CHARACTERIZATION OF THE ACUTE HEPATIC FAILURE SYNDROME ASSOCIATED WITH THE ANHEPATIC STATE

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HEPATECTOMY in animals has been studied extensively to determine the role of the liver in various metabolic processes. Little was known about the function of the liver until Minkowski studied its function in birds in 1886. Thus, its significance in the metabolism of carbohydrates and proteins was established. Subsequently, Mann (8, 9) showed that intravenously administered glucose is required to keep the anhepatic animal alive, that jaundice develops as rapidly after hepatectomy as after ligation of the common bile duct, and that amino acids accumulate while the formation of urea ceases. Information on hepatectomy in animals was reviewed by Markowitz and his colleagues.

Besides its biologic significance, however, total, one stage hepatectomy is of intense clinical interest. It is impossible to produce chronic liver failure regularly in an experimental animal. In contrast, however, it is possible to induce acute hepatic failure consistently simply by resecting the liver, thus providing an excellent model for its study. For the surgeon, this model has marked significance in the study of liver transplantation, since during rejection of a liver homograft changes are observed which are similar to those noted during the anhepatic state.

Also, during liver transplantation, the recipient is without a liver for some time. The information we wished to pursue was how long a person could tolerate the anhepatic state without experiencing detrimental effects. The opinion has prevailed that any measure which reduces the interval between the removal of the recipient organ and the restitution of blood flow through the donor liver will benefit the recipient. We could find no information, however, concerning the length of time a patient can safely be without a liver because observations on the effect of the anhepatic state on the recipient remain scant. Hence, this study was undertaken in an effort to delineate changes in several critical functions after total hepatectomy and to relate these findings to clinical problems that may develop during or after the anhepatic stage of liver transplantation in human beings.

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MATERIALS AND METHODS

The investigation was conducted on 28 mongrel dogs, weighing between 15 and 20 kilograms, and on two Rhesus monkeys, 8 to 10 pounds in weight.

Upon their arrival in the animal quarters, the dogs received distemper vaccine as well as one injection of 400,000 U.S.P. units of penicillin and 1 gram of streptomycin. Peripheral blood smear, complete blood count, hematocrit tests, and blood examination for heartworms were carried out. Dogs with heartworm infestation were excluded from this study. The dogs were also studied for the presence of parasites in the stool, and if the tests were positive, the dogs were dewormed with Difolin® (dichlorophenephenylmethane arecholine hydrobromide). Conditioned monkeys were kept isolated in separate facilities until the time of the experiment.

The animals were fasted for 12 hours before operation. In all dogs, anesthesia was

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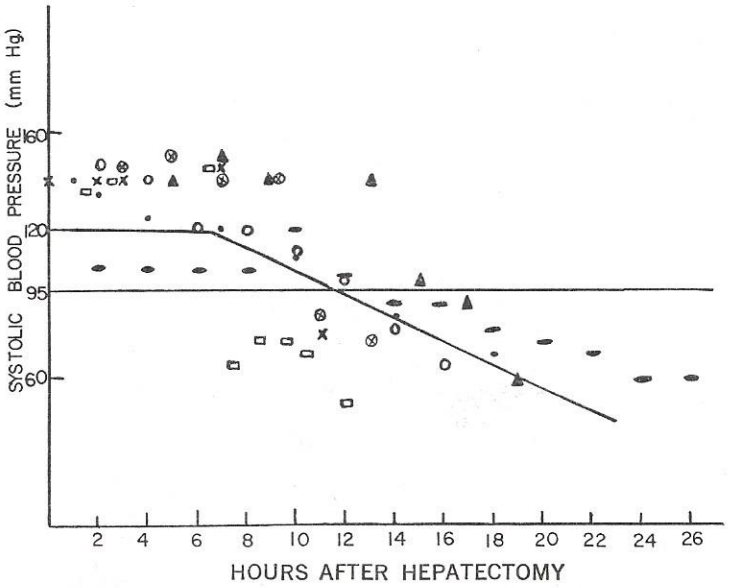

FIG. 1. Changes in systolic blood pressure observed in dogs after total hepatectomy. The pressure remained stable for approximately seven hours after resection of the liver, then it declined in a linear manner. Shock levels, systolic pressures below 95 millimeters of mercury, were reached approximately 12 hours after hepatectomy.

induced with 65 milligrams per milliliter of intravenously administered pentobarbital sodium, 0.4 to 0.5 milliliter per kilogram of body weight. A Foley catheter, advanced into the bladder, was placed on straight drainage. The trachea was intubated, the cuff of the tracheal tube inflated, and the tube connected to a respirator which provided intermittent positive pressure ventilation. The femoral artery and vein on one side were cannulated as was the jugular vein. Blood pressure determinations were obtained from catheters advanced into the aorta, by way of the femoral artery, and right atrium, by way of the jugular vein, with the use of transducers. All pressures were referred to midchest level and registered on a recorder.

Three of the dogs underwent splenectomy one month prior to hepatectomy. All other dogs had no previous operation.

One stage, total hepatectomy in the dog was performed by a previously described technique (4). The inferior vena cava is freed from the right adrenal vein below to the diaphragm above. The portal vein, distal portion of the superior mesenteric vein, and hepatic artery are freed circumferentially. A side-to-side portacaval shunt is created to obviate obstruction of the intestinal venous return. After ligation and division of the portal vein at the porta hepatis, the portal vein stump is sutured against the inferior vena cava to protect the superior corner of the venous shunt from ripping. Only the terminal branches of the hepatic artery are divided close to the liver, preserving the gastroduodenal branch. The hepatogastric, coronary, and triangular ligaments are divided between clamps and transfixed. A meticulous hemostatic technique, as practiced for liver transplantation, will avoid undue postoperative lymphorrhea and continued oozing that tends to persist in this area as a result of the continuous motion of the diaphragm. The liver is removed after ligation and division of individual branches of the extra and intrahepatic portion of the hepatic veins. The inferior vena cava is completely and circumferentially denuded, with no devitalized liver tissue being left behind.

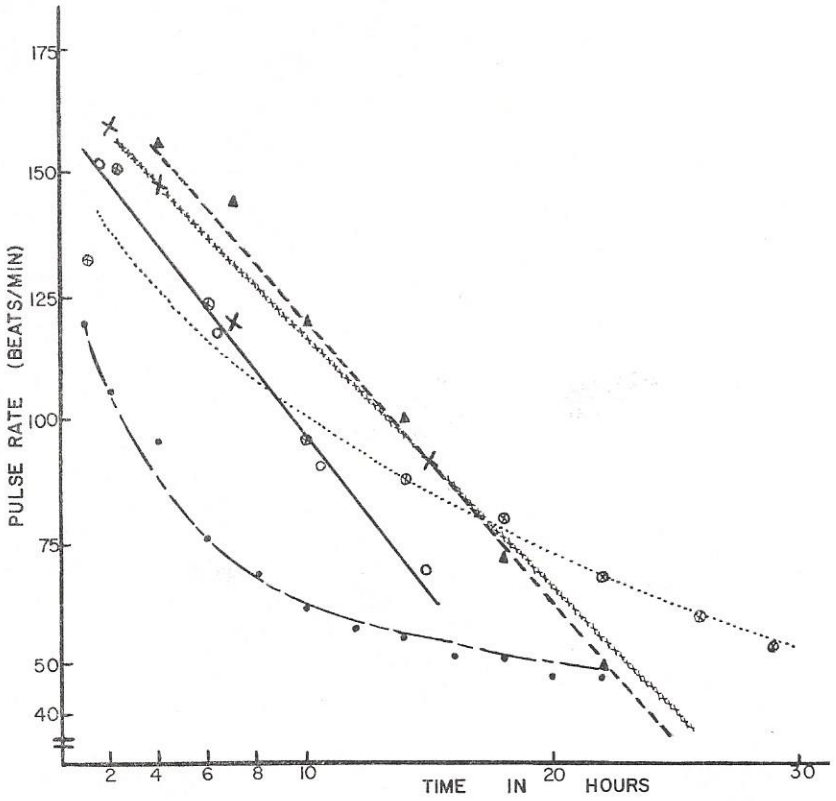

FIG. 2. Changes in pulse rate, in beats per minute, as a function of time, in hours, after total hepatectomy in the dog are shown. Shortly after the resection of the liver, pulse rates invariably declined.

Blood loss during this procedure is negligible. None of the dogs reported upon in this study received blood or plasma during or after operation. All dogs received intravenously administered 5 per cent dextrose in water as a continuous infusion by way of the femoral vein catheter, at a rate of 0.2 to 0.4 gram per kilogram per hour. Achromycin® (tetracycline), 500 milligrams, was added to the first 250 milliliters of glucose solution.

In the monkey, the portal structures are divided after a portacaval shunt is established. The right lobe of the liver is freed by dividing the hepatorenal and hepatodiaphragmatic reflections of the triangular ligament. The left lobe is mobilized upon division of the coronary ligament. The phrenic veins are ligated and then divided. The minor hepatic veins are ligated and divided, as previously described for the human liver (3). Next, the organ is divided in the midline up to the inferior vena cava, as for a hemihepatectomy. Each half is removed separately by gently rotating it away from the inferior vena cava, ligating and dividing every hepatic vein that keeps the organ attached to the vena cava. Blood lost was replaced with 30 to 50 milliliters of human type O-negative blood.

To avoid introduction of infection, a four electrode impedance plethysmographic system was utilized as a noninvasive means for determining cardiac output, as previously described by Kubicek.

Two band electrodes were placed around the neck of the dog, a third around the chest at the level of the xiphisternal joint, and a fourth around the abdomen. The electrode around the upper part of the neck and the one around the abdomen were excited by a

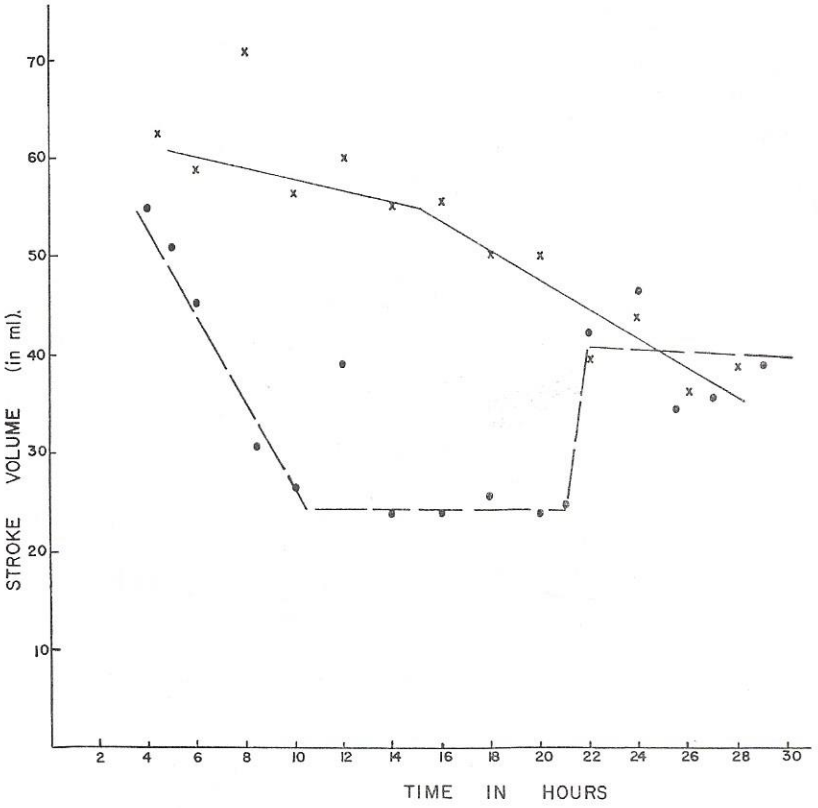

FIG. 3. Changes noted in the stroke volume of the heart after hepatectomy are illustrated. The stroke volume declined shortly after resection of the liver and ranged from a slow, progressive decline to a rapid fall.

100 K Hz constant sinusoidal current, and the resulting voltage or impedance changes which occurred with the cardiac cycle were monitored from the inner two electrodes. Stroke volume was calculated from the impedance change information with the use of a formula relating impedance changes to volume changes in a conducting solid, correcting for changes in hematocrit values.

Heart rate and blood pressure were continuously recorded with the use of a strain gauge transducer and a twin viso recorder.

Initially, blood samples were obtained every two hours. In later experiments, they were obtained every four hours from a three way stopcock attached to the femoral artery catheter by a two syringe technique. The first 10 milliliters, containing saline solution and blood, were returned to the animal after the sample was obtained in a second syringe, and blood pH was immediately determined. Samples were transferred from the syringe to 100 by 13 millimeter test tubes with and without anticoagulant. The anticoagulant was 0.06 milliliter of 15 per cent ethylenediaminetetra-acetic acid solution in 0.2 milligram per milliliter of potassium sorbate. Fibrinogen and euglobulin determinations were performed immediately. The rest of the sample was quick-frozen. Total protein and albumin were determined on plasma and sodium, potassium, and blood urea nitrogen determinations were performed on serum samples.

Body temperature was constantly monitored with a rectal temperature probe and a telethermometer.

Fibrinogen determinations were performed by the technique described by Jacobsson.

Euglobulin clot lysis time and plasmino-

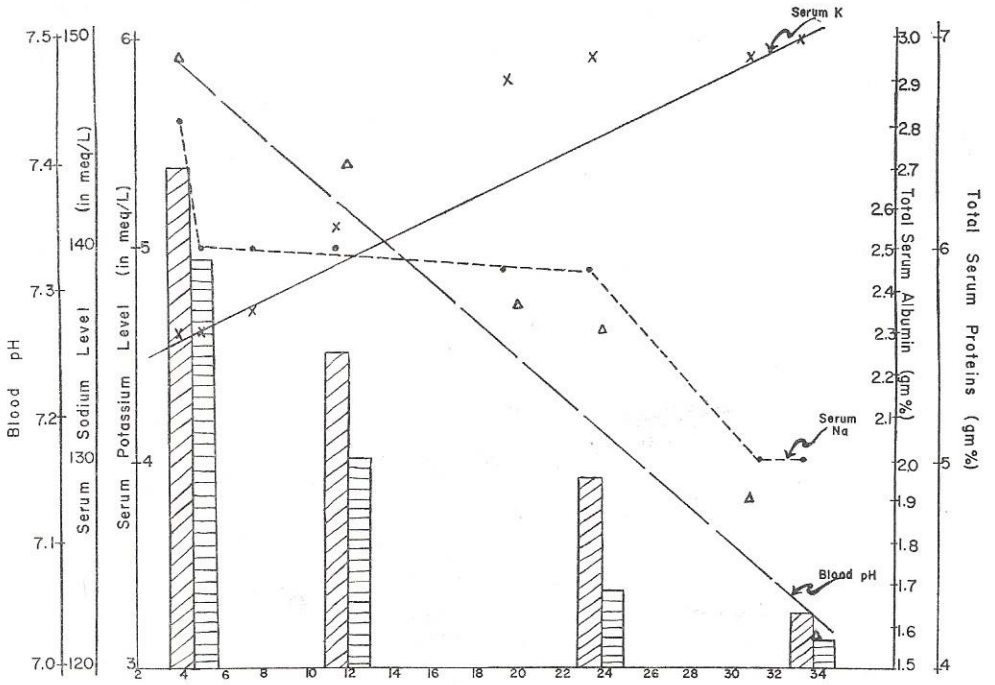

FIG. 4. Changes observed in blood pH, serum sodium, potassium, as well as total protein and albumin values are shown. Severe hyperkalemia, hyponatremia, and acidosis developed after resection of the liver.

gen determinations were performed as previously described (5).

Triplicate platelet counts were obtained on each sample by a technique described by Brecher and Cronkite.

Duplicate microhematocrit calculations were done in a microcapillary centrifuge.

Routine laboratory examinations, that is serum sodium, potassium, bilirubin, blood urea nitrogen, plasma total protein, and albumin concentration, were performed by a clinical laboratory.

RESULTS

Cardiovascular changes.—The blood pressure changed little during the first four to eight hours after hepatic resection, then systolic and diastolic pressures gradually declined. In a few instances, changes in diastolic pressure appeared to precede those in systolic pressure.

The decline in pressure seemed to take place in a linear manner, however, the more determinations were made, the more obvious it became that the blood pressure underwent marked fluctuations. An initial drop in blood pressure, which may occur shortly after resection, was followed by a return to normal or near normal values. Also, the early decline in contrast to the later change in blood pressure hardly ever conforms to a linear pattern.

A regression curve prepared from systolic blood pressure values showed it to remain stable for six hours after which time the pressure declined to reach a systolic value of 60 millimeters of mercury, approximately 12 hours later (Fig. 1). Shock levels, systolic pressures below 95 millimeters of mercury, were not reached, on the average, until 12 hours after resection of the liver.

Changes in the pulse rate also occurred. They preceded the changes in blood pressure by several hours. Rather than a tachycardia, a bradycardia was observed which became more pronounced in the later stages. Pulse rates as low as 50 to 60 beats per minute were observed prior to death (Fig. 2).

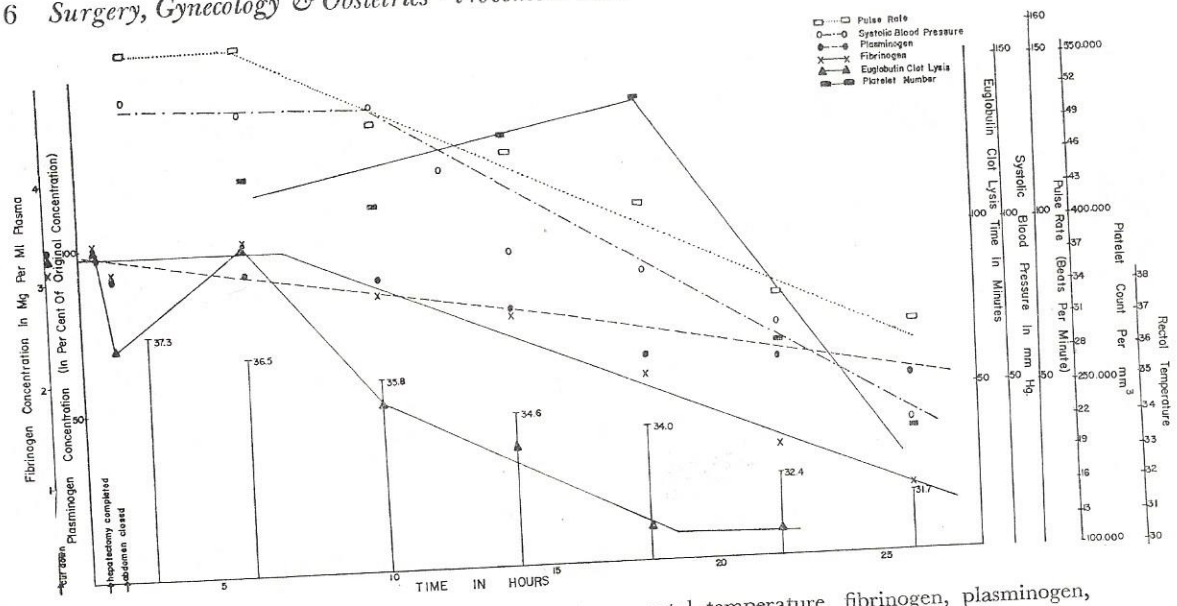

FIG. 5. Changes in pulse rate, blood pressure, rectal temperature, fibrinogen, plasminogen, euglobulin clot lysis time, and platelet count, were observed after hepatectomy. Note the development of defibrination, enhanced proteolysis, and progressive hypothermia.

Concommitant with the slowing of the pulse rate and the decline in blood pressure, cardiac output values fell rapidly; both occurred as a result of a decrease in stroke volume and a progressive bradycardia. These changes occurred early and, as a rule, preceded the changes in blood pressure (Fig. 3). In contrast, venous pressure and right atrial pressure remained essentially the same until shortly before death, when they may rise suddenly.

Ancillary findings.—Urinary output remained good as long as the blood pressure was stable. Similarly, during this time, blood pH values remained within the normal range. Specific gravity of urine samples collected during this period ranged from 1.020 to 1.030; they usually contained traces of sugar.

With the onset of shock, blood pH values declined, and urinary excretion decreased. Urinary output became negligible three to 12 hours before death. Urine specific gravity values were low immediately before renal shutdown and rarely exceeded 1.010. Blood pH values also declined. Sometimes values as low as 7.00 were recorded prior to death.

Serum sodium levels declined gradually yet never became abnormally low. Serum potassium and bilirubin levels, in contrast, rose, the former sometimes reached values as high as 7 milliequivalents per liter. Total serum protein and serum albumin concentrations fell rapidly (Fig. 4). Also quite pronounced were the decline in fibrinogen, plasminogen, and in the euglobulin clot lysis time as well as the progressive hypothermia (Fig. 5).

Platelet counts.—The number of circulating platelets consistently declined (Fig. 5). Thrombocytopenia with less than 20,000 platelets per cubic 3 millimeter was not uncommon prior to death of the animal.

In view of the high histamine and serotonin content of platelets, the effect of histamine was assessed in two dogs before and after hepatectomy. As can be seen from Figure 6, the effect of histamine was significantly prolonged in dogs without livers.

Effect of conventional therapy.—Attempts to prevent the onset of shock or to correct the initial blood pressure change with fresh blood, Achromycin® (tetracycline), methylprednisolone—in doses ranging from 50 to 200 milligrams and given intravenously, dextran Isuprel® (isoproterenol) and mannitol or the addition of sodium bicarbonate

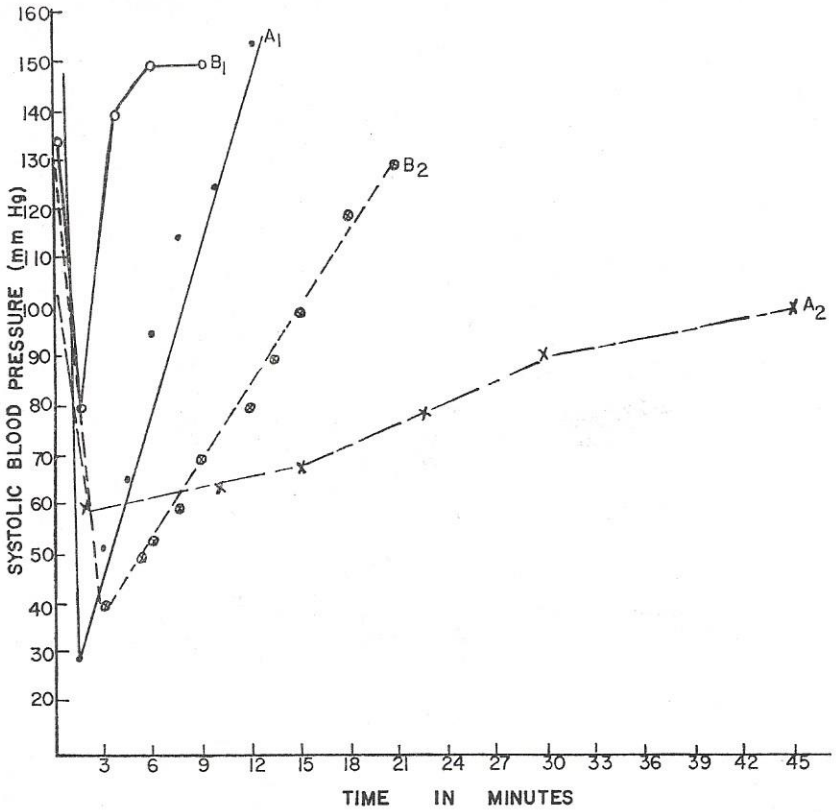

FIG. 6. The effect of histamine on blood pressure is shown before and after hepatectomy. Histamine was injected into two dogs before, A_1 and B_1, and after, A_2 and B_2, total hepatectomy. Dog A received 0.08 milligram per kilogram and dog B received 0.16 milligram per kilogram before and after hepatectomy. After resection of the liver, the effect of histamine was significantly prolonged.

to the infusion fluid did not significantly alter the described postoperative course.

Effect of atropine.—Atropine administered intravenously at the time of the initial change in blood pressure and subsequently in doses ranging from 0.05 to 0.15 milligram per kilogram failed to affect the cardiovascular changes previously described. In particular, it failed to reverse the bradycardia.

Effect of splenectomy.—Three dogs underwent splenectomy one month before hepatectomy. Postoperative survival time of these dogs was 14 ± 3 hours (mean ± 1 standard deviation). Of six successive hepatectomies in dogs which did not undergo splenectomy, it was 25 ± 4 hours (mean ± 1 standard deviation). The blood pressure in those which underwent splenectomy remained stable for approximately six hours. Subsequently, the pressure declined rapidly.

Changes observed in Rhesus monkeys.—Findings obtained in two monkeys were not different from those observed in the dog. Because of the limited blood volume, the monkey subjected to sampling went into a state of shock earlier than the dogs. Otherwise, the changes in this and the other monkey not subjected to blood sampling were identical to those described for the dog. A decrease in cardiac output, a progressive bradycardia, and a gradual onset of shock occurred, while changes in blood pH, fibrinogen, other proteins, and blood electrolytes indicated the development of hyperkalemia, acidosis, and defibrination.

Autopsy findings.—Although the opera-

tive area was completely dry at the time of closure, hemorrhagic fluid, free of clots, was present in the abdomen and varied in amount from 50 to 500 milliliters. The hematocrit values ranged from 4 to 20, suggesting that the leakage of lymph was associated with minimal bleeding. In a few instances, severe hemorrhagic enteritis, as previously observed after endotoxin shock, was noted. Portacaval shunts were patent in all animals. No other gross abnormalities were noted. On histologic examination, renal tubular necrosis of varying severity was the only noteworthy feature.

DISCUSSION

The posthepatectomy state, until recently only of interest as an experimental model used to study the metabolic functions of the liver or to establish features of acute liver failure, has gained significance with the onset of clinical liver transplantation. The findings during rejection are similar to those observed in this study. The opinion prevails that reducing the time during which the recipient is without a liver will benefit the patient. This concept gains validity from the present observations on anhepatic animals. Shortly after resection of the organ, changes not readily apparent occurred in blood pressure, pulse rate, and cardiac output, even with the use of customary clinical laboratory tools. The changes in blood pressure occurred relatively late. In contrast, those in cardiac output, pulse rate, and fibrinogen occurred early. Initially, they may not seem to be significant yet they contribute greatly toward the rapid deterioration of the condition of the animal.

Progressive cardiovascular and hematologic changes terminate in the death of the animal. A decline in cardiac output, bradycardia, and a rapid onset of the defibrination syndrome occur. We assumed that during the early posthepatectomy period, when the stroke volume declined the peripheral resistance rose to maintain a stable blood pressure. Six hours after hepatectomy, however, both the systolic and diastolic blood pressures declined simultaneously. In a few instances, it was noted that the change in diastolic pressure preceded the fall in systolic pressure by one or two hours, suggesting that vasodilation occurred at this time. This and the decreased cardiac output may well account for the development of arterial hypotension. These changes were accompanied by a progressive decline in body temperature, blood pH, serum sodium, total proteins, and urinary output as well as a progressive rise in the serum potassium level. They were absent or remained insignificant, however, during the initial five to eight hours after resection of the liver. In contrast, the change in fibrinogen concentration started early and progressed rapidly. Complete defibrination was noted as early as 16 to 18 hours after completion of hepatectomy. Tissue perfusion deteriorated while acidosis and oliguria developed. The latter rapidly progressed into anuria.

Bradycardia, which is an unusual and striking feature because arterial hypotension ordinarily leads to an acceleration of the cardiac pacemaker by virtue of the arterial baroreceptor reflexes, was previously recognized by Vick as a "paradoxical cardiac response" during endotoxin shock. He related this response to the release of histamine from platelets. Blattberg and Levy subsequently implicated an increased neural activity in the cardiac vagal fibers which could be abolished with atropine. Although we were able to show the delayed breakdown of histamine in these animals, our efforts to affect the bradycardia with atropine were unsuccessful.

The rate at which the observed changes occur varied greatly from one dog to another. In some, they were slow to develop. In others, they were noted shortly after resection of the liver and were followed by rapid deterioration of the condition of the animal. These dogs went into a state of shock early and a severe bleeding tendency developed. Similar changes were also observed in monkeys. Hence, it is probable that during the anhepatic state in man, changes occur

which are similar to those described herein. The fact that rapid defibrination, thrombocytopenia, and enhanced fibrinolysis can develop during the anhepatic stage of a human liver transplantation, similar to that observed during the present experiments and a complication which we had the misfortune to experience in one of our patients, tends to confirm this impression. The cause for these changes, however, remains to be established. It is related in some way to a major loss of reticuloendothelial function since the survival of animals which underwent splenectomy previously was significantly shorter.

SUMMARY

The terminal stage of hepatic failure, secondary to hepatic resection in the dog and Rhesus monkey, was characterized by the classical shock syndrome. This was preceded by a decline in cardiac output and pulse rate.

The shock syndrome was characterized by a slow, progressive decline in blood pressure, pulse rate, body temperature, urinary output, blood pH, serum sodium, blood urea nitrogen, total protein, albumin, fibrinogen, plasminogen, and euglobulin clot lysis time while serum potassium values rose. Treatment with blood, plasma, steroids, antibiotics, mannitol, Isuprel®, or atropine did not appreciably alter the described course of events.

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