen has reported a liver death following the use of Avertin, and she was able to cull sixteen other cases of fatal liver damage from the literature.[180] The hepatic lesions varied from an extreme deposition of fat in the liver cells to central necrosis leading to the diagnosis of acute yellow atrophy. In addition to these, there are further suggestive cases in the literature without postmortem examination,[181] as well as other cases with comparable symptoms following Avertin anesthesia that are described too incompletely for critical evaluation.[182]

The reported effects of *trichlorethylene* (Trilene) upon the liver also vary from minimal dysfunction to the occurrence of fatal massive hepatic necrosis. In acute laboratory investigations, little or no change in hepatic function has been noted, although similar studies carried out with chloroform under the same conditions showed definite adverse effects upon the liver.[183] Chronic exposure to trichlorethylene in experimental animals, on the other hand, can produce pronounced, although usually transient, changes in both function and histology[184-188]; and definite liver damage, including hepatitis and fatty degeneration, has been produced in some animals following repeated anesthesias.[189-192]

Studies of liver function in man during and after trichlorethylene anesthesia have usually shown either no impairment of function or very slight and transient dysfunction. Observations on the level of blood sugar have varied: Hewer noted no rise in blood sugar during trichlorethylene anesthesia,[193] whereas Haworth and Duff reported a slight rise after thirty to forty-five minutes of anesthesia.[194] Armstrong used the cephalin-cholesterol flocculation test to study hepatic function following trichlorethylene anesthesia and found a positive reaction at twenty-four hours in 34 or 35 patients, but all returned to normal between the eighth and fifteenth postoperative days.[195] Gilchrist and Goldschmidt used, in addition to the flocculation test, the bromsulphalein test, the thymol turbidity reaction, and the alkaline phosphatase activity as measures of liver function, and were unable to demonstrate any changes in these values in twenty-nine patients anesthetized with trichlorethylene.[196] In a more recent study which employed a battery of five liver function tests under rigidly controlled conditions, no more effect upon liver function was observed than that produced by either diethylether or cyclopropane investigated under similar circumstances.[197] Blondal and Fagerlund determined the concentrations of serum glutamic acid transaminase, serum pyruvic acid transaminase, and lactic dehydrogenase, perhaps three of the most sensitive indicators of cellular damage, and did not find elevated values postoperatively in any of their thirty-six patients.[198]

On the other hand, the literature now contains reports of eight patients who have died from massive hepatic necrosis following the administration of trichlorethylene anesthesia.[199-205] A cause and effect relationship is by no means established in these instances; and, indeed, in the majority of these patients there were complicating diseases such as malnutrition,[201] eclampsia,[201, 203, 204] or burns,[202] or they had received blood[206] or morphine,[207] which could account for the liver disease. The hepatic necrosis remains a pathologically-established fact, however; and since trichlorethylene is a chlorinated hydrocarbon, an aura of suspicion must remain around it.

Studies of the effect of *cyclopropane* upon liver function that have been carried out by the application of a single liver function test reveal little impairment. Bromsulphalein excretion in the normal patient is not reduced following cyclopropane anesthesia; and in one eclamptic patient with 55 per cent retention prior to delivery there was a retention of only 50 per cent after anesthesia and delivery.[143, 208] The drug produces a moderate hyperglycemia,[209] mild ketosis,[210] and little change in the quantity of bile secreted.[139]

When a battery of liver function tests are employed, on the other hand, in normal pa-

tients with neither a history nor clinical evidence of liver disease or other systemic disease, some abnormality of liver function can be noted in almost every instance.[155] The abnormalities noted in this type of study, however, are no greater than those produced by such other potent anesthetic agents as ether or halothane, and then are noted in only a single, isolated test on a single postoperative determination, and often are of such limited deviation from the normal that they are of questionable significance.[157]

The effect of cyclopropane upon liver histology has been studied in the normal dog and also the dog whose liver has been injured by chloroform poisoning. Repeated administration of the drug produced only a 10% retention of bromsulphalein dye and no histological damage comparable to that produced by chloroform. Even prolonged administration (three hours) did not alter the rate of recovery in dogs with livers previously damaged by chloroform poisoning.[208] Significant histological damage can occur following the administration of cyclopropane anesthesia in man, however, and massive hepatic necrosis has been noted following apparently-uneventful cyclopropane anesthesia.[211, 212]

A very low degree of toxicity or, indeed, a total absence of toxicity, is usually ascribed to *nitrous oxide* when it is employed as an anesthetic in the presence of 20 per cent or more oxygen,[213] and it is generally held that under such circumstances the drug has little or no effect upon liver function or histology.[142, 144]

Riker, however, has suggested that the progressive activity of depressant drugs must be considered as a continuous pattern of functional depression stretching from full wakefulness on the one hand to cessation of medullary action and death on the other.[214] Nitrous oxide, considered under this schemata, is capable of only a limited range of depression without incurring anoxia, but the valid question has been raised whether there is not a very real difference between "nontoxic" and "weak anesthetic."[215] In point of fact, Price and Helrich have produced experimental evidence suggesting that nitrous oxide has depressant properties upon the heart that are very similar in degree to those of other inhalation anesthetics if equipotent doses are considered,[216] and it is possible that this also applies to other organ systems of the body, including the liver.

Most studies support the view that nitrous oxide has little effect upon liver function. Dye excretion is not impaired (in the absence of anoxia), bile secretion is not suppressed if the drug is administered with 20 per cent or more oxygen (although a marked fall in secretion occurs in the presence of anoxia), and there is only a minimal rise in blood sugar.[135, 139] In man, Coleman noted some impairment of dye excretion that occurred within twenty-four hours and persisted up to eleven to thirteen days[153]; however, satisfactory anesthesia with nitrous oxide as the sole anesthetic agent is seldom obtained without some degree of anoxia, and these studies may well reflect the effect of anoxemia rather than the drug itself.

When nitrous oxide anesthesia is complicated by frank anoxia, not only derangements of function but also frank hepatic necrosis may result,[217] but this of course would be true no matter what anesthetic drugs were being employed under such circumstances.

Much of what has been said concerning the effect of nitrous oxide upon the liver applies also to *ethylene* which, while a somewhat more potent anesthetic drug than nitrous oxide, falls nevertheless in the class of a "weak anesthetic." Frank derangement of function will of course occur in the presence of anoxia; but under conditions of normal oxygenation, ethylene produces only a transient impairment of hippuric acid excretion,[151] a slight decrease in bile secretion,[139] and a mild rise in blood sugar.[135]

The introduction of *halothane* (Fluothane) aroused the usual suspicions about hepatotoxic damage which have been accorded to all of the new halogenated hydrocarbon anesthetics recently, but the early laboratory and clinical investigations did not reveal any extraordinary degrees of liver dysfunction. Within the past two years, however, a storm of controversy has raged around this drug and the question of its effects upon the liver has produced both front-page newspaper copy and great public concern.[218–224]

In the experimental animal, halothane has not demonstrated the characteristics of a hepa-

totoxin. Hippuric acid excretion in the urine of rats was not affected by even chronic exposure to halothane for one hour a day for five days,[225] and bromsulphalein dye excretion in dogs and monkeys remained within normal limits despite both prolonged and chronic exposures to the drug.[226,227] Histological studies of mouse liver following exposure to halothane have shown vacuolar formation (fatty change), nuclear changes (excessive numbers of binucleated cells, excessive numbers of large nucleated cells, and pyknosis of nuclei), and zonal areas of cloudy swelling with pallor of cells.[228] Even in protein-deficient mice exposed to halothane, no gross changes were noted and the microscopic changes consisted of nonspecific cytoplasmic alterations or focal necrosis.[229] In the dog, chronic toxicity studies revealed no gross pathologic changes attributable to the drug, but at a histologic level mild to moderate centrilobular fatty alteration and glycogen depletion were noted.[230] Even when administered in a hypoxic atmosphere, halothane had no more effect upon the dog liver than the inhalation of an oxygen-deficient mixture alone.[231] When the portal circulation, and hence the liver, was exposed to a very high concentration of the drug by direct instillation into the stomach, however, massive fatty infiltration could be produced, although not the frank necrosis produced by both chloroform and divinyl ether using this same experimental technique.[147] Chloroform is also a great deal more toxic to the liver than halothane under conditions of hypoxia.[232]

In man, halothane affects carbohydrate metabolism and produces glycogenolysis, there being a rise in blood sugar and a corresponding fall in both liver and muscle glycogen.[233] Since the drug does not produce significant changes in catecholamine concentrations during a steady state of anesthesia,[234] the changes in carbohydrate metabolism are assumed to be due to either surgical stimulation inducing a sympathetic response or perhaps the type of insulin resistance that has been postulated to occur during ether anesthesia.[150] Others have been unable to show comparable changes in the level of blood sugar during halothane anesthesia, however.[235,236] Considerable data have been collected in a number of clinical investigations on patients undergoing surgery which indicate that hepatic function is not unduly affected by halothane anesthesia.[237–241] Most of these studies employed a battery of hepatic function tests to compare the results after halothane with those following other forms of general anesthesia, and when the drug was administered to patients with normal livers there was no more, if indeed as much, postoperative liver dysfunction than occurs with either cyclopropane or ether.[242]

Nevertheless, and despite halothane's innocuous effects upon the liver in several million anesthetic administrations, the literature now contains reports of about four dozen instances of significant postoperative damage, a number of which progressed to fatal massive hepatic necrosis.[243–263] The morphologic changes in thirteen of these cases of necrosis following halothane anesthesia have been reviewed recently; the degree of hepatic necrosis varied from mild centrilobular acidophilic degeneration and fatty change to massive central, midzonal, or complete lobular coagulation necrosis with coarse cytoplasmic vacuolization, fatty change, and ghost cell formation.[264] Only a minimal degree of inflammatory change was reported, and it was concluded that viral infection probably was not the underlying etiology and in fact that halothane may have acted as a hepatotoxin similar in nature to chloroform or carbon tetrachloride.[41] There are other reports suggesting that the effects of chloroform and halothane are similar clinically[123,126,265,266] and also as far as their effect upon liver function tests[267] are concerned even in the absence of hepatic necrosis. Many other competent observers insist that the drug is by no means a true hepatotoxin, however, and, indeed, halothane does not satisfy the definition of a true hepatotoxin.[268] An alternative suggestion has been that cases of hepatic damage may represent a hyperallergic reaction, since a number of these patients have demonstrated fever, skin rash, eosinophilia, and other features suggesting hypersensitivity reaction; on the other hand, others did not show such manifestations. It has also been pointed out that many of these patients had repeated exposure to the drug before liver damage became evident; but it is also true that halothane has been

employed for repeated anesthesias (up to 49 exposures in one patient) without provoking signs[269] or histologic evidence of liver damage.[244] An impurity in the form of a butene has been detected in halothane that has been exposed to copper, and the method of vaporization has been indicted as the possible etiology of liver damage,[270,271] but the evidence is not very convincing.

In point of fact, the exact nature of the liver damage following halothane anesthesia remains unknown: it is a rare and unpredictable reaction, and to date no firm cause and effect relation between the drug and liver damage has been established. A number of prospective and retrospective studies of liver damage following anesthesia are under way, and (hopefully) will provide an answer to the riddle. The results of such of these studies as have been reported so far, while not statistically significant, do suggest that halothane is probably not more hepatotoxic than a number of other types of anesthesia in common use.[158,159,212,272,273,274] It seems likely that other factors associated with the period of anesthesia and operation, as well as some purely coincidental causes, may be far more important than the anesthetic drug itself in the production of postoperative liver damage.

Several other fluorinated hydrocarbons have followed halothane as new inhalational anesthetic drugs, and have been introduced at least for clinical trial, if not actual clinical usage. *Methoxyflurane* (Penthrane) administered to dogs for prolonged, repeated exposures produced bromsulphalein retention at the end of forty-eight hours in less than 20% of the animals,[275] although their livers showed some fatty infiltration in the centrilobular areas; and even when dogs were exposed to methoxyflurane under conditions of overdosage, hypoxia, and hypovolemia, the liver showed only a fine, diffuse watery vacuolization of the hepatic parenchyma about the central lobular portion that was considered to be "a reversible and nonspecific process."[276] In man, methoxyflurane produced a sharp initial rise in blood sugar that was almost as pronounced as that occurring during ether anesthesia, and since this was a constant finding during controlled respiration it was believed to be a true effect of methoxyflurane rather than a concomitant of the hypercarbia from respiratory depression.[277,278] Liver function tests, including estimations of bromsulphalein retention, serum bilirubin, alkaline phosphatase activity, thymol turbidity and flocculation, and serum transaminase (SGOT, SGPT) have shown only a temporary, moderate reduction of liver function following anesthesia.[277,279,280,281] However, when hypercarbia was produced during anesthesia, by adding 10–25 per cent carbon dioxide to the inhaled mixture to produce a P_{CO_2} in excess of 70 mm. of mercury, severe interference with bromsulphalein dye excretion occurred by the second postoperative day.[282] Furthermore, as is true of almost all of the general anesthetic agents, fatal massive liver necrosis can follow the use of this drug.[251] *Halopropane* did not produce significant histological alteration in the livers of dogs subjected to daily anesthesia, nor any significant interference with the excretion of bromsulphalein dye in either the dog or man.[283] Insufficient data exists concerning halopropane or *Teflurane* (CF_3CHBrF) to assess their effects on the liver to any useful degree, however.[284]

The ultra-short-acting barbiturates employed in anesthesia also can have an adverse effect upon the liver. *Thiopental* (Pentothal) produces a mild hyperglycemia in animals, and the liver glycogen of dogs on normal diets is progressively depleted during long anesthesia.[285–287] Intermediate metabolism of carbohydrate is depressed as shown by a rise in lactic acid, as is intermediary protein metabolism.[288,289] Hepatic impairment, as measured by liver function tests, follows the use of thiopental in the experimental animal:[286,290] there is a progressive decrease in the ability of the liver to remove bromsulphalein from the blood,[287] and an increase in both the prothrombin time and the level of serum bilirubin.[291] Some of this liver dysfunction can be avoided by adequate pulmonary ventilation of the experimental animal with oxygen if small doses of thiopental are employed, but adequate oxygenation does not reduce the toxicity of repeated large doses of the drug.[291,292]

In man, a slight hyperglycemia usually occurs during thiopental anesthesia; but this is not an invariable finding[293,294] and, in fact,

the drug will not prevent the occurrence of the hyperglycemia that almost always accompanies ether anesthesia.[294] Liver dysfunction is also a variable finding and is definitely dose-related: when large doses are employed, liver dysfunction as measured by liver function tests occurs fairly frequently, and the reverse is true when small doses are the rule. Dundee employed urinary urobilinogen excretion as a test of function, and was able to demonstrate that liver dysfunction occurred consistently when the dosage of the drug was over 750 mg.[296] Pohle, using a battery of hepatic function tests, found that liver impairment occurred in fifty per cent of the patients after operation.[154] In contrast to this, Carraway, using the hippuric acid excretion test, found no alteration in liver function after thiopental in one hundred cases.[297] Sufficient hepatic damage to produce jaundice has been reported in at least one patient.[298] The effects of the several new ultrashort-acting barbiturates, which have been introduced within recent years, differ quantitatively, but not qualitatively, from those produced by thiopental anesthesia.

Local anesthetic drugs, such as *Procaine*, have little effect upon the liver of themselves. Local infiltration with large doses of procaine has no effect upon liver function,[153] and repeated massive doses of procaine administered to rats and dogs in acute and subacute experiments produced no abnormalities of liver function and no histological evidence of liver damage.[299] Liver function tests following the intravenous administration of procaine in surgical patients for the control of postoperative pain also show no evidence of liver damage.[299,300] The local anesthetic drugs can produce severe liver damage, however, not by a direct effect but owing to reactions that occur as a consequence of their administration. Spinal anesthesia, for example, has been followed by extreme liver damage, including a number of instances of fatal massive hepatic necrosis.[272,301,302] When the damage is truly attributable to the anesthesia, it undoubtedly occurs because of the hypotension and tissue anoxia that spinal anesthesia may produce; in most instances, however, there are undoubtedly other factors that should be considered. Liver damage can also be produced in a similar manner when severe systemic toxic reactions and subsequent cardiovascular collapse occurs in response to the administration of a local anesthetic drug.[303]

Anesthetic Techniques

Not only can the drugs that are employed for the production of anesthesia have profound effects upon the liver, but in addition there are several specialized techniques employed in anesthesia that have their own unique liabilities for liver dysfunction and damage.

In the use of *controlled hypotension*, for instance, it must be remembered that the anatomy and physiology of the hepatic blood supply are such that a higher critical level of hypotension exists for the liver than for most other tissues. As noted previously, the blood supply of the liver is derived from two sources, the hepatic artery and the portal vein: normally, the former supplies about 20 per cent of the total hepatic inflow at a relatively high oxygen tension (95 per cent saturation), whereas the portal vein supplies the remaining 80 per cent (approximately) of the blood at a much lower degree of oxygen saturation.[304] During the intentional reduction of blood pressure, which is most usually accomplished in the techniques of "controlled hypotension" by producing sympathetic paralysis,[305] the circulation is slowed and a point may be reached at which such a high degree of oxygen desaturation occurs in the intestinal capillaries that the oxygen tension in the portal vein is nearly as low as that of the blood in the hepatic vein.[304] The liver will then be dependent primarily upon the hepatic artery for its oxygen supply. If the flow through the hepatic artery is reduced it may become inadequate for the total needs of the liver and tissue anoxia will occur. This, in fact, occurs during hypotension. The liver which has been subjected to anoxia becomes unable to form urea from ammonium salts or amino acids,[306] loses the power to inactivate the vasodepressor material described by Shorr,[307] and the deterioration of hepatic function is progressive until a point of irreversible change is reached.[306]

This is the sequence of events that may occur during "controlled hypotension." The

estimated hepatic blood flow is reduced by 33 per cent, and the brachial artery-hepatic venous oxygen difference is increased.[308] The increased extraction of oxygen from the splanchnic blood is thought to be due to the more prolonged contact between the blood circulating in this bed and the tissue cells. When the circulation in the splanchnic region is slowed excessively, the risk of hypoxic damage to the liver and the failure of liver function is great.[309] It has been observed, during a series of laparotomies conducted under epidural block, which were sufficiently extensive to cause the blood pressure to fall to 45 to 60 mm. of mercury, that the livers were dark and cyanotic in appearance, and turgid and rubbery in consistency; these changes were reversed when the blood pressure was raised by the administration of methedrine or noradrenaline.[310]

Occult liver damage may result from this temporary hypoxia.[311] Patients with normal preoperative liver function showed abnormal bromsulphalein retention for three to seven days after high spinal analgesia,[312] and pathological changes have been shown to occur in the livers of experimental animals after hypotension induced with methonium compounds.[313] Indeed, hepatic damage may not necessarily be occult, for at least one fatal case of liver necrosis has been attributed to the use of these techniques.[314]

Hypothermia increases the liver's tolerance to ischemia,[315] but it also depresses the function of the liver, as it does the functions of other organs.[316] Studies on liver function in the experimental animal, many of which have been carried out on isolated, perfused livers, have shown a decreased metabolism[317,318]; a decreased bile secretion[319]; rapid depletion of liver glycogen stores[320]; and a depressed ability to clear blood of bromsulphalein and $CrPO_4$.[318] Splanchnic blood flow has been shown to decrease progressively and in linear fashion as the body temperature falls during acute hypothermia.[321] Portal blood flow is reduced to 70 per cent of normal during hypothermia in the dog[322] and hepatic artery blood flow to 69 per cent of normal.[323] The liver can apparently continue to utilize oxygen and avoid hepatocellular hypoxia even at a body temperature of 25° C.,[324] but there is suggestive evidence that during prolonged hypothermia at lower temperatures the liver may contract an oxygen debt.[325]

Investigations in the human also suggest that function of the liver is depressed during total body hypothermia, with a return to normal upon rewarming. In instances in which hepatic function was normal preoperatively, acute hypothermia seldom produced hepatic dysfunction during the first week after operation.[326]

Extracorporeal Circulation precipitates a number of subtle metabolic and organic alterations, and these frequently include liver derangements because of this organ's sensitivity to hypoxia.[327] Studies in dogs show a marked, though transient, rise in portal venous pressure; splanchnic congestion; a less pronounced elevation of pressure in the inferior vena cava; and definite depression of bromsulphalein dye extraction during and immediately after the period of extracorporeal circulation.[328,329] However, hepatic metabolism of lactic acid is maintained at essentially normal levels, and the oxygen supply available to the liver is not depressed to the extent that there is any unusual liberation of potassium from that organ.[330] Total hepatic blood flow is reduced at perfusion rates less than 2.2 liters per minute per square meter, as is the oxygen consumption; since hepatic artery blood flow remains relatively constant at all perfusion rates, the decrease in total flow and oxygenation are attributable to reduced portal venous flow.[331]

Clinical observations in man show that a number of patients complain of unusual crampy abdominal pain in the early postoperative period following bypass and bromsulphalein extraction studies in some of these patients indicate a definite degree of liver impairment.[332] This is corroborated by the finding of an elevation of serum glutamic oxalacetic transaminase levels in patients submitted to total body perfusion.[333,334] Occult gastrointestinal bleeding is detected in occasional patients during the postoperative period[335] and may represent evidence of splanchnic congestion similar to that observed in the experimental animal. Deaths occur following extracorporeal circulation with jaundice being present terminally, and there is little doubt

that the technique can produce sufficient liver damage to be a significant factor in the outcome in certain patients and under certain circumstances.[262]

Mechanism of Liver Injury

The effects of anesthesia upon the liver thus vary greatly. In its most innocuous form, anesthesia may have absolutely no effect upon the liver or may produce extremely mild functional disturbance as revealed by one or more postoperative hepatic function tests. More important degrees of liver dysfunction will produce significant abnormalities in postoperative liver tests and histological changes in the liver itself. Severe liver damage will produce true hepatitis that may progress to acute massive hepatic necrosis; and this, of course, is the significant liver complication following anesthesia.

The pathogenesis of severe liver injury following anesthesia remains the subject of considerable debate, but at least three mechanisms appear possible: (1) the anesthetic drug acts as a true hepatotoxin and produces a toxic hepatitis; (2) the anesthetic drug initiates a sensitivity ("hypersusceptibility") reaction or in some other manner produces a drug-induced hepatitis; or, (3) the liver damage after anesthesia is not due to the action of anesthetic agents upon the liver at all but is, in fact, caused by factors other than the anesthetic drugs.

Toxic hepatitis is produced by a true hepatotoxin which is a rather rigidly-defined substance; and while a great many drugs are capable of producing injury to the liver, yet, paradoxically, few qualify as true hepatotoxic drugs according to Klatskin's classification,[336] which requires that the drug (1) invariably provoke hepatic injury in all individuals if administered in sufficient doses, (2) produce a lesion of a severity that is directly related to the dose, (3) be capable of reproducing identical lesions in most, if not all, experimental animals, (4) exhibit a distinctive histologic pattern that is highly characteristic, and (5) have a latent period between acute exposure and the appearance of the hepatic injury that is constant and almost always relatively brief. Most hepatotoxins behave as general protoplasmic poisons and affect other tissues profoundly in addition to their effects upon the liver; but some attack the liver exclusively, despite the fact that they enter cells elsewhere in the body, and it has been proposed that they may be chemically altered in the liver and their metabolites be responsible for their specific hepatic actions.[337] Carbon tetrachloride and phosphorus are cited as typical examples of hepatotoxic drugs, with chloroform included as the only true hepatotoxin among the anesthetic agents. The latter suggestion, that chloroform may be a hepatotoxin, has, however, been challenged vigorously.[121,124]

Several mechanisms have been proposed to account for the action of hepatotoxins.

Direct cytoplasmic effects may be produced, and the hepatic cells injured directly by interfering with enzyme systems essential for energy production or protein synthesis.[98] Carbon tetrachloride, for instance, alters the permeability of the mitocondria of the hepatic cells,[338,339] with a resultant loss in diphosphopyridine nucleotide and interference with the Krebs cycle. However, anoxia will produce similar changes, and the in vivo changes in mitochondrial enzymatic activity may be due to ischemia.[340] Carbon tetrachloride also affects the endoplasmic reticulum of liver cells,[341] which are known to play a role in protein synthesis,[342] and it has therefore also been suggested that the inhibition of protein synthesis by hepatotoxins may be responsible for the subsequent alterations in mitochondrial morphology and function that ultimately lead to cellular necrosis.

A second possibility is that a relative deficiency of essential amino acids may be induced, since diets that are deficient in sulfur-containing amino acids produce massive hepatic necrosis. Himsworth believes that this effect is dependent upon a specific deficiency of cystine, and that lesions of this type may be produced not only by dietary restriction but also by the creation of a relative deficiency of cystine as a consequence of excessive losses or increased demands.[343] A deficiency of this type could lead to hepatic necrosis by interfering with intracellular enzymatic oxidation-reduction systems dependent upon an adequate supply of sulfhydryl groups.[100] However, it is difficult to reconcile this hypothesis

with the observation that a dietary deficiency of sulfur-containing amino acids will not produce hepatic necrosis unless the diet is also deficient in vitamin E[344] and Factor 3[345]; and it is possible that the protective effects of methionine and cystine are dependent not on their content of sulfhydryl groups but rather upon the presence of traces of selenium.

A third hypothesis has been that hepatotoxins impede blood flow through the liver, and that the degenerative changes and necrosis are the result of ischemia, since the lesions produced by carbon tetrachloride and a number of other agents occur in the centrilobular areas where the circulation is most impaired. Exposure to carbon tetrachloride, for example, produces an immediate but transient intralobular vasoconstriction and a more sustained obliteration of the sinusoids as a consequence of hepatocellular swelling.[346] Brody and Calvert propose that this action on liver parenchymal cells is an indirect one and is due to stimulation of the central sympathetic areas, resulting in a prolonged discharge of the peripheral sympathetic nervous system and increased secretion of epinephrine.[347] This sympathetic discharge causes constriction of the blood vessels supplying the liver, resultant decrease in blood flow, and consequent anoxia. Transection of the spinal cord, a procedure that of course blocks the transmission of sympathetic stimuli and prevents hepatic vasoconstriction, fully protects against hepatic necrosis and the alterations in mitochondrial enzymatic activity usually seen following carbon tetrachloride poisoning; and adrenergic blocking agents and adrenalectomy also provide some protection, although not as great as that provided by spinal cord transection.[348]

A second effect of the catecholamines is the release of fatty acids from depot fat with an increase in the blood levels of free fatty acids, and one of the striking features of the hepatic lesions produced by carbon tetrachloride and a number of other hepatotoxins is an accumulation of fat within the parenchymal cells. This has led to the concept that carbon tetrachloride mobilizes lipid from the depots by stimulating the sympathetic nervous system and adrenal medulla and thus produces fatty infiltration of the liver. This does not fully account for the mechanism underlying the fatty infiltration induced by hepatotoxins, however, since the fact that marked fatty infiltration is still observed after adrenergic administration of blocking agents,[348] and in some experiments after adrenalectomy,[349] appears to be inconsistent with the theory that fat mobilization is mediated by sympathetic stimulation and increased epinephrine secretion.

Since none of these theories entirely explains the production of toxic hepatitis in all instances, it is highly improbable that all hepatotoxins attack the liver in precisely the same way. Furthermore, there are several other factors, including the nutritional state,[110] alcoholism,[350] pre-existent liver disease, and infection,[111] that can modify the effects of hepatotoxins and are of importance in the pathogenesis of toxic hepatitis. Nevertheless, the remarkable uniformity of the biochemical findings in the liver after exposure to a number of hepatotoxins of diverse character suggests that although these agents may initiate cellular injury in different ways, the subsequent chain of biochemical events leading to necrosis follows a common pathway.

Most drugs that produce hepatic damage appear to behave as sensitizing agents rather than true hepatotoxins, and Klatskin[336] has enumerated the features that characterize the lesions of *drug-induced hepatitis* and serve to distinguish them from those of toxic hepatitis: (1) the hepatic lesion cannot be induced with regularity and, in fact, only a small proportion of the total number of individuals exposed are affected; (2) neither the occurrence of such lesions nor their extent can be correlated with the dose; (3) the morphological features of the lesion are usually more variable and less distinctive than in toxic hepatitis; (4) the latent period between exposure and the appearance of the lesion is highly variable; and (5) clinical manifestations of hypersensitivity, such as fever, skin rash, arthralgia, and eosinophilia, often accompany the hepatic lesion.

Both the frequency with which drug-induced hepatitis is accompanied by manifestations of hypersensitivity and its sporadic occurrence suggest that it is an allergic process in nature and may represent an acquired hypersensitivity.[351] In support of this view is

the fact that certain chemical compounds are capable of serving as antigens which induce hypersensitivity[352] and that the tissue changes in drug reactions often resemble those produced in experimental anaphylaxis.[353] In fact, it has recently been shown that an antigen-antibody reaction in the liver of a sensitized animal will cause widespread liver necrosis, the initial changes in the hepatic cells appearing as soon as fifteen minutes after exposure to the antigen and the basic pathology being an infarctive process due to occlusion of the sinusoidal system by the immune complexes or the so-called antigen-antibody "thrombi."[354]

On the other hand, and despite the fact that the theory of acquired hypersensitivity is based on an impressive body of evidence, some aspects of these drug reactions appear to be inconsistent: circulating antibodies and skin hypersensitivity can only rarely be demonstrated, the interval between the institution of drug therapy may be as long as months or as short as hours, and the clinical manifestations are highly variable and inconstant. It is possible that auto-immunization may be responsible for the liver injury in some of these instances and account for the great variabilities and inconsistencies noted above.[355] The auto-immune concept of the pathogenesis of liver injury postulates a process which causes persisting damage to liver cells, the process having been triggered initially by liver injury produced by a virus or some other mechanism, or even having started as a primary process entirely due to an immunologic dysfunction. However, although Popper and his colleagues have demonstrated sites of antibody-antigen linkage in plasma cells of patients with chronic hepatitis and postnecrotic cirrhosis,[356] and have suggested that the piecemeal necrosis encountered in many cases of chronic active hepatitis may be "self-perpetuating,"[357] there is not at present convincing morphologic evidence that autoclasis is a mechanism of initiative or of self-perpetuation of liver injury.[358, 359, 360]

Some drugs do not produce a hepatocellular injury, but rather a *cholestatic type of hepatitis* in which the clinical and laboratory findings mimic those found in instances of extrahepatic biliary obstruction. The liver lesions are characterized by stasis of bile within the canaliculi, particularly in the centrilobular zone.[361] The portal triads are infiltrated to a variable degree with a variety of wandering cells, mainly monocytes and eosinophils. Hepatocellular necrosis and intralobular inflammation are not entirely absent, but parenchymal damage is considerably less than in injury classified as the hepatocellular type.[362] Many features of cholestatic hepatitis point to an underlying hypersensitivity reaction (as in the hepatocellular type of drug-induced hepatitis), including sporadic occurrence in patients receiving such drugs, the immunity of laboratory animals, and the association with fever,[363] rash[364] and eosinophilia.[365]

To summarize the mechanism by which anesthetic drugs may produce liver damage, then, they may injure the liver directly (true hepatotoxin), or they may induce liver injury indirectly (hypersensitivity) by acting on the liver parenchyma to produce necrosis and fatty metamorphosis (hepatocellular injury) or by acting on bile canaliculi (cholestasis).[366] Yet this classification is obviously much too rigid as to criteria to define the roles of the anesthetic drugs. Chloroform has been called a true hepatoxin by many pharmacologists; but as already noted above the designation has been vigorously denied by a vociferous minority of anesthesiologists. Halothane has many of the attributes of a drug that could cause hepatic damage on the basis of a hyperallergic reaction; but the connection between halothane and hepatic damage is a tenuous and inconstant one. Chlorpromazine, a paraanesthetic drug, is the present prototype of a drug causing cholestasis and jaundice; and perhaps fits into the pharmacologist's classification the most completely of all the drugs employed in anesthesia. The fact of the matter is, however, that most of the other anesthetic drugs do not fit into these categories, although they may contribute to the development of hepatotoxicity in corroboration with other factors. The latter, in most instances, are probably far more important in the etiology of postoperative liver dysfunction and damage than the anesthetic drug employed.

Effects of Other Factors Upon the Liver

There is now an increasing realization that factors other than the anesthetic agent or technique can be of great significance in the development of postoperative liver damage, since the latter occurs in patients anesthetized with all of the conventional anesthetic agents and methods in common use today. Liver damage following medical or surgical treatment has been reported with increasing frequency during the past twenty years or so,[367] and it is clear that many instances of postoperative liver damage attributed to anesthetic drugs may in fact be due to other therapy.[368]

There are, for instance, certain aspects relating to the anesthetic administration other than the drug *per se* which can play an important role in the development of postoperative liver problems. *Repeated exposures* to a number of drugs and other chemical compounds, including some anesthetic agents, can produce hepatic dysfunction by inducing a hypersensitivity reaction in the liver.[366] Chlorpromazine is a prime example, for although jaundice may appear upon first exposure to the drug,[369] it is much more likely to appear upon chronic administration and then recur promptly when a challenging dose of the drug is given.[370]

The correlation between the severity of the lesion and the dose of the causative poison is only approximate, of course; but the *depth of anesthesia* (concentration, or dose) is a factor in the production of liver injury; and the greater the dose of the protoplasmic poison employed, the greater will be the effect upon all of the organ systems, including the liver.[371] Deep third plane anesthesia produced with ether will expose the liver cell to greater risks of toxicity than ether analgesia of the first stage as described by Snow[372] and, more recently, by Artusio.[373]

The *duration of exposure* is also a factor and animals exposed to a given concentration of anesthesia for a prolonged length of time will regularly show more liver dysfunction than litter mates exposed to the same concentration of anesthetic drug but for a shorter period of time.[109] There is reason to believe, however, that when the mechanism of liver injury is that of a drug-induced hepatitis based upon an inherent or acquired sensitivity to the drug, the duration of anesthesia may be of far less importance than when the injury to the liver cells is a direct one.

During the past thirty years, considerable investigation has been devoted to the role played by *nutritional status* and the interrelationship between certain dietary factors and the development of hepatotoxic effects. It has been shown that starvation,[110] protein-depletion,[374] and high fat intake[375] increase the susceptibility to hepatic damage by chloroform, and that diets rich in protein[110] and carbohydrate[110] are protective when fed prophylactically. Furthermore, it has been shown that protein, methionine and, to a lesser extent, cystine protect protein-depleted animals against chloroform toxicity if given prior to exposure to the drug.[376] The precise way in which dietary factors affect susceptibility to hepatotoxins is not known, but there is at least suggestive evidence to indicate that it is by altering either the fat content or the size of the protein stores of the liver. Clinical experience suggests that these same dietary factors are of importance too, in patients exposed to anesthesia, but the evidence concerning nutritional factors in man is not as convincing as in the laboratory animal.

Probably the most important of all of these factors is the occurrence of *hypoxia,* for the exposure of the liver cells to atmospheres deficient in oxygen will lead rapidly to severe liver damage.[146] This is true whether there is insufficient oxygen in the blood because of inadequate pulmonary ventilation during anesthesia, a decreased amount of oxygen delivered to the hepatic cells because of circulatory failure,[377,378] or when the needs of the liver are elevated above normal oxygen supply because of hyperthyroidism.[379] The actual amount of oxygen in a given unit volume of blood is not significant (*i.e.,* in anemia) but the tension of oxygen in the blood is crucial,[304] and it is the essential function of the liver's blood supply to provide oxygen to the parenchymal cells at a sufficiently high tension to prevent cellular damage. Since the portal pressure of oxygen in portal blood is already partially reduced, the hepatic artery must augment the oxygen tension by the necessary amount to accomplish this purpose.

Obviously, then the maintenance of an adequate *blood pressure* is essential to the prevention of liver damage. The cause of the hypotension is immaterial—it may be from hemorrhage,[380,381] from surgical[382] or medical shock, or from any other cause—but its occurrence leads to necrosis of the liver. The precise level of systemic arterial blood pressure necessary to provide hepatic arterial flow that can maintain adequate oxygenation of the parenchymal cells of the liver will vary greatly according to many individual conditions.

Closely related to both hypoxia and hypotension in the production of hepatic damage is the effect of *hypercarbia*.[383] Carbon dioxide retention during anesthesia and operation is not infrequent, and it will produce liver dysfunction as measured by hepatic function tests[384] and histologic damage in the form of necrosis.[385] The mechanism appears to be an increased splanchnic vascular resistance during hypercapnia which results in a reduction of the estimated hepatic blood flow and so exposes the liver cells to lowered oxygen tensions during anesthesia.[13] The vasoconstrictive response is mediated through the central nervous system since it is elicited by increased P_{CO_2} in the blood only if the splanchnic nerve supply is intact.

The *site of surgery* is another pertinent factor and upper abdominal surgery,[386] and particularly biliary tract surgery,[387] are followed quite regularly by evidences of liver dysfunction. In one study of the effects of major upper abdominal surgery, biopsies of the liver were taken on opening the abdomen and again immediately prior to closure, and in all instances the second biopsies showed capsular and subcapsular inflammation, focal collections of leukocytes around the central veins of lobules, and even necrosis of some liver cells.[388] None of the control biopsies showed these pathologic evidences of acute inflammation. These changes would appear to be related to mechanical manipulation of the liver and its associated structures during such operations, and the effects of packs and retractors on blood flow to and through the liver.

The *transfusion of blood* can contribute to liver damage if its administration is complicated by transfusion reaction. A severe reaction is naturally accompanied by jaundice because of the hemolysis that forms its basis; but in addition, hepatic injury may occur, and most fatal transfusion reactions show areas of hepatic necrosis.[389] These lesions probably occur as a result of the shock that is present clinically in severe transfusion reactions, but it has also been suggested that they could result from impaction of the sinusoids with agglutinated erythrocytes.

Viral hepatitis (infectious hepatitis, epidemic hepatitis, or homologous serum jaundice) is a very real cause of postoperative liver dysfunction and massive hepatic necrosis, and is difficult to distinguish pathologically from toxic hepatitis or massive hepatic necrosis due to other cause.[390] The incidence of the disease (or, at any rate, the number of cases that are reported) has been increasing during recent years, and surgery is being performed more frequently in patients during its incubation period or in patients with preclinical or subclinical (anicteric) hepatitis.[391] Transmission by blood, plasma or parenteral injections is likewise continuing to increase, and of course all of these modes of therapy are common in the surgical patient.[392-395]

The production of liver injury is possible with other *infectious processes*, particularly those that are accompanied by sepsis or high fever. It seems likely that the mechanism may be similar to that invoked by other forms of hyperpyrexia,[396] in that the available oxygen supply is insufficient to meet the increased metabolic demands of the liver tissue.[379] If septicemia is overwhelming, the adrenal glands will show deterioration and be accompanied by hepatic necrosis, probably on the basis of shock accompanying the former.[201]

Other forms of *liver disease* will obviously predispose to liver damage also, since liver injury is already a fact and, although the disease is perhaps quiescent at the time of operation, needs only one of these other factors to flare into clinically-recognizable activity. The liver has great regenerative and recuperative powers,[371] as well as tremendous functional reserve, so that the insult to the liver at the time of anesthesia and operation may or may not trigger hepatic decompensation. Liver disease, and particularly chronic liver disease, is apt to be a dynamic process, and the re-

sponse to added stress will depend generally on the stage of activity of the disease process plus the amount of functional reserve remaining to the organ.

There are several other well-defined *disease processes and metabolic disturbances* associated with liver injury. Both impairment of hepatic function and severe liver damage can occur in the burned patient,[397,398] but whether this is due to infection, reduced blood flow through the liver,[399] or other factors remains unknown. Pancreatitis is a common complication of gallbladder disease if a stone becomes impacted in the ampulla of Vater or spasm of the sphincter of Oddi refluxes bile into the pancreatic duct.[400,401,402] Pregnancy is associated with liver disturbance on occasion, specifically if complicated by eclampsia or hyperemesia gravidarum; and the occurrence of viral hepatitis in the pregnant female is a fulminating and often-fatal disease—possibly the nutritional and dietary factors mentioned above contribute to the hepatic lesion.[110,374]

Finally, the *drugs* and other therapeutic agents that are employed in the treatment of the surgical patient can contribute significantly to the production of postoperative liver damage. The list of those capable of inciting iatrogenic hepatic disease is formidable, and includes a great number of the commonly-prescribed medicines of the day: antibiotics steroids, phenothiazines, anti-convulsants, hypoglycemic agents, sedatives, amine oxidase inhibitors, anti-arthritic drugs, hormones, isoniazid, and a vast array of other drugs that defy convenient classification.[366,403,404] Some of these produce cholestasis; some produce hepatic necrosis with inflammatory reaction; and some are associated with a variety of hepatic injuries that do not fit easily into any formal scheme. Special mention must be made, however, of vasopressor drugs. Brunson and his colleagues have observed an increase in the incidence of liver necrosis in the years since vasopressor agents have been used extensively in the treatment of shock.[367] In the dog, administration of any one of the sympathomimetic amines can be associated with the development of diffuse hepatic necrosis, and the larger doses of these pressor amines are associated with more severe and extensive liver lesions.[367] The suggestion is that splanchnic vasoconstriction is contributing to liver injury and results from vasopressor therapy; on the other hand, as already noted, central necrosis of the liver can be produced by shock alone,[382] and, furthermore, hepatic artery flow is usually almost equal to control flow after the administration of levarteranol in shock.[405]

Most of the factors enumerated, by and of themselves, can produce liver injury, and even severe liver injury. They do not usually do so. Far more frequently, it is a combination of such factors that precipitates hepatic decompensation and damage following anesthesia and surgery. The liver that is not under stress may be able to weather one or more insults, but the liver under stress may be incapable of handling a series or combination of such insults.[406]

Effects of the Liver Upon Anesthesia

Of as much concern to the anesthesiologist as the effects of anesthesia on the liver are the effects of the liver on anesthesia. This stems from the fact that, with the exceptions of the volatile agents and gases, most of the drugs which are employed in anesthesia undergo biotransformation in the liver or by substances manufactured in the liver. When these metabolic mechanisms are impaired by liver disease, congenital absence, the activities of other drugs, or any diminution of hepatic function for whatever reason, anesthesia may be altered significantly.

The *narcotics*, as a class in general, undergo degradation in the liver. Morphine is conjugated there, the conjugation involving mainly the phenolic hydroxyl of the morphine molecule, prior to being excreted by the kidney. The conjugation of morphine in animals has been shown to be greatly decreased after liver damage,[407] and liver injury increases the ratio of free to conjugated drug excreted in the urine to a substantial degree. In man, the duration of action of morphine is prolonged in patients with severe liver disease. The liver is also the chief site of inactivation of meperidine, apparently by de-esterification and demethylation, and the drug can induce prolonged narcosis in patients with severe liver disease, although the effect is not as

prominent as that produced by morphine.[408] Methadone also appears to be metabolized by the liver, and is in a class with morphine in producing prolonged sleep in patients with liver disease.

Many of the hypnotics and sedatives undergo metabolism in the liver, and studies which have been performed in laboratory animals have demonstrated that reduced liver function, produced by various means, prolongs the action or slows the rate of metabolism of chloral hydrate, paraldehyde, and ethinamate.[409] In man, chloral hydrate is converted to both trichloroethanol and trichloracetic acid,[410] and prolonged action follows failure of this mechanism. The metabolism of paraldehyde in man is not entirely understood: apparently depolymerization to acetaldehyde occurs and then oxidation of the latter to acetic acid, following which it is further metabolized to carbon dioxide and water.[411] Many instances of hepatic coma have been seen which appear to have been induced or accelerated by the administration of paraldehyde to patients with severe liver disease.

There is now fairly conclusive evidence that the liver is the primary site of inactivation of the *barbiturates*, particularly the shorter acting ones. The early work of Pratt demonstrated a prolongation of pentobarbital anesthesia in proportion to the extent of the impairment of liver function (bromsulphalein test) in dogs with liver damage due to chloroform,[412] and the enzyme systems responsible are now known to be located chiefly in the liver microsomes.[413] The major mechanism of inactivation of barbiturates in vivo is by side-chain oxidation, and 5-de-alkylation has also been described; ring cleavage is of theoretical importance, but it has not yet been demonstrated to occur in man.[414] Apparently a significant amount of liver dysfunction is essential before any appreciable alteration in the duration of action of the barbiturates is apparent,[296] but it certainly can occur.

Avertin (tribromoethanol) is combined with glycuronic acid in the liver, and tribromoethylglycuronide is excreted in the urine. About 70 per cent of the dose is found in the urine within thirty minutes, and nearly 100 per cent is excreted in two to four hours[409]; but the detoxification, and therefore the excretion, is much impaired when hepatic function is diminished and this can lead to profound, prolonged narcosis.

The action of the *neuromuscular blocking drugs* is altered by liver disease or its functional impairment. Detoxification of *d*-tubocurarine and dimethyl tubocurarine occurs, at least in part, in the liver[415,416]; yet it has been reported that patients with liver dysfunction exhibit decreased sensitivity to *d*-tubocurarine,[417] when it might be anticipated that less drug, rather than more, would be required to produce a given degree of muscular relaxation in such individuals. However, the liver is also the main site of synthesis of plasma cholinesterase, and the plasma cholinesterase level decreases in proportion to the severity of the liver involvement.[418] Decreased plasma cholinesterase activity, with resultant higher concentration of acetylcholine ions at the motor end-plate, may account for the decreased sensitivity to *d*-tubocurarine detailed in the report referred to above.[417] As a general rule, however, patients with severe liver disease usually show an increased sensitivity to all types of muscle relaxant drugs, probably because of the poor physical status of the patients, hypoproteinemia, and fluid and electrolyte imbalances.[419]

The level of serum cholinesterase also is important as a factor controlling the duration of action of succinylcholine administered as a neuromuscular blocking agent,[420] and prolonged muscle relaxation may be produced by succinylcholine in patients with abnormally-low levels of plasma cholinesterase.[418,420] In severe liver disease, in which the level of plasma cholinesterase is low, excessively long duration of neuromuscular block may occur,[421] due to severe parenchymal damage which interferes with the synthesis of cholinesterase. Low serum cholinesterase level can also occur in the absence of severe parenchymal liver damage, however, and is inherited as a familial trait.[422] In addition, Kalow has demonstrated that there may be a qualitative difference, as well as a quantitative difference in serum cholinesterase of certain individuals, and that this atypical cholinesterase has a genetic basis, too.[423,424] Thus, it has been suggested that prolonged apnea after a single dose of succinylcholine is generally due to

delayed hydrolysis by low or atypical cholinesterase, while the prolonged apnea after repeated doses of succinylcholine result from a reduction in the activity of the normal form of cholinesterase in the presence of liver disease with extensive parenchymatous insufficiency.[425]

Detoxification of most *local anesthetic drugs* is accomplished almost entirely by the liver. The ester and amide types undergo partial or complete hydrolysis in the body, and the ester type of compounds are hydrolyzed to their respective acid and amino alcohol. Procaine, for instance, undergoes hydrolytic cleavage into p-aminobenzoic acid and dimethylaminoethanol, and the reaction is catalyzed by the so-called "procaine esterases,"[426] which have been shown to be identical with the pseudocholinesterases.[427] Plasma pseudocholinesterase levels are decreased in hepatic dysfunction, and detoxification of local anesthetic drugs may be retarded and symptoms of systemic toxicity may appear in patients with liver disease.

Procaine can also inhibit the enzymatic breakdown of succinylcholine by human plasma cholinesterase,[428] and the inhibitory effect of procaine and the other local anesthetic drugs on plasma cholinesterase is of clinical importance. The intravenous injection of procaine will potentiate the neuromuscular block produced by succinylcholine in anesthetized patients,[429] for instance, and it has been suggested that care should be exercised when hydrolyzable muscle relaxant drugs and local anesthetic agents are employed simultaneously during anesthesia in the same patient.[430,431]

Finally, although the effects of *hypothermia* upon the liver have already been detailed above, mention must be made of the fact that the reduction of liver function during hypothermia can have profound effects upon the anesthetic drugs employed. Those drugs which are detoxified by the liver have a prolonged action during induced hypothermia (or accidental hypothermia, for that matter). The half-life of morphine increases from 3.7 minutes at 37° C. to 94 minutes at 24° C., a twenty-three-fold increase in the time necessary for the liver to conjugate free morphine.[432] A similar, although less extensive, effect on the detoxification of thiopental has also been demonstrated, and may well apply to the conjugation and detoxification of other drugs. Hyperglycemia occurs, not only as the result of shivering in early hypothermia,[320] but also because the conversion of dextrose to glycogen is inhibited by hypothermia and when dextrose solution is infused it is retained and causes electrolyte changes due to dilution of the extracellular fluid.[433] Lowering the body temperature increases the magnitude and duration of action of the depolarizing neuromuscular blocking drugs such as decamethonium and succinylcholine; whereas the intensity of neuromuscular blockade produced by the nondepolarizing muscle relaxants such as *d*-tubocurarine is reduced by cooling.[434]

The Choice of Anesthesia in the Patient with Liver Disease

Great stress is laid in a number of textbooks upon the choice of anesthesia for the patient with liver disease.[435,436,437] Regional analgesia in the form of nerve block or local infiltration is believed to affect the sick liver the least; and spinal analgesia, when its use is appropriate to the occasion and if hypotension is avoided, is also considered a good choice. The gaseous agents (cyclopropane, nitrous oxide, and ethylene) are said to be less harmful to the liver than the ethers and the various halogenated hydrocarbons. Intravenous agents, specifically the barbiturates and the muscle relaxants, are to be used with great care, since the liver plays a role in their biotransformation.

These are sound advices, but they tend to overemphasize the choice of drug at the expense of all other considerations. French and his colleagues, for instance, found little difference in postoperative liver function studies in a group of patients with quite severe liver disease despite the use of an ether in some as against the use of cyclopropane in others.[156] Ebeling and his associates analyzed one hundred and forty shunt procedures in cirrhotics, and found that the incidence of postoperative liver failure was almost identical after ether or cyclopropane anesthesia.[438] Furthermore, halogenated anesthetics can be employed successfully in patients with liver disease, and are even the

choice in the hands of some.[439] Much the same is true of barbiturates: the use of sedatives in patients verging on hepatic coma is not recommended, but the specific dangers ascribed to barbiturates in patients with liver disease appear to have been overemphasized and Sessions and his co-workers found no evidence that patients with severe liver disease were more sensitive to either single injections or prolonged administration of pentobarbital.[440]

This is not to imply that the choice of drug or technique is not important, but it must be emphasized that the skill with which the anesthesia is administered is of considerably more importance to success in the patient with impaired liver function than the anesthetic itself. The occurrence of hypotension, the accumulation of carbon dioxide, and above all the development of hypoxia, will jeopardize the remaining functional reserve of the liver much more decisively than the use of any particular drug. For as has been noted earlier in this review, there is surprisingly little difference between the conventional anesthetic drugs in common usage as judged by their effects on hepatic function.[155, 156, 157] Meticulous attention to the details of anesthetic administration, however, and to preoperative preparation and to postoperative care, are essential to safe anesthesia in the patient with an impaired liver.[441] Replacement of blood volume by transfusion and restoration of albumin levels to as near normal as possible by intravenous infusions of salt-free albumin should be accomplished prior to operation. A high-protein, high-calorie diet, with tube feeding if necessary, should be supplemented with generous amounts of vitamins and the addition of vitamin K intramuscularly during the preoperative period. Quantitative blood replacement during operation is of the utmost importance since blood volume deficit can result in hypoxia and precipitate liver-cell necrosis.[371] Great care must be taken to maintain pulmonary ventilation and adequate oxygenation in the postoperative period, and the tracheobronchial tree must be kept clear of secretions and mucous. Water and salt retention occur easily in patients with liver disease, since the latter is often associated with abnormalities of water and salt metabolism, and the intake of both should be limited in the immediate postoperative period. Adequate caloric intake should be assured, but protein feeding must be resumed with care in the postoperative period because of the dangers of ammonia intoxication.[442]

The use of specialized anesthetic techniques is desirable in certain operations on the liver and in some patients with liver disease. Induced hypotension, employing either spinal[443] or halothane[442] anesthesia to lower the blood pressure, has found useful application in shunt surgery for portal hypertension. Blood loss and the subsequent need for transfusion are significantly reduced, and operating conditions are enormously improved. The use of induced hypothermia rather than induced hypotension not only will reduce blood loss but at the same time will reduce metabolic requirements. It has been employed for protection of the liver during portacaval anastamosis for portal hypertension with the reported advantages of decreased requirement of anesthetic drug, better oxygenation, decreased metabolic requirements of the liver, and decreased blood loss.[444]

Hypothermia has also been advocated for partial hepatectomy, to allow resection of primary or metastatic tumors in a dry operating field during temporary vascular occlusion.[445] Severe, seemingly intractable, hemorrhage is associated with partial resection of the liver, and hypothermia will not only aid in controlling blood loss by lowering blood pressure but more importantly will provide protection for the liver by lowering the oxygen demands of the liver cells.[446]

Summary

The liver, the largest of the body's glands, has so many and such varied functions that it is inevitable that anesthesia should effect a number of them under certain conditions. The basic functions of the liver include its metabolic properties concerned with the majority of the metabolic systems of the body, its secretory function for the secretion of bile into the gastrointestinal tract, and its vascular function relating to the storage and filtration of blood and to its role as a part of the hematopoetic system. These functions can be measured by tests depending mainly on biliary excretion, such as

measurement of serum bilirubin, bile derivatives and dye excretions; and by tests mainly independent of excretion, such as measurement of serum proteins, serum enzymes, flocculation, plasma prothrombin and fibrinogen, amino acids in blood or urine, blood ammonium, serum lipids, and hippuric acid or galactose tolerance.

The use of such hepatic function tests reveals that almost all of the drugs employed to produce anesthesia can have some effect upon the liver, but that the more potent drugs, not unreasonably, have the most profound effects. Similarly, such specialized anesthetic techniques as "controlled hypotension," induced hypothermia, and extracorporeal circulation also profoundly affect the liver. Furthermore, not only may anesthesia produce important degrees of liver dysfunction, but severe liver damage that can progress to acute massive hepatic necrosis has been known to occur following the use of almost all of the anesthetic drugs employed.

The mechanism of injury in such instances may be direct damage to the liver (true hepatotoxin), or an indirect affect (hypersensitivity) which acts on the liver parenchyma to produce necrosis and fatty metamorphosis (hepatocellular injury) or which acts on biliary canaliculi (cholestasis). Perhaps of even greater importance, are the number of factors other than the anesthetic agent or technique that can lead to the development of postoperative liver damage. These include repeated exposure to anesthetics, the depth of anesthesia, duration of anesthesia, nutritional status, hypoxia, hypotension, hypercarbia, the site of operation, transfusion of blood or blood derivatives, pre-existing viral hepatitis, infectious processes, preexisting liver disease, certain disease processes and metabolic disturbances, and the coincident administration of a great many other drugs.

Of as much concern to the anesthesiologist as the effects of anesthetics on the liver are the effects of the liver on the anesthetic process. The activity of the liver can influence the actions of narcotics, barbiturates, tribromoethanol, neuromuscular blocking drugs, and most local anesthetic drugs.

Choice of anesthesia for the patient with liver disease must take into consideration all of the above factors. Conduction anesthesia, if hypotension is avoided, is thought to affect the sick liver least, and gaseous agents less than the volatile and halogenated compounds. Drugs which undergo biotransformation in the liver should be used with great care. Far more important than the choice of anesthetic agent or technique, however, is the application of skill in anesthetic administration, in preoperative preparation, and in postoperative care.

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