ACUTE LIGATION OF THE PORTAL VEIN

by

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A B S T R A C T

A review of the literature on ligation of the portal vein has been presented. A brief survey of the literature on the ligation of the hepatic veins and the hepatic artery has been included. The review reveals that while there is no disagreement that the result of sudden acute ligation of the portal vein in dogs is inevitably death, there is disagreement as to the cause of death. The main theories are (i) that exsanguination into the splanchnic vascular bed occurs, (ii) that the loss of blood is insufficient to cause death, and that other factors must be implicated, the "toxic" theory. The species difference in the effects of ligation appears to lie in the degree of porto-systemic venous anastomoses.

The experiments described in this thesis were performed with the dog as the experimental animal. A measurement of the decrease in circulating blood volume following ligation of the portal vein, using the "labelled" red cell method, was made. It was considered that valid consecutive estimations of blood volume could be made using the "labelled" red cell method. With 11 dogs, 30 minutes after portal vein ligation, the decrease amounted to 57.9% of the original blood volume. The measurement of the normal splanchnic vascular blood volume was made using 10 dogs. This amounted to 21.7% of the circulating blood volume, or 17.7 ml. per kilogram body weight. As the total vascular bed had been reduced by the exclusion of this splanchnic portion, the smaller circulating blood volume was required to serve a smaller vascular area, and it was considered that the true decrease in circulating blood volume was therefore 44.8%. It was considered that this amount of blood loss was not adequate

to account for the inevitability of death, or the short period of survival (79.7 minutes) when compared to the effects of bleeding comparable quantities of blood, or bleeding to comparable levels of blood pressure.

Haematocrit estimations were made on the systemic arterial blood and portal venous blood before and after ligation of the portal vein. There was a significant decrease in the systemic arterial haematocrit, and rise in the portal venous haematocrit. By the injection of latex into the portal vein of 3 dogs, the main porto-systemic venous anastomoses were found to occur in relation to the vagus nerves at the lower end of the oesophagus. Other porto-systemic venous anastomoses were of minor importance. It was not possible to influence the outcome of acute portal vein ligation by splenectomy, or by antibiotics under the conditions of the experiments.

TABLE OF CONTENTS

TABLE OF CONTENTS

continued

ACUTE LIGATION OF THE PORTAL VEIN

INTRODUCTION

Ligation of the portal vein, which at one time was only performed by the experimental physiologist, has now become of clinical importance. With the increasing scope of ablative cancer operations, few structures still command respect. Of these, the portal vein is one. When disease has spread to involve its wall, removal of the diseased segment is not contemplated, for until recently ligation was thought to be fatal. This belief is based for the most part on experimental work with the dog. The review of the literature which follows includes also the effects of chronic obliteration, of partial obstruction and of ligation of the branches of the portal vein, for though the result of these incomplete ligations differs markedly from that of sudden acute ligation, the explanations must be related.

The liver is remarkable in drawing its blood supply from two sources, which join within the parenchyma, and drain by common venous outlets into the inferior vena cava. The one source, the hepatic artery, supplies well oxygenated blood at a high pressure; the other, the portal vein, supplies relatively poorly oxygenated blood at a low pressure. But the portal vein supplies nearly two thirds of the total quantity of blood delivered to the liver.

When the literature is reviewed concerning the results of interference with the supply of blood by the hepatic artery there seems to be little correspondence with the effect of ligation of the portal vein.

But it is, nevertheless, necessary to consider these results, for the common distribution of the blood from these two sources brings them into relation.

HISTORICAL SURVEY

1. Acute Ligation of the Portal Vein

Oré in 1856 during an investigation into the formation of bile first recorded the fact that sudden obliteration of the portal vein resulted in the death of three dogs within an hour. Claude Bernard (1859) and Schiff (1863) independently found the same result. Bernard postulated the cause of death as a bloody congestion of the intestines. "If one suddenly ties a ligature, death is the inevitable consequence. The animal dies half to three-quarters of an hour later. The mechanism of death is easy to understand. All the blood tends to accumulate in the vessels of the intestine, where the arteries carry it without cease, without it being taken away immediately. The brain and other organs become exsanguinated and the animal dies, in fact, of anaemia." Schiff (1863) by tying all the veins of the liver claimed to suppress biliary secretion, and he considered that the accumulation of bile intoxicated the animal. He injected blood from the right heart into the dorsal lymph sac of a liverless frog. The frog's circulation failed, his reflexes were lost, and death ensued. Blood from a normal animal did not produce this result. These two theories, that of exsanguination, and that which supposes toxic substances to accumulate in the blood, have continued to have their adherents to the present time. Schiff's theory appeared to receive support from the work of Tappeiner (1873).

In the rabbit he estimated that 16.2% of the blood was trapped in the intestines after the portal vein had been ligated, but probably little weight can be attached to his figures, for he estimated the total blood volume to be only 4.68% of its body weight, and that 3.08% of its weight as blood could be bled without death occurring. Nevertheless, this paper was much quoted, and in 1877 Lautenbach in Philadelphia thought he had disposed of anaemia as the cause of death because (1) the arterial blood pressure rises immediately following ligation, (2) the animals never show convulsions prior to death, (3) ligature of the hepatic veins, which produces an analogous stasis, is not followed by the same symptoms.

As an alternative, he maintained that an unknown poison caused death, and to prove this thesis injected 3 cc. of blood from the portal vein of dogs into frogs. All died in three hours, in a fashion similar to the dogs which had their portal veins ligated.

This work was quickly refuted by Mouselman and Liénaux in 1885, who in a careful series of experiments, after ligation of the portal vein (1) injected portal vein blood into frogs without results, (2) could maintain the dog alive longer, and restore its pressure with blood transfusion, (3) could prolong life by ligating the feeding arteries, (4) could allow survival by releasing the ligature, (5) showed that complete ligation of the hepatic veins only was extremely hard to perform. Accordingly they maintained that death was indeed due to diminution of the quantity of circulating blood, and also to "an insufficiency in the qualities of the blood, that is, its oxygen or carbon dioxide content." Their work received support from Castaigne and Bender in 1899, who also showed that

life was prolonged by transfusion and by ligation in this case, of the aorta above the coeliac axis. "We have been struck, in all our experiences, by the fact that the animals die absolutely as if they had been bled." Castaigne and Bender also quote Netter in 1884 as originating the suggestion that toxins are produced in the bowel and these, unable to be detoxified by the liver, cause death. They felt that they had disproved this hypothesis of Netter.

In 1913 Neuhof took up the investigation again, and noticed that the acute engorgement of the intestines and the manner of death were analagous to death from shock. He was the first to contemplate ligation of the portal vein as a surgical procedure. Until 1932 no other effort than Tappeiner's seems to have been made to measure the amount of blood trapped within the gastro-intestinal tract. This is obviously the crux of the matter. If death is due only to exsanguination into the bowel, it should be possible to produce death in a comparable time and manner by bleeding from a normal dog a volume of blood equal in amount to that trapped in the gastro-intestinal tract. In 1932, Elman and Cole made an attempt to measure this amount of blood. They weighed the eviscerated intra-abdominal gastro-intestinal tract, including the spleen and pancreas, following ligation of the portal vein, and compared this weight with the weight of eviscerated organs of normal dogs of similar weight and sex in whom the portal vein had not been tied. The increase in weight of the organs of the dog with a ligated portal vein was assumed to be due to the passage of blood into the splanchnic vascular bed. In four dogs this increase was found to be 5.2% of the body weight. They, too, recorded the fact that death could be temporarily prevented by ligation either of the aorta

above the coeliac axis or of the splanchnic artery or by blood transfusion, usually 1,000 ml. and more to maintain the blood pressure above the critical level of 50-60 mm. of mercury. However, death was eventually caused by gangrene of the gut. They could not substantiate the presence of any toxin in the thoracic duct lymph when it was injected into guinea pigs. Finally, if, after ligation of the portal vein, the intestinal tract was removed, death was postponed. They concluded that the rapid death produced by ligation is due to loss of blood from the systemic into the portal system, which reduces the blood pressure below that compatible with life. In 1933, McMichael and Smirk, working with rats recorded as an incidental observation that in two rats with complete obliteration of the portal vein, the weight of the gut increased from an average of 5.5% of the body weight to 11.5% and 12.5%. Both these rats died in a few hours. But in 1935, Boyce, Lampert and McFetridge repeated this work using seven dogs. Their figure for the increase in weight of the gut was 3.05% of the body weight. Naturally their conclusions differed, for they were able to bleed a control series of dogs 4-5% of their body weight without shock or death. Beyond 5.8% the animals died of shock. Their theory was that death following ligation of the portal vein was due to neurogenic shock, which produced the rapid initial fall, and the fall was maintained by the loss of blood. Despite these discrepant findings, probably the result of using small numbers of animals in rather crude experiments, little further was done until 1950, when Mallet-Guy, Devic and Gangolphe repeated Elman and Cole's work. They found that 5.0% of the body weight was trapped within the gastro-intestinal tract. By using Chicago-blue dye they also measured the preligation and postligation blood volumes, and found a decrease of 4.9%

of the body weight, or 49.3% of the circulating blood volume.

2. Chronic Obliteration

Oré's paper (1856) recorded the fact that dogs survived chronic obliteration of the portal vein. His method was to place a ligature about the vein bringing the ends out onto the abdominal wall, and after an interval, gradually obliterating the vein over a period of days. Examination of his dogs showed that an anastomosis between the great mesenteric vein and the inferior vena cava had developed. Claude Bernard recorded a similar experiment, and in 1875 Solowieff first demonstrated that dogs could survive occlusion of the portal vein if the branches were ligated at different times. He ligated the superior mesenteric vein at the first operation, the gastrosplemic vein a few days later and finally the portal vein above the gastrosplenic. His dogs survived for some time. Neuhof (1913) repeated Solowieff's experiments, and confirmed them, though they had not been confirmed by Ito and Orni in 1901. He found, as had the previous authors, that a well marked collateral circulation developed. It was to this type of collateral circulation that Pick (1909) gave the name "hepato-petal". Neuhof was also able to narrow the lumen of the portal vein to occlusion by successive operations. Further confirmation was provided by Dragstedt (1931), McMichael (1933) and Boyce, Lampert and McFetridge (1935). Boyce noted that two-thirds occlusion of the vein could cause death, and that ligation of one branch of the portal vein, when followed seven days later by ligation of the other, was also followed by death. Time had to be allowed for collaterals to form. Interest again arose with attempts to produce ascites by experimental subtotal obliteration of the portal vein. All attempts (Kunkel and Eisenmenger (1949) -

rats; Volwiler et al. (1950); Morris and Miller (1951), Laufman et al (1952) - dogs) failed to produce permanent ascites because of the development of adequate collateral circulation. In any event, it has been known since Eck (1877) first produced a total bypass of the portal venous blood from the liver into the inferior vena cava, that such blood was not necessary for survival.

3. Intermittent Occlusion of the Portal Vein

Several authors have noted that intermittent complete occlusion of the portal vein is tolerated (Mosselman and Liénaux - 1885, Mallet-Guy - et al, 1950). Boyce et al (1935) quote two Russian papers (Roger and Duchinowa, and Tschernikoff) as saying that 35 minutes is not fatal, while Rafucci and Wangensteen (1951) have recorded that 20 minutes is the maximum period for the occlusion of the total afferent supply to the liver.

4. Species Difference

The experiments quoted above were performed mainly with the dog, although some workers used the rabbit and the rat. In these animals, death inevitably follows sudden occlusion of the portal vein. Claude Bernard ligated the portal vein of a pigeon. The bird survived the ligation, but died next morning from an unknown cause. Birds have a vein, a tributary of the renal vein, which receives blood from the tail and lower rectum, and then joins its fellow of the opposite side to form a trunk which drains the blood of the large intestine. At the upper part of the rectum it becomes continuous with the trunk of the veins draining the small intestine to form the portal vein. By this large communication in the pelvis

between portal and systemic veins, blood from the viscera can flow indifferently into the vena cava, or into the portal vein and thence to the liver, (venous system of Jacobson). Bernard found that liquid injected into the inferior vena cava would not flow into the portal system, but when injected into the portal vein, would flow into the vena cava. He remarked that only in mammals does the portal vein form a closed system communicating with the systemic circulation only through the liver.

In 1949 Milnes and Child showed that sudden, complete occlusion of the portal vein in Macacus Rhesus monkeys was not fatal. Of 7 monkeys so ligated, all survived 16 to 51 days postoperatively. Portal venography showed that pelvic porto-systemic anastomoses occurred naturally, and immediately carried much of the blood. Observers had early noted that unless the ligature was placed on the hepatic side of the last portal vein tributary, survival could occur (Castaigne and Bender - 1891, Kusnetzow - 1900). Douglass et al. (1951) noted survival of a dog after ligation of the portal vein, the ligature being on the intestinal side of a small pancreatic vein. Both Oré and Claude Bernard had noted that peritoneal adhesions carried portal systemic anastomoses, and that the portal vein could be ligated in such animals. Brunschwig et al. (1945) had no success when attempting this, however, as an experimental method to enable dogs to survive acute ligation. It would appear that when there is adequate collateral circulation, either by naturally occurring porto-systemic venous communication, by adhesions, or by malposition of the ligature, survival occurs after portal vein ligation. In those animals which die after ligation of the portal vein (dog, rabbit and rat), there is no literature concerning the extent of such collateral circulation.

5. Occlusion of the Portal Vein in Man

Neuhof proposed, in 1913, the necessity for knowing the results of ligation of the portal vein in man. His specific indication at that time was suppurative pylephlebitis. On the basis of his own experimental work, carried out in the laboratory of Professor Pick in Berlin, and the work of others already reviewed, he realized the necessity of an adequate collateral circulation between the portal and systemic veins before ligation could be considered. He suggested the requirements for such an operation, but he did not seem to have performed it on any patient.

Neuhof records the report of 6 cases by Gintrac (1857) where at post mortem the portal vein was found occluded, and the anastomotic collaterals resembled those occurring in cirrhosis of the liver, as later described by Frerichs (1861), Charpy (1898) and Pick (1909). He quotes Brewer as having ligated the portal vein as a result of accidental injury, but Brewer's patient had actually a hydatid cyst which had so reduced the calibre of the portal vein which was stretched over it as to allow the formation of adequate collaterals. The ligation had no effect on the patient. In 1926 Colp reported the results of ligation in three patients with pylephlebitis, all of whom eventually died. The first case, reported in 1915 by Beer, had an omentopexy three days prior to ligation of the portal vein. The ligation had no effect on the pulse rate and at autopsy four days later there was evidence of a well formed collateral circulation. In the second case, ligature followed 36 hours after partial occlusion. Death occurred seven days later, and the autopsy showed thrombus within the portal vein, with no evidence of collateral circulation but without stasis of the vessels leading to the portal vein. In the last case, death

occurred three hours after ligation of the portal vein which contained fluid blood, but there was no autopsy report. In 1944 Brunschwig, in the course of extensive resections for carcinoma of the pancreas, divided the portal vein accidentally. The patient died after two hours. In 1945 a further case of Brunschwig et al. arose in which the portal vein was tied without death occurring, but a previous pelvic operation had produced porto-systemic anastomoses. In 1952, as a result of their work on the Macaca Mulatta monkey, Child et al. decided to ligate the portal vein deliberately in patients, as a two-stage procedure during operations of radical pancreaticoduodenectomy where the portal vein had been invaded by neoplasm. They had already tried to perform a radical pancreaticoduodenectomy together with ligation and excision of a portion of the portal vein, but had failed due to the massive haemorrhage which occurred from the bed of the pancreas. For this reason they planned to allow time for a collateral circulation to enlarge. The operations were performed on two patients, without death occurring after the first stage ligation. In the first case, previous portal venography showed that there did not seem to be any obstruction to the portal vein, though the neoplasm was in close relation, but in the second there was angulation of the vein by the growth. The existence of collaterals was not commented upon. A post-operative portal venogram showed well marked pelvic anastomoses.

In an earlier report (1952) Child et al. record that they had ligated the portal vein in a single stage in five patients who had carcinoma of the stomach or head of the pancreas. None died. One had venographic evidences of obstruction, four had not. They further quote Barclay (1951) and Person (1951) as having resected the portal vein, but

in both these cases the impression was that there was partial occlusion from the neoplasm. These clinical experiences would seem to show that acute ligation of the portal vein is not lethal in man, though in all the cases reported there is no clear evidence of lack of previous obstruction to the portal vein. Such obstruction, if present, might have caused the development of porto-systemic anastomoses.

6. Ligation of a Main Branch of the Portal Vein

McIndoe and Counsellor (1927) by injection of the main right and left branches of the portal vein, hepatic artery and hepatic duct, showed that the main plane of division between right and left lobe of the liver lies between the fossa of the gall bladder and the inferior vena cava at the entrance of the hepatic veins, thus confirming previous investigation (Cantlie - 1898, Serégé - 1901). Further, there was no communication between the right and left branches across this plane in the liver. These observations have been borne out by experimental work and by autopsy material. Injections into either of the portal venous branches are distributed only to the ipsilateral lobe (Bartlett et al. - 1914, Copher and Dick - 1928). If a main branch of the portal vein is ligated, the ipsilateral lobe will atrophy (Rous - 1920, Loeffler - 1936, Grindlay and Bollman - 1952). Autopsy material has shown that obstruction of a main branch of the portal vein has resulted in atrophy of the lobe of that side (Cantlie - 1898, Rolleston and McNee - 1929, Benz et al - 1952). This division into two lobes has functional significance as well. Olive oil injected into the stomach, spleen, duodenum, upper jejunum and rectum passes to the left and central portion of the liver and when injected into the lower jejunum, ileum and proximal three-quarters of the

large intestine, it passes to the right lobe (Bartlett et al. - 1914). Copher and Dick (1928) were able to watch this streamlining effect directly by injecting trypan blue into the organs, and transilluminating the portal vein. Their work was confirmed by Hahn et al. (1945), who used radio-active phosphorus. Daniel and Prichard (1951) were unable to confirm this in laboratory animals by injection into a branch of the superior mesenteric vein, for the Thorotrast they used perfused the whole liver, and similar findings were recorded by Dreyer and Budtz-Olsen (1952) when they carried out percutaneous splenic venography with 70% diodone. It has also been well known that animals with an Eck fistula fail to regenerate ablated liver (Grindlay and Bollman - 1952, Mann and Magath - 1922). Therefore, though occlusion of a branch of the portal vein is not fatal, the portal venous blood is necessary for the proper nutrition of the ipsilateral lobe, the hepatic artery by itself being insufficient. Deprivation of the total portal venous blood supply is not followed by atrophy, but regeneration is impossible. Burnett et al. (1951) has shown in rats that deprivation of portal venous blood results in failure of the liver to develop, whereas increasing the amount of portal venous blood results in an increased rate of liver development. However, it is not portal venous blood which is essential for regeneration. Child et al. (1953) carried out, in dogs, portocaval transposition, so that all portal blood was diverted from the liver directly into the inferior vena cava; the intra-hepatic portal bed was filled with systemic venous blood. Approximately one month later, partial hepatectomy was carried out. In normal dogs, the liver regenerated to 75% of the weight of the excised portion; in those with portocaval transposition, the regeneration was 50%. The

substitution of systemic venous blood for portal venous blood still allows adequate regeneration. There does not appear to be any factor peculiar to portal venous blood which is necessary for liver regeneration. The difference in amount regenerated is probably to be attributed to the lesser flow of blood in the inferior vena cava below the hepatic veins, when compared with the portal venous flow.

7. Ligation of the Hepatic Veins.

Whereas ligation of the portal vein is relatively easy, all its tributaries eventually forming a single vessel well placed for a ligature, ligation of the hepatic veins is most difficult. Simonds and Brandes (1925) first described a method of occluding the hepatic veins without occluding the inferior vena cava. They used dogs, and passed a rubber tube, 0.5 cm. in diameter, 2 feet long around the liver in such a way that traction on the ends of the tube, with counter traction on the liver, would produce occlusion of the hepatic veins only. Such occlusion produced a precipitate fall in blood pressure, and elevation of pressure within the portal vein. Engorgement of the liver was marked, that of the intestines not so marked. The liver engorgement produced a cessation of flow in the hepatic artery. Once the pressure fall had stabilized, if the constriction was maintained, no further fall occurred. It has been shown, however, that it is really very hard even in this way to ensure complete occlusion of the hepatic veins. Simonds was interested in the problem as an explanation of the effect of peptone "shock" in dogs. He and Arey (1920) had already called attention to the large amount of plain muscle in the walls of the hepatic veins of the dog and suggested that such muscle, thrown into spasm upon the introduction of the protein

to which the animal had been sensitized, restricted the flow through the liver. It is difficult to correlate these findings with those of acute ligation of the portal vein, for it is not possible to determine whether the hepatic veins were completely ligated, in the experiments cited.

Armstrong and Richards (1944) succeeded in a chronic ligation of the hepatic veins in three dogs with similar results. Bolton (1914), using cats and monkeys, noted that complete ligation, or more than three-fifths occlusion of the inferior vena cava above the hepatic veins resulted in death within a few hours. When the occlusion was between two-fifths and three-fifths of the calibfe of the vein ascites appeared which only lasted for two to three months, until adequate collaterals developed.

Subsequent investigators have also been content to ligate the inferior vena cava at the diaphragm (Kirschner et al. - 1945, Laufman et al.- 1951, Berman and Hull - 1952, Milnes - 1952, Jefferson et al. - 1953). All have noticed that ascites appeared in a few days and disappeared within a few months. Kirschner et al. (1945) noted, as a major collateral trunk, the presence of a large diaphragmatic vein which joins a left hepatic vein just before its entry into the inferior vena cava.

8. Hepatic Artery Ligation

The result of ligation of the hepatic artery has been a contentious subject for many years. When the dog was used as the experimental animal, it was realized as long ago as 1898 (Doyon and Dufourt) that survival was the rule if adequate collateral circulation remained from the other branches of the coeliac axis, and this was confirmed as the

years went by (Haberer - 1905, Segall - 1923). It is not sufficient to ligate the hepatic artery just before its divisions, for branches may join distal to this. The phrenic vessels contribute branches between the capsule and neighboring vessels, and further vessels run along the ligamentum venosum, and along portal vein, vena cava, and common bile duct (Jefferson et al. - 1952). Further, branches may arise early, and pass to the lobe, thus bypassing the site of the ligature. It is the absence of such well marked collateral circulation in the rabbit and guinea pig which leads to their death when a central branch is ligated. The cat behaves in the same manner as the dog (Behrend et al. - 1922). In man, the results of ligation are based on clinical observations in cases having either accidental ligation or thrombosis of the artery. In a review of 28 cases to 1932, Graham and Cannell confirmed an observation of Ritter that the hepatic artery trunk, or the artery proper, before the right gastric artery is given off, can be ligated without necrosis ensuing. Where the ligation takes place beyond this point, necrosis ensues, if the artery was previously healthy (Graham and Cannell - 1932, Zimmerman - 1930). However, so far, no bacteriological study has been made in such cases, for its importance, as will be seen, has only lately been recognized.

In the Macaca Mulatta monkey, Child et al. (1952) found that ligation of the hepatic artery was not necessarily followed by death. By careful resection of all branches of the hepatic artery from its origin at the coeliac axis to its disappearance into the liver, and by checking the efficacy of the resection by diodrast and India ink injections into the aorta, it was thought that the source of all hepatic arterial blood was removed. But others have pointed out that in dogs the only certain

evidence of the absence of arterial blood, is the careful postmortem dissection of all vessels, the aorta having been injected to display any collaterals however filamentous. (Jefferson et al. - 1952, Popper et al. - 1952). Previous discrepancies in results of ligation were due to failure to observe this criterion.

It was an accidental observation of Markowitz, Rappaport and Scott (1949) which furnished a clue to the cause of death. During attempts to arterialize the portal vein, by using a splenic artery to splenic vein anastomosis, penicillin was exhibited to cover any breaks in the aseptic technique. At the conclusion of the operation the hepatic artery was ligated as completely as possible. The dog survived, but at postmortem examination later the anastomosis was found to be thrombosed. Thus penicillin seemed to have had the power of inhibiting the fatal effect of hepatic artery ligation. Their work has been confirmed many times (Davis et al. - 1949, Tanturi et al. - 1950, Chau et al. - 1951). The explanation offered is that the antibiotic inhibits the growth of anaerobes and the production by them of lethal enzymes such as lecithinase, until the development of an adequate collateral arterial supply (Markowitz and Rappaport - 1951, Tanturi et al.- 1950). If such an arterial collateral supply does not develop, the animal will die despite antibiotics (Popper - 1952). But such an explanation does not account for all the factors involved. This investigation, in fact, had its first beginnings in some investigations that Jackson had been making into the effect of various conditions on the latent period and rate of aseptic postmortem autolysis (Jackson - 1909). He asked Wolbach and Saiki in the same year to investigate a bacillus with peculiar morphological and cultural characteristics which he had found in the liver.

They used 23 dogs, killed them, burnt the abdominal wall, and removed the greater portion of the liver. The pieces were incubated aerobically and anaerobically, and in 21 dogs under anaerobic conditions, there were marked changes after 18 to 24 hours. The liver was soft, green and rancid, with much gas production. Control cultures of the spleen and kidney failed, (except in one case) to produce the same organisms. The bacillus was 8-9 μ spore-bearing, non-motile, gram positive. The filtrate from the liver cultures had no effect on intraperitoneal inoculation of guinea pigs or other dogs. Two livers were sterile. This organism was considered to be a definite specific bacillus of dog's liver. There the matter rested for 16 years until Mann (1925) showed that a piece of liver (0.5 gms. per kilo of body weight) detached and left free in the peritoneal cavity, produced death from peritonitis in 18 to 30 hours. Ellis and Dragstedt (1930) by autoclaving the piece of liver and then placing it in the peritoneal cavity, failed to produce death. They also showed that liver obtained by Caesarian section from a dog foetus was innocuous. However, the work was repeated by various others, and the results ceased to be as clear-cut. Trusler, Martin and Reeves (1934, 1935, 1937) investigated the problem. They first pointed out that the organism in the dog's liver was not Cl. Welchii of toxic strain, but a strict anaerobe, thermophilic and of the nonsucrose fermenting, putrefactive gas-forming type of the genus clostridium. This same organism was present in the muscle of dogs, and it failed to produce an exotoxin. As a result they wondered whether it had any significance in disease. If over 30 grams of liver was implanted, all dogs died (though this was nearly 6 times greater than the amount that Mann found necessary to cause death). In this case there was a picture of shock

and the dog liver anaerobe could be found in the peritoneal cavity. By separating the parenchymal elements from the liver connective tissue, bile ducts and blood vessels, they found that implantation of the latter elements was associated with the picture of shock and peritonitis. Further, they found that if the liver was incubated and then sterilized by heat, death occurred promptly, but was not due to bacteria. They also showed that bile salts cause intense irritation of the peritoneal surfaces with the production of severe shock. Ligation of the hepatic artery will produce necrosis of the gall bladder and allow the escape of bile into the peritoneal cavity.

Mason and Davidson (1924-25) confirmed the presence of a toxic substance in the saline extract of autolyzed liver, but did not make any comment about its relation to a bacteriological origin. Andrews and Hrdina (1931) because they found that autoclaved liver produced the same picture - peritoneal haemorrhage and exudation, with overwhelming infection from a gas bacillus - considered that the reaction was provoked by the sterile material. Dvorak (1932) found that ground liver always killed, but sterile liver never did so; a 40 ml suspension of anaerobes was necessary to kill on intraperitoneal injection, and peritoneal fluid filtrates failed to kill probably because of absorption of toxins by the host. Bile salts were not present in the normal liver of a dog in sufficient quantity to cause death. From this, he concluded that no toxin produced in the liver was responsible for death, but that anaerobic bacteria or their toxins were the cause. Boyce and McFetridge (1937) repeated many of these experiments, without however giving clear accounts of their experimental methods. As they seemed to be able to produce

death with sterile autoclaved liver and with foetal liver in adequate amounts and could not cause death by the intraperitoneal or intravenous injection of the whole peritoneal exudate of a dog dead from autolytic peritonitis, they decided that the role of the gas bacillus was entirely secondary.

Chau et al. (1951) found that all dogs in whom the hepatic artery had been completely ligated, died, and all had positive blood cultures of Clostridia within 2 to 3 hours after ligation. The cultures remained positive until death. Succinyl sulphathiazole had no effect on survival, though clostridia disappeared from the stools. Pre-operative penicillin had no effect, but penicillin one hour postoperative was effective, and the blood culture remained negative. Similar results were found when aureomycin was used instead of penicillin. Eze (1952) also found that a single dose of potassium penicillin G subcutaneously immediately after operation protected the dogs. Nelson (1951) showed that intravenous infusions of pure cultures of paracolon bacilli can produce rapid death in dogs in 2 to 3 hours with a picture of metabolic acidosis. Thus, there are two well divided opinions, those who feel the cause of death is due to anaerobic organisms and their toxins and those who believe the liver, when autolysed, produces toxins which are lethal. Human liver is generally considered to be sterile (Lewis and Wangensteen - 1950, Romieu and Brunschwig - 1951, Sborov et al. - 1952).

PURPOSE OF INVESTIGATION

This review of the literature reveals that while there is no disagreement that the result of sudden acute ligation of the portal vein in dogs is inevitably death, there is disagreement about the cause of

death. It is not certainly known what effects acute ligation has in man, or even in other animals. This lack of agreement extends also to the effects of acute ligation of the hepatic artery and the hepatic veins.

The effects of acute ligation of the portal vein in man are still based on the results of animal experimentation, but this is shifting sand, if even these results are uncertain. Before ablative operations are undertaken, more certain information must be obtained, and it is the purpose of these investigations to employ recent technical advances in a research of the problem as it affects the dog.

PLAN OF EXPERIMENTS

Following acute ligation of the portal vein, the length of survival was measured, with and without obliteration of the major porto-systemic anastomoses. The position of these anastomoses was investigated. The reduction in circulating blood volume was measured and the validity of the method employed was examined. The normal capacity of the splanchnic vascular bed was measured. Further investigations which are required have been indicated. The methods employed are detailed under the heading "Experimental" and the results obtained are recorded under "Observations". A specific discussion follows each set of observations, the general discussion being employed for more general speculation.

EXPERIMENTAL

EXPERIMENTAL METHOD

1. General

Pound dogs were used, unselected as to weight, sex or general condition. They were starved overnight, but were without water restrictions.

Prior to being anaesthetized, they were encouraged to empty their bladders, and were then weighed. Anaesthesia was produced by the intravenous injection into a forepaw vein of sodium pentobarbital, using 30 mgm/kg body weight. The dogs were intubated with an endotracheal tube and placed on a warmed operating table. The abdomen was opened by a midline incision, care being taken to reduce bleeding to a minimum; (by measuring the increase in weight of dry gauze sponges used for mopping, blood loss did not exceed 10 to 20 ml.). During the period between manipulations, the abdominal wall was closed if it was possible to do so, usually by Allis tissue forceps; if impossible, the wound was protected by towels soaked in saline. The length of any experiment seldom exceeded 2 hours, and it was usually unnecessary to give a further dose of sodium pentobarbital. The animals were unconscious during the whole of the experiment. They received no intravenous therapy nor fluid by oesophageal tube. The temperature within the operating room was fairly constant between 70° and 75° F. The instant of death was taken as the last contraction of the left ventricle of the heart sufficient to be recorded by a mercury blood pressure manometer. This point was usually preceded by several convulsive respiratory movements.

2. Blood Pressure

A continuous record of the blood pressure was obtained by a mercury manometer. The left common carotid artery was exposed by dissection, ligated distally, and the proximal portion cannulated with a No. 12 blunt-ended cannula which was tied in. The cannula and tubing were filled with 3.6% sodium citrate solution. The tubing was vinyl plastic which resists lateral expansion of its walls (Arst et al. - 1951).

3. Blood Samples

These were obtained using dry, siliconed, all glass syringes (Jaques et al. - 1946).

4. Haematocrit Estimation

Wintrobe's mixture was used as an anticoagulant, and the samples of blood were spun for 30 minutes at 2,210 R.C.F. The samples used were portions of the blood obtained for the blood volume determinations. When portal venous blood was required, a needle was inserted directly into the portal vein. It was found that clots formed often in this portion of the vein, and therefore heparin was usually given in these experiments (15 mgm/ kilo of body weight).

5. Acute Ligation of the Portal Vein

Under the standard conditions described, the portal vein was identified, and the overlying peritoneum of the free edge of the lesser sac divided. The vein was cleared upwards to the bifurcation, and a black silk ligature applied on the hepatic side of the last tributary, and the ends brought out through the abdominal wound. The traction necessary to expose the portal vein usually caused violent fluctuations in the blood pressure, and time was allowed for this to return to normal. When the pressure finally settled, the ligature was tied, disturbing the viscera as little as possible. The abdominal wound was closed with Allis forceps, and the dog left undisturbed until death.

When simultaneous records were obtained of both intra-arterial pressure and portal venous pressure, the arterial pressure was obtained using a mercury manometer as described above. The portal venous pressure

was obtained by cannulating a splenic vein in the gastro-splenic ligament, using size 16 polythene tubing, and passing the tubing into the main splenic vein. The tubing was then connected to a physiological pressure transducer (Statham model P23A), the output being amplified by a Brush universal amplifier (Model BL320). A continuous ink record was obtained by means of a Brush oscillograph (Model BL202). The tubing was filled with saline, and clotting prevented by heparinization of the animal.

6. Estimation of Blood Volume

The blood volume determinations were made using Reeve and Veall's (1949) modification for the procedure of Hevesy and Zerahn (1942). Ten ml. of venous blood was withdrawn from a forepaw vein of the dog into a 10 ml. syringe containing heparin. Eight ml. of this blood was incubated with 40 microcuries of carrier free P_{32} of high specific activity for approximately one and a half hours in a 10 ml. centrifuge tube rotated in a water bath at a constant temperature of 37° C. The cells were then separated from the plasma by centrifuging, and resuspended in saline. The separation and resuspension was done three times.

Two ml. of the freshly prepared suspension of labelled red cells was injected into a femoral vein. After allowing five minutes for mixing to occur, 10 ml. of blood was withdrawn from the contralateral femoral artery and placed in a small glass beaker containing sodium citrate crystals as an anticoagulant and powdered saponin to produce lysis of the red cells. Five 1 ml. samples of this blood were counted separately for activity, using a glass Veall re-entrant type liquid beta Geiger counter.

The activity of the specimen of blood withdrawn from the femoral artery was compared with the activity of the original 2 ml. suspension of labelled red cells. The activity of this was obtained by using the same 2 ml. syringe to draw up the suspension, and diluting it to approximately the same volume as the blood volume of the dog by injecting it into a Winchester bottle containing 2000 ml. of water, and again counting 5 samples of 1 ml. of the dilution for activity.

If the total activity of the P_{32} labelled red cells is A counts per second, and the activity of 1 ml. of the blood withdrawn from the animal is B counts per second then the blood volume, V, is given by the formula BV = A, or V = $\frac{A}{B}$. When a second blood volume determination was required, 10 ml. of blood was withdrawn from the ipsilateral femoral artery, and counted for background activity. Immediately following the withdrawal, a further 2 ml. of P_{32} labelled red cells was injected into the femoral vein not previously used, and again, after 5 minutes, 10 ml. of blood was obtained from the femoral artery not previously used. By inserting the needle (22 SWG) at an angle into the artery, and by finger pressure on the hole for three minutes after withdrawal, no blood escaped despite heparinization.

7. Mixing of Activated Red Cells with the Circulating Red Cells.

In order to discover whether adequate time was allowed for mixing of the injected red cells with the circulating red cells, two types of experiments were carried out.

(a) Serial Estimation of the Activity

A two-way stop-cock attached to an 18 SWG needle was inserted

into the left femoral artery. Two ml. of P_{32} activated red cells were injected into the right femoral vein. At 2 minute intervals thereafter 2 ml. samples of blood were obtained from the femoral artery. Before each sample was collected, 1 ml. was allowed to flow through the needle and stop-cock to flush out the blood remaining from the previous sample. To obviate clotting within the needle, heparin was given to the dog.

(b) Continuous Record of Activity

The femoral vessels on both sides were exposed. On one side the femoral artery was divided and cannulated with No. 16 polyethylene tubing filled with heparinized saline, and arranged so that a helix was formed, through which the blood flowed. The helix was placed between two self-quenching thin end window Geiger-Müller counters, wired in parallel (Tracer Lab. TGC-2). Two ml. of P_{32} labelled red cells were injected into the contralateral femoral vein. By means of a rate meter (Nuclear instrument corporation, Model 1615-B) arranged to record through an Esterline Angus graphic ammeter recorder, a continuous record of the level of activity of the circulating blood could be obtained. In order to check the patency of the system, a bleeding tap was placed on the distal side of the helix. Heparin was given to prevent clotting within the tubing.

8. Determination of Communications Between the Portal and Systemic Venous Circulations

As previously described, dogs were anaesthetized with sodium pentobarbital, the abdomen opened, and the portal vein ligated to raise the portal venous pressure, thus opening up any small anastomoses with the systemic circulation. After 45 minutes the dogs were killed by

removing the anterior chest wall, dividing the thoracic aorta, and allowing blood to flow from both ends. Heparin was given prior to ligation of the portal vein (5 mgm/kilo of body weight) in order to prevent blockage of the smaller vessels with clots. The ligature around the portal vein was then cut. A cannula was placed in the thoracic aorta and attached to a water tap. At a pressure of 150-200 mm. of mercury the blood within the vessels was washed out, drainage being provided by a cannula within the inferior vena cava, and another in the portal vein. Washing was continued until the water returned clear. This usually took about one hour. The water was then allowed to drain out and two hours later, latex (Guttapercha L180 latex solution) was injected through the cannula within the portal vein at a constant pressure of 100 mm. of mercury. The injection material flowed quickly and easily to fill all the small venules of the portal venous system. In order to be certain of filling all vessels, the injection was maintained at this pressure for one hour. At the conclusion of the injection, the portal vein cannula was closed, and the animal kept overnight to allow the latex to set. It was then carefully dissected, the symphysis pubis being divided, and the pelvis distracted and opened like a shell to display all pelvic communications. The diaphragm was not incised prior to injection, but this did not interfere with the filling of the communications at the lower end of the oesophagus.

9. Measurement of Splanchnic Blood Volume

When the circulating blood volume is estimated using P_{32} labelled red cells, the injected cells are equally distributed throughout the blood of the recipient. If during the measurement, the feeding arteries and draining veins of any organ are simultaneously occluded, the blood vessels

of the organ will contain their normal quota of blood, and a proportion of the red cells will show activity. A measure of the total activity of that organ will therefore give the quantity of blood contained within the organ.

Pound dogs anaesthetized with sodium pentobarbital intravenously were used. Ten ml. of blood was obtained from the right femoral vein for incubation with P_{32}. After approximately one and a half hours, the abdomen was opened, and ligatures were placed around the intra-abdominal oesophagus and around the rectum as close to the anal canal as possible, and tied. The coeliac axis and great mesenteric artery were identified, and with the minimum of dissection were cleared so that a heavy haemostat could occlude them. Similarly, the portal vein was identified and cleared. The lesser mesenteric artery was cleared, ligated and divided. The circulating blood volume was estimated in the usual manner with the injection of 2 ml. P_{32} labelled red cells. Immediately following withdrawal of the sample of blood for determination of the blood volume, clamps were applied simultaneously to the portal vein and great mesenteric artery. By dividing these vessels, cutting across the oesophagus and rectum, and cutting the attachment of the mesentery to the posterior abdominal wall and of the lesser omentum to the liver, it was but a moment's effort to remove the whole of the intra-abdominal gastro-intestinal tract from the lower oesophagus to the lowest part of the rectum, together with spleen and pancreas, without losing any of the contained blood. These organs were then placed in a large jar and concentrated hydrochloric acid added to render the contents into a homogeneous liquor. This process took approximately 48 hours during which time the decay of radioactive

phosphorus occurred at a known rate. The fat rose to the surface and was discarded, for it contains only about 1% of the activity compared with an equal quantity of liquor. The diminution of counting rate which occurs due to self-absorption when this liquor is used, compared with the counting rate in water, is only 3.3%. The specific gravity of the liquor in three experiments was 1.115, 1.116 and 1.086, after the fat had been skimmed off. The volume of the liquor was measured and counts were then made of the activity of 10 ml. samples. Having corrected for the natural decay of the activity of the radioactive phosphorus, the total activity contained within the intra-abdominal gastro-intestinal tract was obtained. If the total activity of the injected P_{32} labelled red cells is A counts per second and the activity of 1 ml. of the blood withdrawn from the animal after mixing has occurred is B counts per second, then the total circulating blood volume V is given by the formula BV = A. Also if the activity of the liquor of the digested organs is X counts per second per ml., and the total volume is Y, then the total activity of the liquor is XY counts per second. By simple proportion, if the volume of the blood contained within the digested organs is V_1 then

$$\frac{V_1}{V} = \frac{XY}{A} \quad \text{or} \quad V_1 = \frac{XY \times V}{A}$$

OBSERVATIONS

1. Acute Ligation of the Portal Vein

(a) Length of Survival Following Acute Ligation

Table I shows the survival time following acute ligation under three different circumstances, (i) acute ligation of the portal vein only, (ii) acute ligation of the portal vein, together with ligation of the oesophageal anastomotic veins, (iii) acute ligation of the

portal vein, the dogs being given heparin.

Discussion.

Acute ligation in 14 dogs caused death in an average of 79.7 (± 18.9) minutes, a figure which is in accord with that recorded in the literature. When, in addition, a ligature was placed around the intra-abdominal oesophagus in 11 dogs, the time of survival was shortened to 56.0 (± 8.5) minutes. In 9 dogs with acute ligation of the portal vein, without oesophageal ligature, but given heparin (10 mgs/kg), time of survival was 88.6 (± 23.26) minutes. There was a significant difference between the length of survival with or without oesophageal ligatures, but no difference between survival with or without heparin. In four dogs the ligature was placed on the intestinal side of a pancreatico-gastric vein, and was therefore incomplete. Two of these dogs survived, and were killed after two hours. In one, the tributary measured 1.5 mm. in diameter, and the systemic blood pressure at sacrifice was 90 mm. Hg. Of the other two dogs which died, one was an old dog, with a tributary measuring 1.5 mm., the other was a young dog, with a tributary measuring 0.5 mm. in diameter.

(b) Observations on Blood Pressure

Immediately following ligation of the portal vein the arterial pressure drops rapidly in the first few minutes and then more slowly to reach a plateau at 30-40 mm. Hg. after about 10-20 minutes. It stays at this level with only minor fluctuations until just prior to death.

If simultaneous records are taken of the portal venous pressure and arterial pressure it is shown that the portal venous pressure rises from a preligation level of around 7 mm. Hg. to a maximum of 50-60 mm. Hg. in about 2 mins; thereafter the portal venous pressure declines paralleling the fall in the systemic arterial pressure to a level mid-way between the diastolic and systolic pressures. A typical result is shown in Fig. I.

Discussion.

Following ligation, blood is continuously supplied to the splanchnic vessels, from which it cannot escape. As the circulating blood volume is rapidly reduced, so the systemic blood pressure will fall, until it is equal to the level to which the portal venous pressure rises. While the pressures remain equal, during the period of the plateau, the only blood entering the splanchnic vascular bed will be to replace the blood escaping from the bed by the porto-systemic anastomoses, and the blood lost by haemorrhage into the bowel wall. The splanchnic bed is to all intents excluded from the circulation. If the porto-systemic anastomoses are occluded the exclusion is more complete. Therefore a measurement of the blood volume during this period will measure only the circulating systemic portion.

It is interesting to note that there is no apparent attempt to compensate for the pooling of the blood within the splanchnic circulation. There are two possible explanations, (i) any attempt by the dog to compensate for the falling blood volume by vasoconstriction will raise the pressure, which will cause further blood to be lost into

the splanchnic bed. The blood pressure records show no evidence of this, (ii) compensation may fail to occur. Peck and Grover (1952) have suggested that the initial rapid fall in arterial pressure is reflex in nature, while the ensuing slower fall is due to a decline in circulating blood volume. They stated that it was not possible for the reduction in blood volume to be so great as to produce such a fall in blood pressure in the time recorded, but this possibility cannot be excluded until the reduction in blood volume, and the rate at which it proceeds, is known.

2. Blood Volume Estimations

The results of eleven experiments are summarized in Table II. Following sodium pentobarbital anaesthesia and the trauma attendant on the abdominal incision, the average circulating blood volume was 76.9 (± 6.55) ml. per kilogram body weight. Thirty minutes after occlusion of the portal vein and 10 minutes after ligation of the oesophagus and its vessels, the average systemic circulating volume was 32.7 (± 8.23) ml. per kilogram, a reduction of 44.2 ml/kg. or 57.9% (± 8.77) of the original blood volume.

Table III lists the true counts per second per 10 ml. utilizing the constant geometry provided by the same Veall counter for each of 5 counts for each experiment. Following ligation of the portal vein, the average counting rate of the systemic blood fell to 85.0% (± 13.8) of the pre-ligation value, while the portal venous count rose to 117.2% (± 15.9) of its original value. Five minutes after the second injection of labelled red cells, the average counting rate of the portal venous blood rose only

1.3% (± 7.5%) above the background count for the blood immediately prior to the second injection, whereas the average systemic count rose 178.8% (± 80.2).

In a preliminary series of seven dogs, a similar type of experiment was undertaken, except that the portal vein only was ligated and collateral vessels were ignored. After the second injection of P_{32} labelled red cells a rise in the average portal venous blood counting rate of 17.8% (± 22.2) was noted, when the average systemic blood counting rate rose 175.6% (± 53.0). This indicated the degree of leakage of labelled red cells into the splanchnic vascular bed, when these main anastomotic channels were not occluded.

It was as a consequence of the preliminary experiments that the situation of the main anastomoses between the systemic and portal venous circulations was investigated, as will be described later.

Discussion.

It is possible to carry out accurate determinations of circulating blood volumes by using red blood cells labelled with radioactive phosphorus (P_{32}) (Hevesy and Zerahn - 1942). In this experiment the determinations were made using Reeve and Veall's (1949) modification of the method of Hevesy and Zerahn. By using the Veall counter, it is not necessary to estimate the haematocrit to calculate blood volume, for the activity of whole blood is counted, and it is unnecessary to apply any correction factor for plasma trapped with the red blood cells.

Figures for the circulating blood volume of dogs have been given by several observers, Table IV.

In general, in human patients the value given by the P_{32} method has been found to be lower than that based on the dye T-1824. The value for dogs obtained in these experiments (76.9 ml/kg) is remarkably consistent, but nevertheless it cannot be compared with those given by other workers, for it was obtained after the trauma of opening the abdomen.

Both Hahn et al. (1942) and Delorme et al. (1952) have stated that mixing of the labelled red cells in the circulation is complete within 4 minutes following injection. Figure II shows the mixing curves in two experiments after the injection of 2 ml. of P_{32} labelled red cells, corrected counts of activity being obtained by 2 ml. samples of blood withdrawn at the times shown. Mixing is barely complete in 5 minutes. The activity of the injected cells does not remain constant but shows a persistent steady decline as has been found by other investigators (Hahn et al. - 1942, Krieger et al. - 1948, Reeve and Veall - 1949), and in contradistinction to Delorme et al. - (1951).

Figure III shows similar results using the method of continuous records of the counting rate employing the end window Geiger counters and a rate meter recording through an Esteline Angus recorder. Again mixing is shown to be barely complete in 5 minutes.

Following ligation of the portal vein, with the sequestration of blood within the portal vascular bed, mixing of injected labelled red cells with the systemic circulating blood is slowed, due to the reduced cardiac output and reduced blood flow. Figure IV shows the rate of mixing occurring in the systemic circulation at intervals, for 20 minutes after injection of P_{32} labelled red cells in two experiments. The red

cells were injected 20 minutes after the portal vein was ligated. Again, mixing is barely complete after 5 minutes, but the counting rate starts to fall by the tenth minute. It is during this short period that it is necessary to withdraw the blood to avoid the error - on the one hand, of incomplete mixing; on the other, of the decline in the counting rate resulting from both the sequestration within the splanchnic vascular bed and the normally occurring decrease in counting rate.

The injection of P_{32} labelled red cells for the second blood volume determination was made into the inferior vena cava and the systemic sample taken from the femoral artery in order to attempt to reduce the effect of sluggish peripheral flow (Gregersen and Rawson - 1942). The error introduced by incomplete mixing will be such that dilution will not be completed, and thus too low a value for the circulating blood volume will be obtained. As the error is likely to be greater in the second blood volume estimation than in the first, the values obtained for the decrease in circulating blood volume are likely to be too great.

The estimation of the circulating blood volume was made 30 minutes after the occlusion of the portal vein during the period of the blood pressure plateau and about midway in the time of survival. Though blood continued to be lost into the bowel, this was to some extent offset by the return of blood from the splanchnic bed as the arterial pressure declined prior to death, and possibly by plasma returned from the bowel by the lymphatics.

These experiments have shown that the reduction in circulating blood volume following sudden and acute ligation of the portal vein is

57.9% of the original volume, but this value cannot be compared with those obtained by Elman and Cole (1932) or Boyce and others (1935). Their values reflected only the quantity of blood introduced into the splanchnic vascular bed and ignored that portion normally contained within the vessels of the bed.

An experiment similar in design to the one described in this thesis was performed by Mallet-Guy, Devic and Gangolphe (1950). Unfortunately they chose the dye method to estimate the blood volume. This meant that 48 hours had to elapse between the first and second blood volume estimations, to allow the dye of the first estimation to disappear, though even this was probably not long enough. Because they could not find thiocyanate, subtosan or methylene blue in the portal vein when it was injected systemically after portal vein ligation, they ignored the collateral paths. But this is not justified. Moreover, they made no mention of the details of their methods particularly during the second estimation. Finally, the value they obtained of a reduction in circulating blood volume of 49.3% is not comparable to that of Elman and Cole (1932) or Boyce et al. (1935) for it too includes the blood normally present in the splanchnic vascular bed. The comparable figure is 36.7% as will be seen later.

In order to discover whether consecutive estimations of blood volume could be made using the P_{32} method, two experiments were carried out, and the results are found in Table V. In the first experiment, the second determination followed immediately after the first, the third 30 minutes after the second. The differences were 3.1% and 2.2% respectively. In the second experiment, the second determination followed immediately

after the first and the difference was 3.1%

3. Estimations of Splanchnic Blood Volume

The results are shown in Table VI. The circulating blood volume in these 10 dogs was 81.1 (± 17.4) ml. per kg. compared to the previous figure of 76.9 (± 6.55) ml. per kg. The splanchnic blood volume, that is, the blood contained within the vessels of the intestines, from cardia to rectum, together with the spleen and pancreas, was found to be 17.7 (± 5.9) ml. per kg. body weight. This represents 21.7 (± 5.5) % of the circulating blood volume.

Discussion.

Mass ligation of the oesophagus will occlude the main anastomosis between the systemic and portal venous systems, but provided the portal vein is not obstructed, it will not lead to increased pooling of blood within the viscera. Ligation of the lower rectum interrupts even fewer anastomoses, and ligation of the lesser mesenteric artery probably reduces the inflow by very little in proportion to the great amount of arterial blood provided from the coeliac axis. The spleen in these dogs remained remarkably constant in size provided that gross manipulation was avoided, probably as a result of the sodium pentobarbital anaesthesia, though undoubtedly the quantity of blood contained varied from dog to dog. It is easy to apply the clamps to coeliac axis and portal vein simultaneously so that the errors of uncompensated drainage by the portal outlet, or congestion from obstruction to the portal outlet can be avoided. Removal of the intestines is possible without any escape of the contained blood.

The only other comparable figures are those produced by Delorme et al. (1951) using the "exclusion" method. "The method of measuring circulating blood volume by labelling erythrocytes with radioactive isotope P_{32} may be modified to measure the volume of a part of the circulation by excluding that part from the general circulation immediately before the injection of labelled corpuscles (Nylin - 1947). The blood volume so measured, is the total blood volume less that of the excluded section. When the excluded area is opened, the blood in which there are no labelled corpuscles mixes with and dilutes the radioactive blood in the general circulation. This dilution is a matter of the volume of the excluded section." In their experiments the splanchnic bed was taken as stomach, intestines, spleen, pancreas and liver. This was estimated to contain between 20% and 50% of the total blood volume in 13 dogs, with an average of 34.8%. While this method has the advantage of not requiring the evisceration of the dog, it is subject to the serious error of the escape of labelled red cells into the excluded area by anastomotic channels. In addition, it is impossible simultaneously to clamp both the feeding and draining vessels of the constituent components of their splanchnic vascular bed, and thus a considerable error from either congestion or emptying of the vessels will occur. In three animals they estimated the volume in the "proper hepatic supply" to be 16, 6 and 22% of their splanchnic blood volume. In these three dogs, their splanchnic blood volume was respectively 50, 25 and 25%. Therefore, by subtracting the "proper hepatic supply" from their splanchnic blood volume, figures corresponding to our splanchnic blood volume are 41, 23 and 19% respectively.

If the blood volume of the dog is taken as 76.9 ml/kg body weight and the blood volume of the splanchnic vascular bed is 17.7 ml/kg body weight, then after the splanchnic vascular bed has been excluded, the capacity of the remaining systemic vascular bed is 59.2 ml/kg body weight. After ligation of the portal vein the systemic circulating blood volume is reduced to 32.7 ml/kg body weight. It can be argued that the true reduction in the circulating blood volume is therefore the difference between this figure and the value for the circulating blood volume with the splanchnic bed excluded, (59.2 ml/kg), that is, 26.4 ml/kg body weight or 44.6%, for the remaining circulating blood volume is required to fill a vascular bed reduced by the normal capacity of the splanchnic bed. It is this figure which corresponds to that of Elman & Cole (1932).

4. Haematocrit Estimations

Table VII shows haematocrit results obtained prior to and following ligation of the portal vein.

Discussion.

The difference in the haematocrit values for blood drawn from the femoral vein before anaesthesia with sodium pentobarbital, and from the femoral artery following anaesthesia are of doubtful significance ($p < 0.05$). It is not possible to say which of the two variables (the source of the blood or the pentobarbital anaesthesia) is the cause. Thirty minutes and 40 minutes after occlusion of the portal vein, the haematocrit values within the arterial system are seen to have fallen in every case except one. This fall is highly significant ($p < 0.01$). The haematocrit values of the blood within the portal vein are seen to have risen to a

highly significant extent ($p < 0.01$).

The latter reflects a continued escape of plasma into the bowel wall. The cause of the continued fall in the arterial haematocrits is harder to account for. It is pertinent at this point to discuss the effect of pentobarbital anaesthesia. Ingraham et al. (1950) stated that pentobarbital anaesthesia in two-thirds of the dose normally used (21.4 mg/kg body weight) has no effect on the course of events in haemorrhagic shock, but it does, nevertheless, cause enlargement of the spleen, produce haemodilution, and cause congestion of the viscera (Wiggers - 1942). These observations have been supported by Wang and Walcott (1952) who found there was no significant change in the final bleeding volume after pentobarbital anaesthesia, and by Bollman et al. (1938), Hahn et al. (1942) and Courtice and Gunton (1949), all of whom found that the spleen was enlarged after pentobarbital anaesthesia. Haussner et al. (1938) attached lead shots to the spleen, and by x-ray observed its enlargement after pentobarbital anaesthesia.

In order to see whether splenectomy would have any effect on the course of events after ligation of the portal vein, four experiments were done. In two, the abdomen was opened, the portal vein cleared and a ligature placed in the usual manner. The splenic artery was ligated, and when the spleen had shrunk, the splenic pedicle was clamped and the spleen excluded from the circulation. The portal vein was then ligated and the dogs died in 56 minutes and 72 minutes respectively, with no change in the course or in the post mortem appearance of the intestines. The blood pressure fell, after ligation, to a level of between

80-90 mm. Hg over ten minutes, and then declined slowly until a pressure of 30-40 mm. Hg was reached. In the third and fourth experiments, the decrease in circulating blood volume was measured after portal vein ligation, but with the spleen removed (Table VIII). Both these dogs showed a greater degree of extravasation of blood into the mesentery than those without splenectomy. However, their course was uninfluenced, and the decrease in circulating blood volume was within the range of those dogs without splenectomy. In effect, the splanchnic vascular bed seems to have a huge capacity for distension, and this is not diminished notably by splenectomy. The capacity of the spleen in dogs has not been recorded.

This indicates that whatever the effect of sodium pentobarbital is on the spleen, it has little influence on the course of events, for there can be no greater stimulus to splenic enlargement than a rise in portal venous pressure, nor decrease in the splenic volume than total removal.

The effect of pentobarbital anaesthesia on peripheral haematocrits is harder to evaluate. The general effect is to produce an immediate haemodilution which continues unchanged for several hours (Bollman et al 1938, Wiggers 1942, Courtice and Gunton 1949). If however the experiments continue for too long, haemoconcentration will occur, due to dehydration of the animal (Seavers and Price 1949). If haemorrhage occurs, haemodilution is prevented, for dogs under pentobarbital anaesthesia restore no part of the plasma lost by haemorrhage, probably because of arteriolar relaxation which prevents lowering of capillary pressure, and reabsorption

from the tissues. (Courtice and Gunton 1949) The role of the spleen as a blood storage depot for red cells to be mobilized after haemorrhage is now usually discounted (Courtice and Gunton 1949, Gibson et al. 1946, Delorme et al. 1952).

Further, haematocrit values are known to vary widely with the source of the blood used. For this reason, little information can be obtained from the fall of haematocrit values recorded here, but a possible explanation may lie in the return to the circulation of plasma from the intestines through the lymphatic system.

5. Situation of Porto-systemic venous anastomoses.

All specimens had well injected portal tributaries.

Dog No. 1 Weight 9.1 kg. Male

The superior rectal vein was followed down through the muscle layer to its termination, a short distance from the anus. No pelvic systemic veins contained latex. The posterior abdominal wall had a single, thread-like vein containing latex, which ran from the mesentery to the fascia overlying the kidney. From the cardia, small veins filled with latex drained into two main branches which ran with the two vagi nerves, and drained into the systemic veins on the posterior wall of the thorax. No other porto-systemic anastomoses could be found.

Dog No. 2 Weight 15.9 kg. Male

A small branch ran anteriorly from the rectum in the reflection of peritoneum onto the posterior surface of the prostate, and thence into a vein which drained the right ureter

and posterior abdominal wall. A few tiny venules could be seen running in the mesentery of the rectum, but no other veins filled on the posterior abdominal wall. From the mesentery of the duodenum, small branches filled with latex formed a vein (0.5 mm. diameter) which joined a lumbophrenic vein medial to the left suprarenal vein, which then drained into the inferior vena cava 1 cm. above the right renal vein. At the cardia, small gastric branches amalgamated to form main branches which accompanied the two vagus nerves. From these, three branches ran to the posterior thoracic wall veins, draining the lowest 5 cm. of the oesophagus. (See Figure V(a))

Dog No. 3 Weight 15.0 kg. Male

Three cms. from the anus on the left side, a latex filled vein (0.4 mm. diameter) ran posterolaterally to join a vein on the side wall of the pelvis (0.8 mm. diameter). From the anterior aspect of the rectum, a latex filled vein ran in the peritoneal reflection to the posterior aspect of the prostate. This vein was joined by a small vein in the mesentery. At the upper rectum three small veins (0.3 mm. or less in diameter) ran from the rectal network of vessels to the posterior abdominal wall. Two minute veins ran from the duodenal mesentery to join the left lumbo-adrenal vein, but this vein had only traces of latex within it. Along the right vagus a vein ran connecting the veins of the cardia with those of the lower oesophagus and of the posterior thoracic wall in a ladder manner. Along the left vagus, a vein ran connecting with the lower oesophageal

veins, but not anastomosing with the veins of the posterior thoracic wall. (See Figure V b)

Dogs No. 4 & 5 Attempts to display anastomoses by using radio-opaque media failed, only the main portal venous tributaries filling.

Discussion:

These dissections, in which good filling of the smallest venules was obtained, show that in the dog, the main porto-systemic venous anastomoses occur at the lower end of the oesophagus, connecting the gastric portal veins to the oesophageal systemic veins, in relation to the right and left vagus nerves. Two other groups of anastomoses occur, but of a relatively minor degree, those in the mesentery running to the left lumbo-adrenal vein, and those connecting the lower rectum with the prostatic veins. These findings are supported by the counting rates obrained in the portal venous blood when the lower oesophagus and its veins are occluded (see Table III). Without occlusion, the portal venous count rises to a much greater extent on injection of P_{32} labelled red cells into a systemic vein, than when the oesophagus is ligated. In the latter case the rise can be accounted for by the leak of plasma into the bowel. This allows a very small inflow from the systemic circulation to the portal vascular bed.

Little work has been done on portosystemic venous anastomoses save in man. Butler (1951) in an investigation of the veins of the oesophagus in man drew attention to similar venae comitantes of the vagus nerve, joining the left gastric veins to the azygos veins, in addition to subepithelial and submucous networks.

Wermuth (1939) investigating the anastomoses at the other end of the gastro-intestinal tract, using latex injections, remarked on two main groups

a) laterocranial, from rectum to an hypogastric vein on either side,

b) dorsoventral, from the rectum at a lower level than a) to the side of the uterus.

Edwards (1951) by using a barium sulphate suspension injected into the femoral veins in three normal subjects, confirmed a description by Schmiedel (1744); namely, that two main groups occurred.

1) Normal multiple fine vessels above the rectum and in the retroperitoneal areas of the abdomen

2) Abnormal communications between the portal and systemic systems, e.g. termination of the portal vein in the inferior vena cava.

In his article there are no clear-cut descriptions of the normal vessels.

In the presence of portal hypertension, there are numerous articles concerning the situation of dilated portosystemic anastomotic and collateral veins (Sappey 1883, McIndoe 1928) which also develop in the dog when partial obstruction of the portal vein is done. Child et al. (1951) remarked on the well marked pelvic portosystemic collaterals in the Macaca Mullata monkey, whose venous pattern is said to resemble that of man.

6. Exhibition of antibiotics

Six experiments were performed, in three of which the antibiotic was given prior to ligation of the portal vein, in three following ligation. The method of ligating the portal vein did not differ from that previously described. Continuous records of systemic arterial blood pressure were

obtained. Crystalline penicillin G was given intravenously into a femoral vein; the aureomycin was given by mouth by hand feeding. No bacteriological studies were done with these animals.

(a) Antibiotic given prior to ligation

(i) Female. Weight 25.0 kg. 500,000 units of penicillin given 1 hour prior to ligation. Dog died 50 minutes following ligation, without alteration in its course.

(ii) Male. Weight 7.5 kg. 500,000 units of penicillin given $6\frac{1}{2}$ hours, $3\frac{1}{2}$ hours and half an hour before ligation. Death in 65 minutes following ligation, course unaltered.

(iii) Female. Weight 23.2 kg. 250 mgm. aureomycin given in three doses (10 a.m., 1 p.m. and 4 p.m.) on day before, three doses (8 a.m., 11 a.m. and 2 p.m.) on day of ligation. The portal vein was ligated 49 minutes after the last dose. The dog died 73 minutes later, with unaltered course.

(b) Antibiotic given after ligation

(i) Male. Weight 20.4 kg. 500,000 units of penicillin 10 minutes after ligation. Death in 100 minutes, course unaltered.

(ii) Male. Weight 15.9 kg. 500,000 units of penicillin 9 minutes after ligation. Death in 32 minutes, course unaltered.

(iii) Male. Weight 12.2 kg. 500,000 units of penicillin 5 minutes after ligation. Died in 114 minutes. Course unaltered.

Discussion:

Following the observations of Markowitz et al. (1949) on the ability of penicillin to protect against the effect of hepatic artery ligation, these experiments were carried out. In this small number, the

exhibition of antibiotics had no effect whatsoever on the outcome of ligation of the portal vein, whether given before or after ligation. It was thought that perhaps the antibiotics in question might be unavailing against the organisms and that further work should be done to investigate the normal bacterial flora of the dog's liver, and their sensitivity to antibiotics. This work has not been completed.

GENERAL DISCUSSION

These experiments have shown that the average reduction in circulating blood volume after ligation of the portal vein is 57.9% (±8.77) of the preligation volume. This figure is higher than that of Mallet-Guy et al. (1950), but if comparable volumes are taken, that is, if the blood normally present within the splanchnic circulation is subtracted from the volume sequestrated after ligation, then the resulting figure, 44.8%, is midway between that of Elman and Cole and that of Boyce et al.

Efforts to determine the volume of blood which is required to be bled to produce fatal levels of shock have been abandoned, for the response of the dogs is so variable that no figure is useful (Huizenga et al. 1943). Various estimations have been given in the past (see Table IX a). These have little comparable value for the method of determining them was so variable. Of much more value are the figures obtained by bleeding to arbitrary levels of irreversible shock (see Table IX b). Again, comparison is difficult for the levels of shock blood pressure differed. In general the procedure of Wiggers et al. (1946) was used. In this, bleeding (at a rate of around 40 ml/kilo body weight/min) continued until the blood

pressure fell to a level of 50 mm. Hg., at which level it was maintained for 90 minutes, when further bleeding was performed to reduce the blood pressure to 30 mm. Hg. for 45 minutes more. If these amounts are compared to the results of the present experiments (43.1 - 73.2 ml/kg, average 57.9), the latter are generally higher. The times of survival are however shorter. The determinations were made 30 - 40 minutes after occlusion, and oundoubtedly further decrease in the circulating blood volume must have occurred before death. Therefore an adequate explanation of the cause of death after ligation may lie in the decrease of the circulating blood volume to a level incompatible with an adequate cardiac output to sustain life. However, the inevitability of death after portal vein occlusion contrasted with the occasional survival after bleeding to such levels, and the fact that the total vascular bed has been reduced by the exclusion of the splanchnic portion (17.7 ml/kg) so that the smaller circulating blood volume is required to serve a smaller vascular area suggest that other factors are implicated.

An analogy may make this clear. If both legs are amputated, the contained blood, which may amount to 16% of the total circulating blood volume, is removed from the circulation. If the original blood volume was 1,000 ml., then the new blood volume is 840 ml. But this volume is required to serve a vascular bed which has been reduced by 160 ml. Therefore the ratio of circulating blood to vascular bed has not been altered. If now bleeding occurs, and the circulating blood volume is found to be 500 ml., then the reduction in circulating blood volume is not 50%, but the difference between the post bleeding blood volume, and the post amputation blood volume, namely 340 ml., or expressed as a

percentage $\frac{340}{840} \times 100 = 40.5\%$.

If the splanchnic viscera are considered to be the amputated legs, and the loss of blood into the splanchnic bed to be the post amputation bleeding, then the true reduction in circulating blood volume, taking the dog's weight to be 10 kg., can be worked out.

Preligation blood volume =	769 ml.
Volume of blood contained within the splanchnic viscera =	177 ml.
∴ Capacity of reduced vascular area =	592 ml.
Post ligation circulating blood volume =	327 ml.
∴ True reduction is 592 ml. - 327 ml.; or 265 ml., or expressed as a % $\frac{265}{592} \times 100$ =	44.8%

This must be associated with the reduced portal blood supply to the liver. This may produce (i) a decrease in the oxygen supply to the liver, (ii) a decrease in some particular component supplied by the portal blood, (iii) a toxin produced in the congested bowel. Efforts to implicate a toxin have generally failed; this does not necessarily exclude such a toxin. Liver regeneration is not dependent on portal venous blood. Dogs with Eck fistulae survive without detectable difference in biochemistry, or in their general health. However, in such dogs, any portal component can reach the liver eventually by the hepatic artery; again such a possibility

cannot be excluded.

Liver hypoxia is known to occur in shock (Engel et al. 1943, 1944). Survival of dogs following bleeding to otherwise irreversible shock levels can be obtained if the oxygen supply to the liver is supplemented (Frank et al. 1946, Delorme 1951). Ligation of the portal vein will cause hypoxia of the liver by depriving the liver of the oxygen carried by the portal venous blood. Though the hepatic artery is the dominant source of oxygen (Barcroft and Shore 1912, Blalock and Mason 1936), the portal venous blood does supply a substantial portion of the oxygen required (Smythe et al. 1951).

On reduction of the portal vein flow, the hepatic artery flow rises (Schwiegk 1932, Grindlay et al. 1941, Sancetta 1953), thereby increasing the total oxygen supplied by this source. This would compensate if the hepatic artery supply did not itself decline due to the decline in cardiac output.

If ligation is incomplete, when the circulating blood volume is augmented by the escape of portal blood back into the systemic circulation, or if the circulating blood volume is maintained by transfusion, the flow within the hepatic artery is probably maintained and survival follows. Ligation of the aorta above the coeliac axis, when combined with ligation of the portal vein, postpones death and allows survival 4 hours (Elman and Cole 1934). Ligation of the splanchnic arteries after portal vein ligation also postpones death (Boyce et al. 1935). Simultaneous ligation of the hepatic artery and portal vein has not been investigated.

In two dogs the right femoral artery was connected to the portal vein on the hepatic side of the ligature, in an attempt to auto-vivi-perfuse the liver. These dogs lived 105 and 146 minutes, but no alteration in their course was seen. However, this is inconclusive, for if the blood pressure was maintained, there would be a greater escape of blood into the splanchnic bed. This vascular bed would appear to have an inexhaustible capacity to contain blood put into it by the feeding arteries.

There are no results available of measurements of the extent of the hypoxia of the liver or of the amount of the decrease in flow of the hepatic artery following portal vein ligation. Further investigation of these points is indicated.

The preliminary experiments were made using intermittent positive pressure oxygenation using a Burns' valve (Adelman, 1950); in 4 dogs survival times were 50, 70, 56, and 86 minutes, average 65.5 minutes. It does not appear that any advantage is gained by respiration of pure oxygen. In haemorrhagic shock, if the portal venous pressure is reduced, then a much greater decrease occurs in the portal venous flow, than is the case with a comparable fall in systemic arterial pressure and the hepatic arterial flow (Wiggins et al. 1946). This was confirmed by Selkurt et al. (1947) who measured the reduction in portal venous flow after bleeding to a level of 40 mm. Hg. They found that the prehaemorrhage flow of 26.0 ml/min/kg body weight was reduced to 3.7 ml/min/kg. Nevertheless, there appears to be an attempt to maintain portal flow at the expense of the supply to the posterior half of the body (Blalock and Levy 1937).

These observations do not explain what deleterious process follows hypoxia of the liver. Two hypotheses are proposed presently. Shorr et al. (1951) have postulated the occurrence of a vasodepressor material, believed to be identical with ferritin, which is produced in the hypoxic liver, and which can be shown to inhibit the effect of neo-synephrine on the meta arterioles of the rat meso-appendix. Frank et al. (1952) by observing the effectiveness of aureomycin in increasing the survival following haemorrhagic shock (bleeding to 30 mm. Hg.) postulate that death from traumatic shock in which the blood volume deficit had been corrected was due to a toxin of anaerobic bacterial origin. His manner of giving aureomycin was to administer 2.5 gm. twice daily until stool cultures were free of E. coli and clostridia, which usually took 6 days. Compared with a control group, where a 12% survival occurred, 88% survived with this dosage. If 5 gms. were given, only 3-5 hours before bleeding, 45% survived. Penicillin was unable to influence the course of events. The organism responsible was not disclosed. But Hardy et al. (1954) were unable to substantiate the work of Frank et al., and Nelson (1954) found an identical incidence of positive blood cultures in shocked dogs and in controls.

The present experiments have not properly investigated the effect of antibiotics. All that can be said is that in the doses given the course is not influenced. These experiments should be further pursued.

SUMMARY

A review of the literature on ligation of the portal vein has been presented. A brief survey of the literature on the ligation of the hepatic veins and the hepatic artery has been included. The review reveals that while there is no disagreement that the result of sudden acute ligation of the portal vein in dogs is inevitably death, there is disagreement as to the cause of death. The main theories are (i) that exsanguination into the splanchnic vascular bed occurs, (ii) that the loss of blood is insufficient to cause death, and that other factors must be implicated, the "toxic" theory. The species difference in the effects of ligation appears to lie in the degree of porto-systemic venous anastomoses.

The experiments described in this thesis were performed with the dog as the experimental animal. A measurement of the decrease in circulating blood volume following ligation of the portal vein, using the "labelled" red cell method, was made. With 11 dogs, 30 minutes after portal vein ligation, the decrease amounted to 57.9% of the original blood volume. It was concluded that this amount of blood loss was not adequate to account for the inevitability of death, or the short period of survival (79.7 minutes) when compared to the effects of bleeding comparable quantities of blood, or bleeding to comparable levels of blood pressure.

It was considered that valid consecutive estimations of blood volume could be made using the "labelled" red cell method. A measurement of the normal splanchnic vascular blood volume was made using 10 dogs. This amounted to 21.7% of the circulating blood volume, or 17.7 ml. per kilogram body weight.

Haematocrit estimations were made on the systemic arterial blood and portal venous blood before and after ligation of the portal vein. There was a significant decrease in the systemic arterial haematocrit, and rise in the portal venous haematocrit. By the injection of latex into the portal vein of 3 dogs, the main porto-systemic venous anastomoses were found to occur in relation to the vagus nerves at the lower end of the oesophagus. Other porto-systemic venous anastomoses were of minor importance. It was not possible to influence the outcome of acute portal vein ligation by splenectomy, or by antibiotics under the conditions of the experiments.

TABLE I

Survival Times (mins.) after Occlusion of Portal Vein

Dog No.	Oesophageal Vessels Occluded	Dog No.	No Oesophageal Ligature	Dog No.	No Oesophageal Ligature Heparin - 10 mgs/kg
1	75	12	50	26	124
2	59	13	70	27	90
3	46	14	56	28	93
4	54	15	85	29	61
5	53	16	95	30	110
6	52	17	89	31	55
7	58	18	95	32	67
8	61	19	77	33	102
9	48	20	47	34	95
10	63	21	74		
11	47	22	95		
		23	85		
		24	85		
		25	113		
Average with calculated standard deviation.	56.0 ± 8.5		79.7 ± 18.9		88.6 ± 23.26

TABLE II

Reduction in Circulating Blood Volume

Dog	Sex	Wt. (kg)	Preligation circulating blood volume (ml)	Preligation circulating blood volume (ml/kg)	Post-ligation circulating blood volume (ml)	Post-ligation circulating blood volume (ml/kg)	Reduction of circulating blood volume (%)
1	F	9.1	798	87.7	399	43.8	50.0
2	M	18.2	1452	79.8	826	45.5	43.1
3	F	4.5	347	77.1	113	25.1	67.4
4	M	10.0	797	79.7	356	35.6	55.3
5	M	14.1	1023	72.6	468	33.2	54.3
6	M	10.0	675	67.5	181	18.1	73.2
7	F	15.1	1186	78.5	583	38.6	50.8
8	M	15.9	1076	67.1	424	26.7	60.3
9	M	17.3	1435	82.9	570	33.0	60.3
10	M	25.9	1930	74.5	914	35.3	52.6
11	F	10.0	788	78.8	244	24.4	69.0
Average with calculated standard deviation		13.6	1045	76.9± 6.56	462	32.7± 8.23	57.9± 8.77

TABLE III

True Counting Rates in C/S/10 ml. for Systemic and Portal Venous Systems After Injection of Labelled Red Cells

	Systemic Blood					Portal Venous Blood			
Dog	5 mins. after 1st injection (1)	28-31 mins. after occlusion of portal vein (background) (2)	% column 2 is of column 1 (3)	5 mins. after 2nd injection (36-41 mins. after p.v. occlusion) (4)	% column 4 is of column 2 (5)	28-31 mins. after occlusion of portal vein (background) (6)	% column 6 is of column 1 (7)	5 mins. after 2nd injection (36-41 mins. after p.v. occlusion) (8)	% column 8 is of column 6 (9)
1	136.0	132.3	97.3	293.9	222.1	156.6	115.1	153.8	98.2
2	58.0	42.0	92.4	101.4	241.7	72.5	125.0	73.4	101.3
3	651.1	507.8	77.9	1669.1	328.7	622.6	95.6	647.7	104.0
4	140.4	133.9	95.4	372.0	277.9	196.9	140.3	203.8	103.5
5	60.8	47.1	77.5	157.7	334.8	83.3	137.0	83.8	100.7
6	304.5	258.5	84.9	732.5	283.4	338.1	111.0	356.0	105.3
7	127.7	101.9	79.8	307.1	301.4	138.5	108.4	147.6	106.6
8	189.7	143.5	75.6	516.9	360.3	197.2	103.9	231.0	117.2
9	95.0	80.5	84.7	172.0	213.7	95.3	100.4	93.3	97.9
10	107.8	87.3	80.9	187.1	214.4	120.8	112.0	102.0	84.5
11	136.5	117.5	86.1	409.8	348.9	191.5	140.3	181.2	94.6
Average with calculated standard deviation.			85.0 ± 13.8		278.8 ± 80.2		117.2 ± 15.9		101.3 ± 7.5

TABLE IV

Estimation of blood volume of dogs, various authors.

Author	Method	Volume (ml/kg body weight)
Bonnycastle & Cleghorn (1942)	T-1824	82.7
Courtice (1943)	T-1824	79.0
Krieger et al. (1948)	T-1824	105.0
	Iodinated protein	94.0
	P_{32}	97.0
Delorme et al. (1951)	P_{32}	100.3
McLain et al. (1951)	Bleeding	62.0
	T-1824	89.0

TABLE V

Consecutive estimations of blood volume

	Sex	Wt. (kg)	1st Blood Volume determination (ml.)	2nd Blood Volume determination (ml.)	3rd Blood Volume determination (ml.)
Dog 1.	Male	18.8	1338.0	1380.0	1412.3
Dog 2.	Female	6.8	466.0	452.3	

TABLE VI

Measurement of Splanchnic Vascular Blood Volume

Dog No.	Wt. (kg)	Sex	Circulating Blood Volume (ml)	ml/kg	Splanchnic Blood Volume (ml)	ml/kg	% of Circulating Blood Volume
1	5.9	F	393.5	66.7	60.3	10.2	15.3
2	6.6	F	650.8	98.6	99.0	15.0	15.2
3	4.1	F	472.4	115.2	96.3	23.5	20.4
4	5.7	M	337.8	59.3	56.8	10.0	16.8
5	7.3	F	513.9	70.4	103.8	14.2	20.2
6	15.5	F	1299.7	83.9	297.7	19.2	22.9
7	6.8	F	612.8	90.1	186.3	27.4	30.4
8	17.1	M	1514.7	88.6	377.1	22.1	24.9
9	18.6	M	1233.5	66.3	253.1	13.6	20.5
10	9.6	M	692.4	72.1	210.0	21.9	30.3
Average with calculated standard deviation.	9.7		772.2	81.4±17.4	174.0	17.7±5.9	21.7±5.5

TABLE VII

Haematocrits

Dog (1)	Pre-anaesthetic Venous Systemic (2)	Post-anaesthetic Arterial Systemic (3)	Difference (3) - (2) (4)	Deviation From Mean (5)	Following occlusion of portal vein: After 28-31 mins. Arterial Systemic (6)	Difference (6) - (3) (7)	Deviation From Mean (8)	After 36-41 mins. Arterial Systemic (9)	After 28-31 mins. Portal Venous (10)	Difference (10) - (3) (11)	Deviation From Mean (12)	After 36-41 mins. Portal Venous (13)
1	40	34	-6	4.6	36	+2	5.2	37	60	26	4.5	59
2	43	41	-2	0.6	34	-7	3.8	30	66	21	0.5	65
3	46	45	-1	0.4	45	0	3.2	43	75	30	8.5	74
4	28	30	+2	3.4	29	-1	2.2	28	48	18	3.5	52
5	40	40	0	1.4	35	-5	1.8	34	62	22	0.5	---
6	57	56	-1	0.4	55	-1	2.2	56	73	17	4.5	74
7	55	53	-2	0.6	47	-6	2.8	48	72	19	2.5	73
8	52	50	-2	0.6	43	-7	3.8	41	75	25	4.5	75
9	46	44	-2	0.6	40	-4	0.8	40	66	22	0.5	71
10	47	46	-1	0.4	40	-6	2.8	40	65	19	2.5	71
11	43	43	0	1.4	43	0	3.2	42	61	18	3.5	63
			Mean -1.4			Mean -3.2				Mean 21.5		

Standard deviation $= \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$ $= \sqrt{\frac{38.56}{10}}$ $= 1.96$

Standard error of mean = 0.59

$t = \frac{1.4}{0.59} = 2.3$

$\therefore p < 0.05$

Standard deviation $= \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$ $= \sqrt{\frac{100.04}{10}}$ $= 3.16$

Standard error of mean = 0.301

$t = \frac{3.2}{0.301} = 10.6$

$\therefore p < 0.01$

Standard deviation $= \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$ $= \sqrt{\frac{170.75}{10}}$ $= 4.13$

Standard error of mean = 1.26

$t = \frac{21.5}{1.26} = 17.0$

$\therefore p < 0.01$

TABLE VIII

Reduction in circulating blood volume

following splenectomy and portal vein ligation

Dog	Sex	Weight kg	Blood Volume ml	ml/kg	Blood volume following splenectomy and portal vein ligation ml	% reduction	Survival time mins.
1	M	20.9	1893	90.5	754.7	60.1	68
2	M	14.1	874	62.0	471.0	46.1	72

TABLE IX

Volume of blood removed to cause "irreversible" shock

(a) By bleeding definite volumes of blood

Author	Amount ml/kg
Blalock (1931)	45
Boyce (1935)	58
Ireneus (1944)	50
Mallet-Guy (1950)	40

(b) By bleeding to arbitrary "irreversible" shock levels

Author	Range ml/kg	Average ml/kg
Huizenga (1943)	20-56	40.0
Ingraham (1950)	-----	49.9
Hay (1951)	27.5-67.2	42.9
Wang (1952)	48.8-71.5	60.8
Nelson (1954)	-----	52.0

Fig. I

Concurrent recordings of portal vein blood pressure and systemic blood pressure.

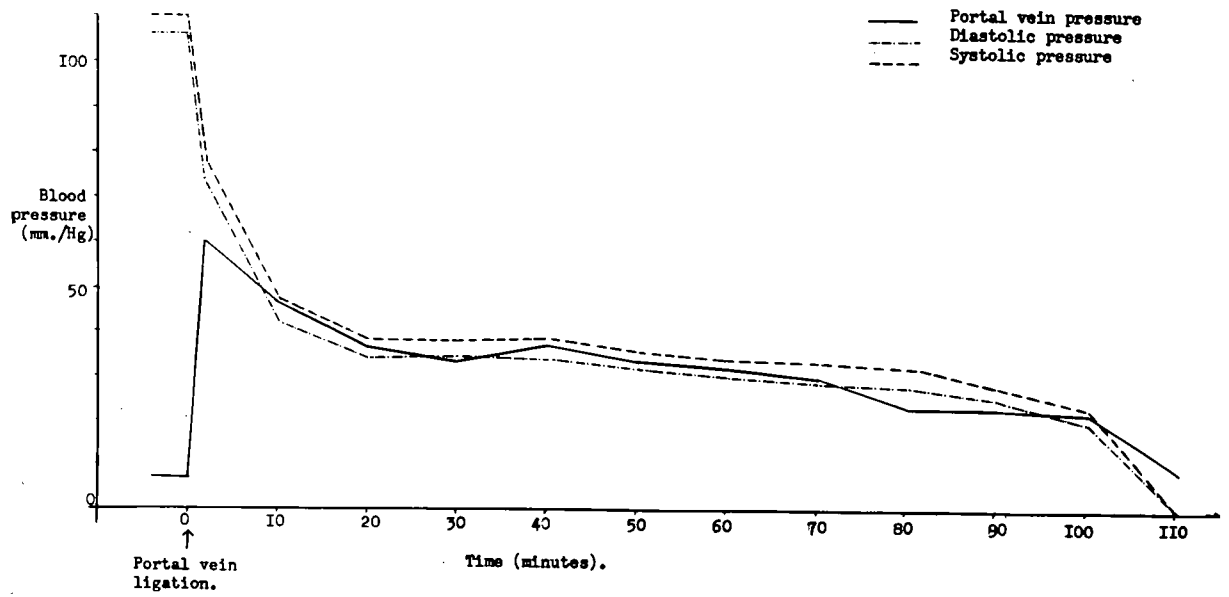


Fig. II

Mixing of P_{32} labelled red cells in the general circulation.

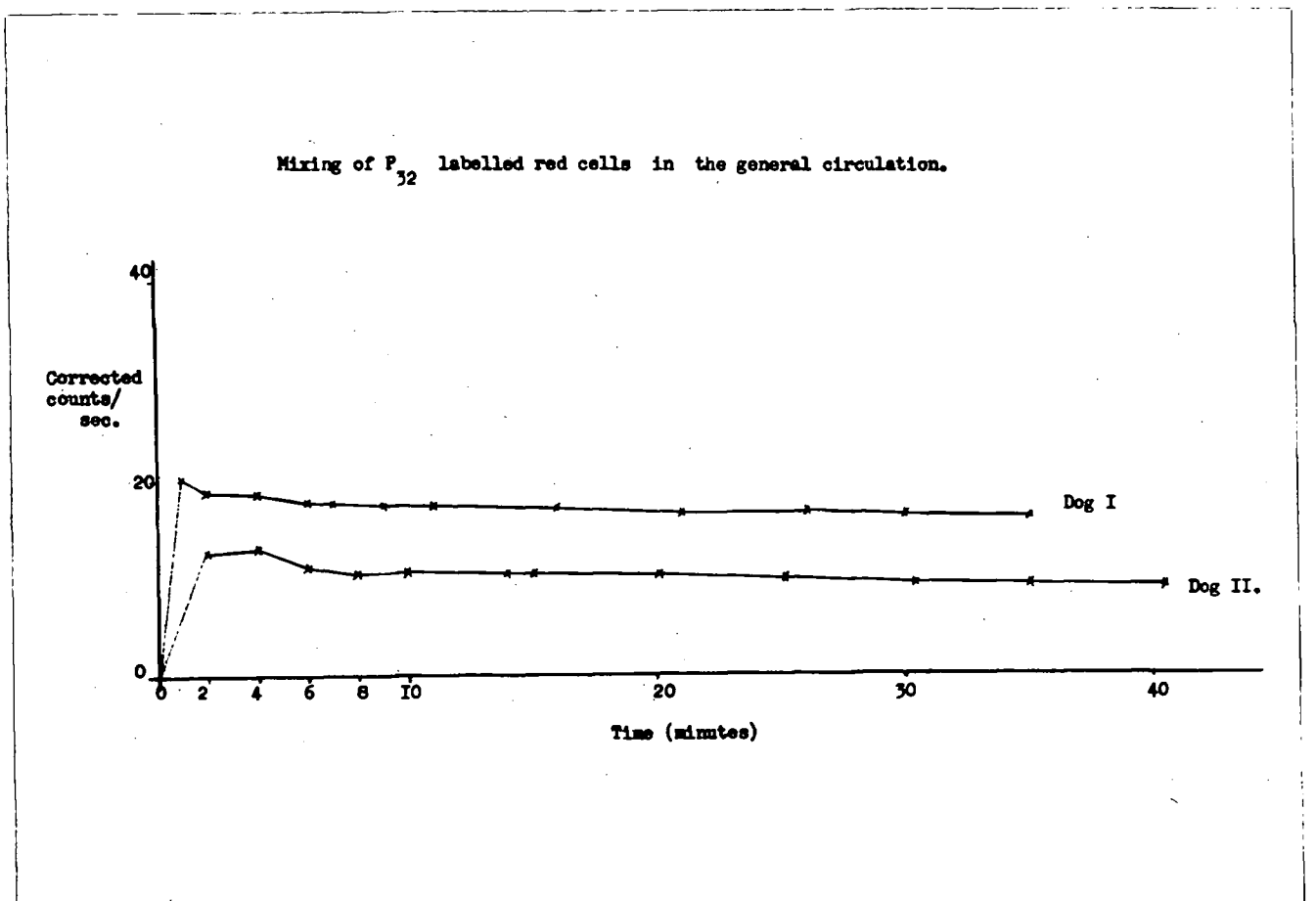
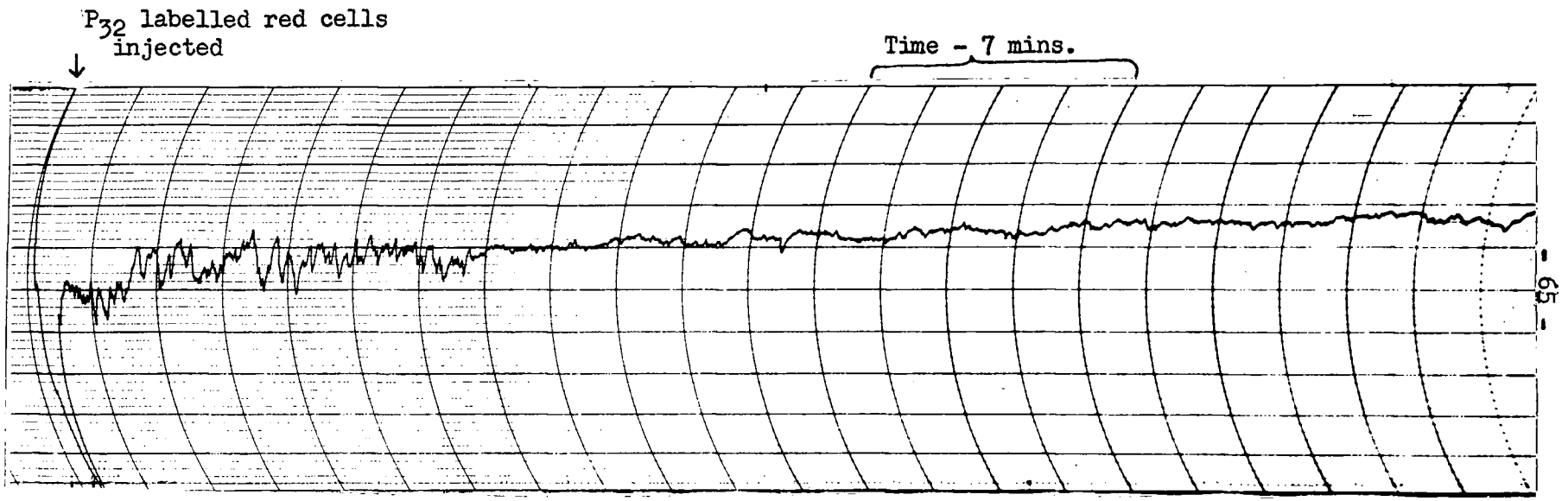


Fig. III

Mixing of P_{32} labelled red cells in the general circulation.
Continuous record of counting rates.



Full scale meter range = 5,000 counts/min.

Fig. IV (a)

Mixing of P_{32} labelled red cells in general circulation 30 mins. after portal vein ligation.

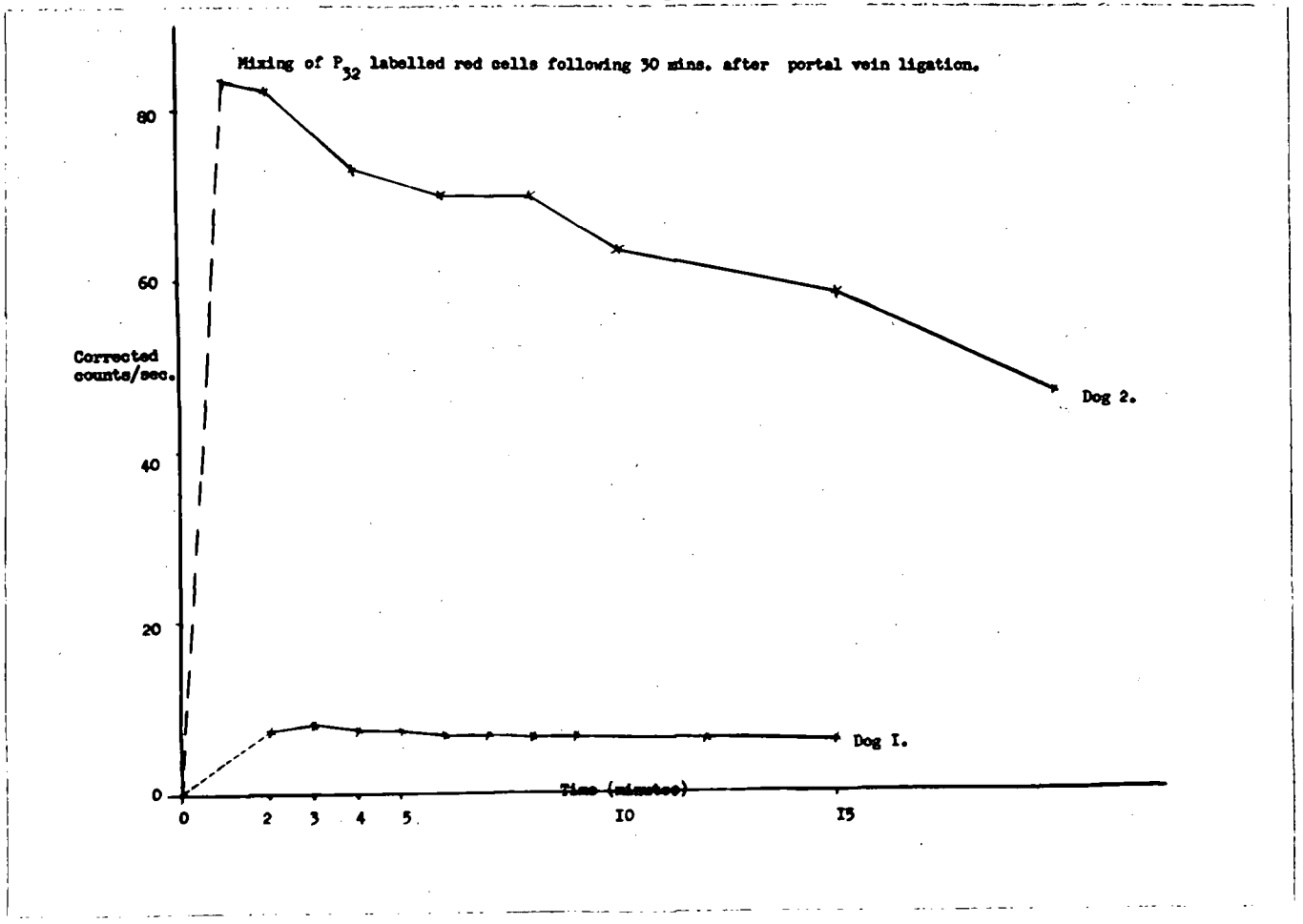


Fig. IV (b)

Mixing of P_{32} labelled red cells in general circulation
30 mins. following ligation of portal vein.
Continuous record of counting rates

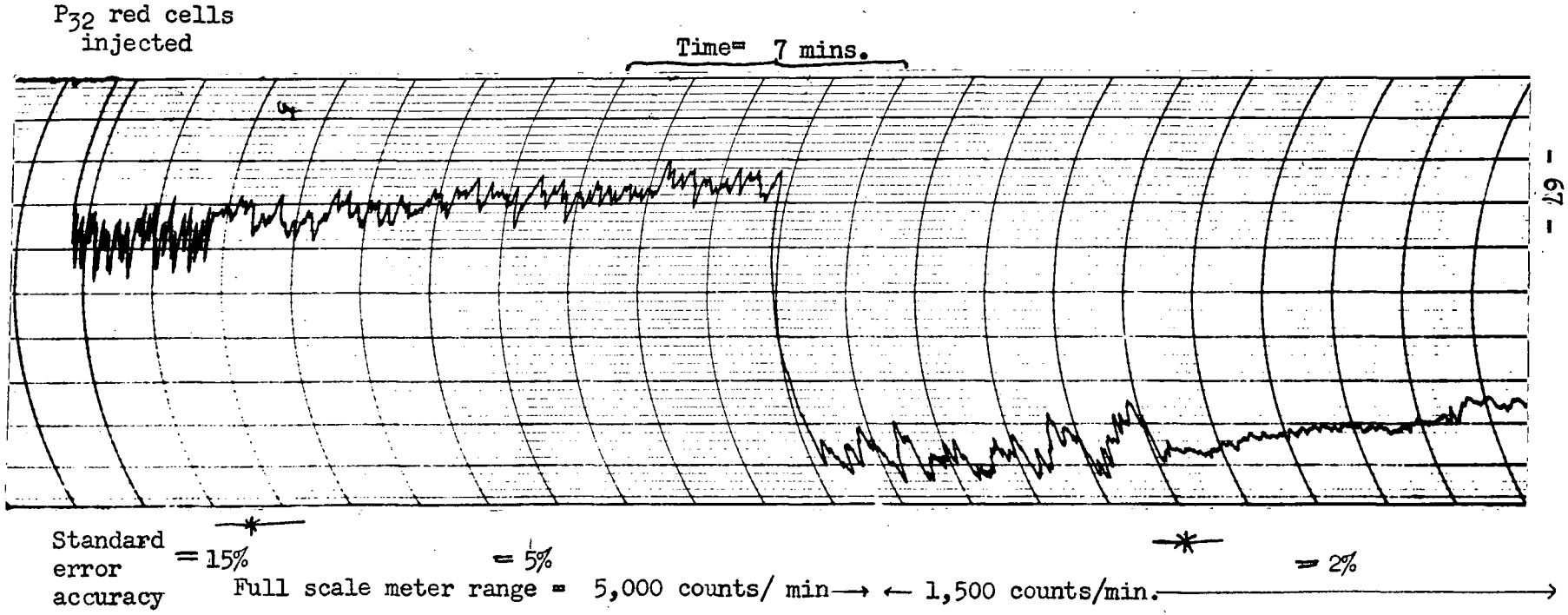
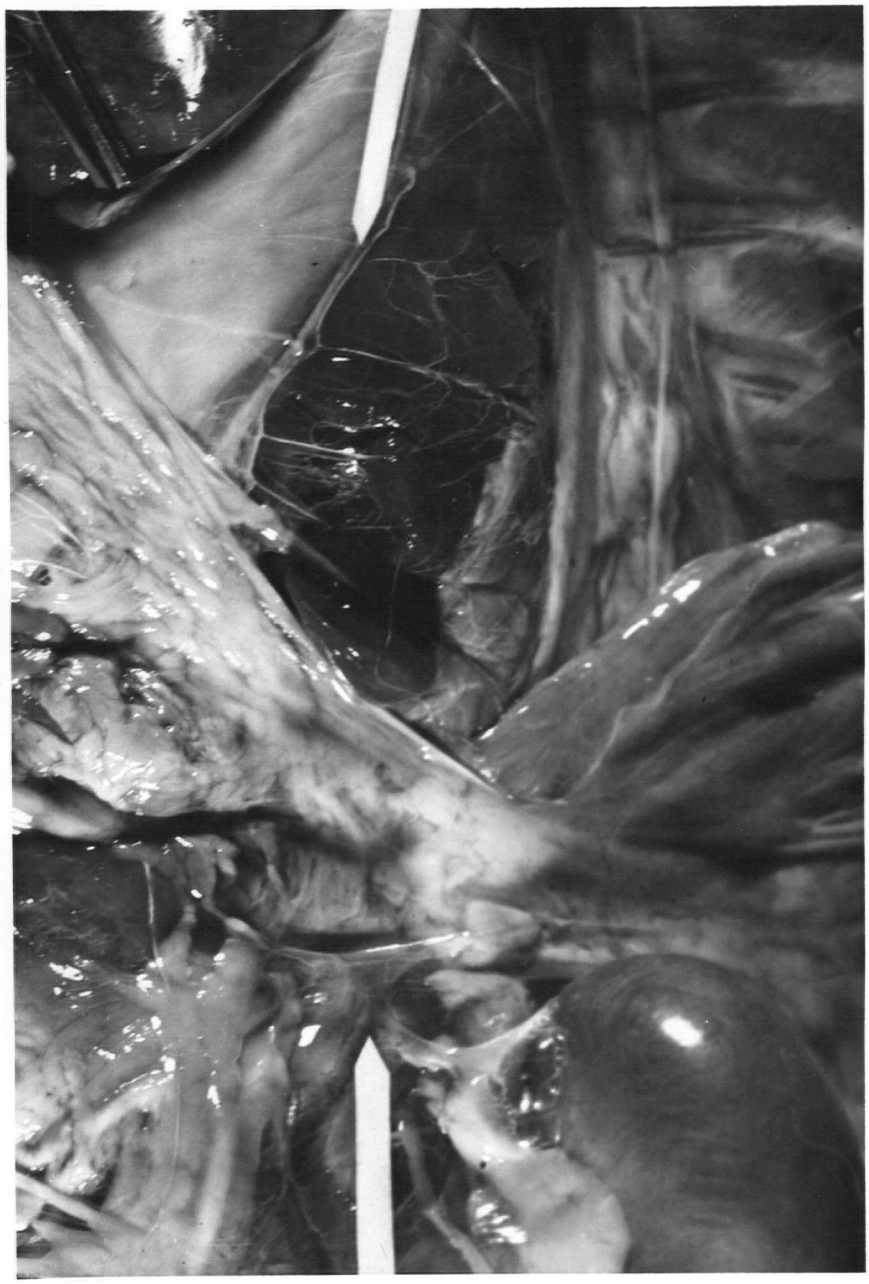


Fig. V (a)

Dog. 2. Portal venous tributaries injected with latex.

Main anastomotic vein accompanying
L. vagus nerve

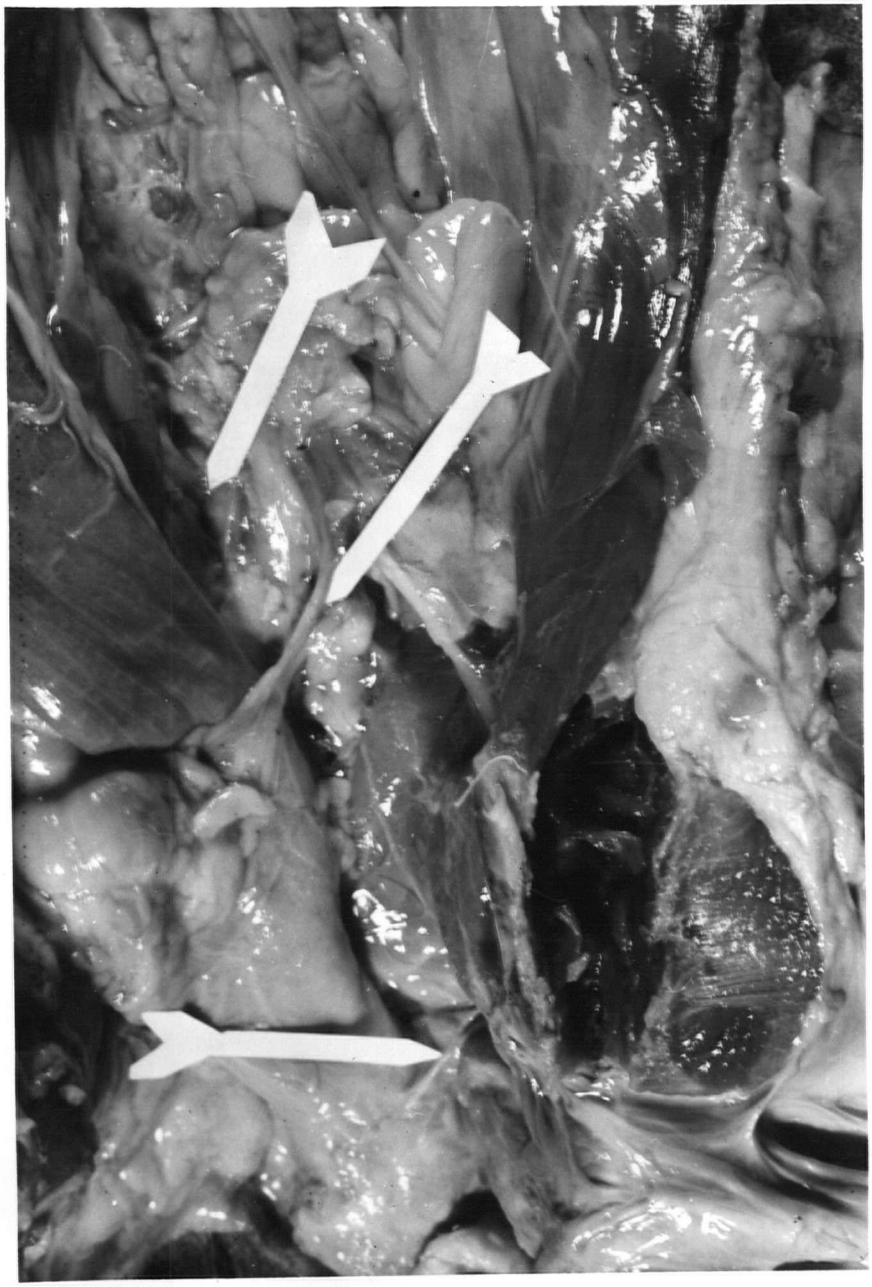


Small venule running in mesentery
of duodenum

Fig. V (b)

Dog 3. Portal venous tributaries injected with latex.

Two small venules running in mesentery of large bowel.



Small venule running from left side of rectum to join systemic vein in side wall of pelvis.

REFERENCES

1. Adams, R.C. Intravenous Anaesthesia. New York, Paul B. Hoeber, Inc. 1944.

2. Adelman, M.H., Megibow, S.J. & Blum, L. A Method of Automatic Controlled Respiration for Anaesthesia in the Dog. Surgery - 28: 1040, December 1950.

3. Andrews, E. & Hrdina, L. The Cause of Death in Liver Autolysis. Surg., Gyn., Obst. - 52: 61, 1931

4. Arst, D.B., Silver, M. & Lahey, W.J. The Use of Vinyl Plastic Tubing in Recording Pressure Phenomenon. Am. Heart J. - 42: 746, 1951.

5. Barcroft, J. & Shore, L.E. Gaseous Metabolism of Liver - in fasting and late digestion. J. Physiology - 45: 296, 1912.

6. Bartlett, F.K., Cooper, H.J. & Long, E.R. The Independence of the Lobes of the Liver. Amer. J. Physiology - 35: 36, 1914.

7. Beer, E. Ligation of the Portal Vein. Am. J. Med. Sc. - 150: 548, 1915.

8. Behrend, M., Radasch, H.E. & Kerschner, A.G. Comparative Results of the Ligation of the Hepatic Artery in Animals, Arch. Surg. - 4: 661, 1922.

9. Benz, E.J., Baggenstoss, A.H. & Wollaeger, E.E. The Pathogenesis of Atrophy of the L. Lobe of the Liver in Man. Gastroenterology - 22: 34, 1952.

10. Berman, J.K. & Hull, J.E. Experimental Ascites, its Production and Control. Surgery - 32: 67, July 1952.

11. Bernard, C. Liquides de L'organisme. Paris, J-B Bailliere et Fils. 2: 465, 1859.

12. Bernard, C. Lecons sur le diabete et la glycogenèse animale. Paris, J-B Bailliere et Fils, page 316, 1877.

13. Blalock, A. & Mason, M.F. Observations on the Blood Flow and Gaseous Metabolism of the Liver of Unanaesthetized Dogs. Am. J. Physiol. - 117: 328, 1936.

14. Blalock, A. & Levy, S. The Effect of Haemorrhage, Intestinal Trauma and Histamine on the Partition of the Blood Stream. Am. J. Physiol. - 118: 734, 1937.

15. Bollman, J.L., Svirbely, J. & Mann, F.C. Blood Concentration Influenced by Ether and Amytal Anaesthesia. Surgery - 4: 881, 1938.

16. Bolognesi, G. Ligature of the Portal Vein in Animals with Circulation of Jacobson: experimental. Arch. italienne de biologie - 46: 51, 1906-07.

17. Bolton, C. The Pathological Changes in the Liver Resulting from Passive Venous Congestion Experimentally Produced. J. Path. & Bact. - 19: 258, 1914.

18. Bolton, C. & Barnard, W.C. The Pathological Occurrences in the Liver in Experimental Venous Stagnation. J. Path. Bact. - 34: 701, 1931.

19. Bonnycastle, D.D. & Cleghorn, R.A. A Study on the Blood Volume on a Group of Untrained Normal Dogs. Am. J. Physiol. - 137: 380, 1942.

20. Boyce, F.F., Lampert, R. & McFetridge, E.M. Occlusion of the Portal Vein. (An Experimental Study with its Clinical Application.) J. Lab. & Clin. Med. - 20: 935, 1935.

21. Boyce, F.F. & McFetridge, E.M. Autolysis of Tissue in Vivo. Arch. Surg. - 34: 977, 1937.

22. Boyce, F.F. The Role of Liver in Surgery. C.C. Thomas, Springfield, Illinois. Chap. 10, 1941.

23. Brewer, G.E. Hydatid Cyst of Liver with Ligature of Portal Vein. Ann. Surg. - 47: 619, 1908.

24. Brewer, G.E. & Gies, W.J. Ligation of Portal Vein for Haemorrhage During Operation on Hydatid Cyst of Liver. J.A.M.A. - 50: 2063, 1908.

25. Brunschwig, A. Surgical Treatment of Carcinoma of Body of Pancreas. Ann. Surg. - 120: 406, 1944.

26. Brunschwig, A., Bigelow, R. & Nichols, S. Effective Occlusion and Excision of the Portal Vein. Surgery - 17: 781, 1945.

27. Burnett, W.E., Rosemond, G.P., Weston, J.K. & Tyson, R.R. Studies of Hepatic Response to Changes in Blood Supply. Surgical Forum, American College of Surgeons, 1951.

28. Burton-Opitz, R. The Vascularity of the Liver - I. The Flow of Blood in the Hepatic Artery. Quart. J. Exper. Physiology - 3: 297, 1910.

29. Burton-Opitz, R. The Vascularity of the Liver - II. The Influence of the Portal Blood Flow Upon the Flow in the Hepatic Artery. Quart. J. Exper. Physiology - 4: 93, 1911.

30. Burton-Opitz, R. The Vascularity of the Liver - III. The Effect of Stimulation of Single Nerves of the Hepatic Plexus Upon the Flow in the Hepatic Artery. Quart. J. Exp. Physiol. - 4: 103, 1911.

31. Burton-Opitz, R. The Vascularity of the Liver - IV. The Magnitude of the Portal Inflow. Quart. J. Exper. Physiol. - 4: 113, 1911.

32. Butler, H. The Veins of the Oesophagus. Thorax - 6: 276, 1951.

33. Cameron, G.R. & Mayes, B.T. Ligation of Hepatic Artery. J. Path. & Bact. - 33: 799, 1930.

34. Cantlie, J. On a New Arrangement of the Right and Left Lobes of the Liver. Proc. Anat. Soc. Gt. Britain & Ireland - 32: 4, 1898.

35. Carr, D.T. & Essex, H.E. The Haemoglobin Concentration of the Blood of Intact and Splenectomized Dogs under Pentobarbital Sodium Anaesthesia with Particular Reference to the Effect of Haemorrhage. Am. J. Physiol. - 142: 40, 1944.

36. Castaigne, J. & Bender, X. Sur les causes de mort apres ligature brusque de la veine porte. Arch. de. Med. Exper. - 11: 751, 1899.

37. Chandler, L.R. Resistance of Hepatic Tissues to Local Anaemia. Proc. Soc. Exper. Biol. & Med. - 18: 23, 1920-21.

38. Charpy, A. Veine Porte in Poirier, P. and Charpy, A. "Traite d' anatomie humaine." 3d. ed. by A. Nicolas, Paris, Masson et eie, Vol. 2, Fasc. 3, Angeiologie. 1920, pages 183-196.

39. Chau, A.Y.S., Goldbloom, V.C. & Gurd, F.N. Clostridial Infection as a Cause of Death after Ligation of Hepatic Artery. A.M.A. Arch. Surg. - 63: 390, 1951.

40. Child, C.G., McClure, R.D. & Hays, D.M. Studies and the Hepatic Circulation on the Macaca Mulatta Monkey and in Man. Surg. Forum, American College of Surgeons, pg. 140, 1951.

41. Child, C.G., Holswade, G.R., McLure, R.D., Gore, A.L. & O'Neill, E.A. Pancreaticoduodenectomy with Resection of the Portal Vein in the Macaca Mulatta Monkey and in Man. Surg., Gyn., Obst. - 94: 31, 1952.

42. Child, C.G., Barr, D., Holswade, G.R. & Harrison, C.S. Liver Regeneration: Preliminary Report. Proc. Soc. Exper. Biol. & Med. - 82: 283, 1953.

43. Child, C.G., Barr. D., Holswade, G.R. & Harrison, C.S. Liver Regeneration Following Portacaval Transposition in Dogs. Ann. Surg. - 138: 600, 1953.

44. Ciba Foundation Symposium on Liver Disease. The Blakiston Co., Philadelphia 1951.

45. Colp, R. The Treatment of Pylephlebitis of Appendicular Origin. Surg., Gyn., Obst. - 43: 627, 1926.

46. Copher, G.H. & Dick, B.M. "Stream Line" Phenomena in the Portal Vein and the Selective Distribution of Portal Blood to the Liver. Arch. Surg. - 17: 408, 1928.

47. Courtice, F.C. The Blood Volume of Normal Animals. J. Physiol. - 102: 290, 1943.

48. Courtice, F.C. & Gunton, R.W. Effect of Nembutal Anaesthesia on Restoration of Plasma Volume After Haemorrhage in Dogs, Cats and Rabbits. J. Physiol. - 108: 418, 1949.

49. Cross, F.S., Raffucci, F.L., Toon, R.W. & Wangensteen, O.H. Effect of Complete Hepatic Vein Ligation on Portal Pressures and Ascites Formation in Dogs with Portacaval Shunts. Proc. Soc. Exper. Biol. & Med. - 82: 505, 1953.

50. Davis, L., Tanturi, C. & Tarkington, J. Reduced Blood Flow to the Liver in Renal Hypertension. Surg., Gyn., Obst. - 89: 360, 1949.

51. Delorme, E.J. Arterial Perfusion of the Liver on Shock; and experimental Study. Lancet - 1: 259, 1951.

52. Delorme, E.J., Macpherson, A.I.S., Mukherjee, S.R. & Rowlands, S. Measurement of Visceral Blood Volume in Dogs. Quart. J. Exp. Physiol. - 36: 219, 1951.

53. Delorme, E.J., Mukherjee, S.R. & Rowlands, S. Studies of the Circulation in Haemorrhagic Shock by Means of Erythrocytes Labelled with Radio Phosphorus. Quart. J. of Exper. Physiol. - 37: 107, 1952.

54. Dick, B.M. "Streamlines" on the Portal Vein - Influence in Selective Distribution of Blood in the Liver. Edinburgh M. J. - 35: 533, Sept. 1928.

55. Douglass, T.C., Mehn, W.H., Lounsbury, B.F., Swigert, L.L. & Tanturi, C.A. Attempts at Experimental Production of Portal Hypertension. A.M.A. Arch. Surg. - 62: 785, 1951.

56. Doyon, & Dufourt. Contribution a l'etude de la fonction ureopoietique du foie. Arch. de physiol. norm et path. - 10: 522, 1898.

57. Dragstedt, L.R. Effect of Diversion of Bile into Vena Cava & Portal Vein in Dogs. Proc. Soc. Exper. Biol. & Med. - 26: 303, January 1929.

58. Dragstedt, L.R. Gradual Obliteration of the Portal Vein as a Substitute for Eck Fistula. Science - 73: 315, 1931.

59. Dreyer, B. & Budtz-Olsen, O.E. Splenic Venography; demonstration of portal circulation with diodone. Lancet - 1: 530, 1952.

60. Dvorak, H.J. Liver Autolysis in the Peritoneal Cavity of the Dog. Proc. Soc. Exper. Biol. & Med. - 29: 431, 1931-32.

61. Eck, N.V. Kvoprosu o perevyazkie vorotnoi veni. Pudvaritelnoye soobshl shinze. Voenno - meditsinskii Zhunual - 130: 2 Sect., 1, 1877.

62. Edwards, E.A. Functional Anatomy of the Portosystemic Communications. Arch. Int. Med. - 88: 137, 1951.

63. Ellis, J.C. & Dragstedt, L.R. Liver Autolysis in Vivo. Arch. Surg. - 20: 8, 1930.

64. Elman, R. & Cole, W.H. Loss of Blood as a Factor in Death from Acute Portal Obstruction. Proc. Soc. Exper. Biol. & Med. - 29: 1122, 1932.

65. Elman, R. & Cole, W.H. Cause of Death in Acute Obstruction of Portal Vein. Tr. Am. Gastro-enterol. A. - 36: 136, 1933.

66. Elman, R. & Cole, W.H. Haemorrhage and Shock as Causes of Death Following Acute Portal Obstruction. Arch. Surg. - 28: 1166, 1934.

67. Engel, F.L., Winton, M.G. & Long, C.N.H. The Metabolism of Amino Acids and Carbohydrate during Haemorrhagic Shock in the Rat. J. Exper. Med. - 77: 397, 1943.

68. Engel, F.L., Harrison, H.C. & Long, C.N.H. The Role of the Liver and the Hepatic Circulation in the Metabolic Changes during Haemorrhagic Shock in Rat and Cat. J. Exp. Med. - 79: 9, 1944.

69. Eze, W.C. Cause of Survival of Dogs without Hepatic Artery. A.M.A. Arch. Surg. - 65: 684, 1952.

70. Fine, J. Recent Advances in Traumatic Shock. Advances in Surgery - 1: 1, 1949.

71. Foreman, R.C. Redistribution of Residual Blood Volume in Haemorrhagic Shock: relation to lethal bleeding volume. Proc. Soc. Exper. Biol. & Med. - 65: 29, 1947.

72. Frank, H.A., Seligman, A.M. & Fine, J. Traumatic Shock - XII The prevention of irreversibility in Haemorrhagic Shock by vivi perfusion of the liver. J. Clin. Invest. - 25: 22, 1946.

73. Frank, H.A., Jacob, S.W., Schweinburg, F.B., Goddard, J. & Fine, J. Traumatic Shock - XXI Effectiveness of an Antibiotic in Experimental Haemorrhagic Shock. Am. J. Physiol. - 168: 430, 1952.

74. Fraser, D., Rappaport, A.M., Vuylsteke, C.A. & Colwell, A.R. Effects of Ligation of the Hepatic Artery in Dogs. Surgery - 30: 624, 1951.

75. Frerichs, F.T. Pathologisch-anatomischer Atlas zur Klinik der Leberkrankheiten. Braunschweig, F. Vieweg u. Sohn, 1851.

76. Gibson, J.G., Seligman, A.M. Peacock, W.C., Aub, J.C. & Fine, J. The Distribution of Red Cells and Plasma in Large and Minute Vessels of the Normal Dog, Determined by Radioactive Isotopes of Iron and Iodine. Clin. Invest. - 25: 848, 1946.

77. Gilding, H.P. Studies of Tissue Maintenance; Service to Liver and Digestive Tract after Haemorrhage. J. Exper. Med. - 50: 213, 1929.

78. Gintrac. Schmorl. Jahrb. - 93: 1857.

79. Glenard, F. Des resultats objectifs de l'exploration du foie chez les diabetiques. Lyon Med. - 44: pages - 5, 80, 115, 189, 259, - 1890.

80. Goldschmidt, S., Ravdin, I.S. & Lucke, B. The Protective Action of Oxygen Against the Necrotizing Effect of Certain Anaesthetics on the Liver. J. Pharmacol. - 59: 1, 1937.

81. Graham, R.R. & Cannell, D. Accidental Ligation of the Hepatic Artery. Brit. J. Surg. - 20: 566, 1932-33.

82. Grant, J.L., Fitts, W.T., Ravdin, I.S. Aneurysm of the Hepatic Artery. Surg., Gyn., Obst. - 91: 527, 1950.

83. Gregersen, M.I. & Rawson, R.A. The Disappearance of T-1824 and Structurably Related Dyes from the Blood Stream. Am. J. Physiol. - 138: 698, 1942-43.

84. Gregersen, M.I., Boyden, A.A. & Allison, J.B. Direct Comparison in Dogs of Plasma Volume Measured with T-1824 and with Antigens. Am. J. Physiol. - 163: 517, 1950.

85. Grindlay, J.H., Herrick, J.F. & Mann, F.C. Measurement of the Blood Flow Through the Liver. Am. J. Physiol. - 132: 489, March 1941.

86. Grindlay, J.H., Mann, F.C. & Bollman, J.L. Effect of Occlusion of the Arterial Blood Supply of the Normal Liver. Arch. Surg. - 62: 806, 1951.

87. Grindlay, J.H. & Bollman, J.L. Regeneration of Liver in Dog after Partial Hepatectomy - Role of Venous Circulation. Surg., Gyn., Obst. - 94: 491, 1952.

88. Haberer. Experimentelle unterbindung der Arteria hepatica. Verhandl. d. deutsch. Gesellsch. f. Chir. - 34: 167, 1905.

89. Hahn, P.F., Ross, J.F., Bole, W.F., Balfour, W.M. & Whipple, G.H. Red Cell and Plasma Volumes (circulating & total) as Determined by Radio Iron and by Dye. J. Exper. Med. - 75: 221, 1942.

90. Hahn, P.F., Bale, W.F. & Bonner, J.F. Removal of Red Cells from the Active Circulation by Sodium Pentobarbital. Am. J. Physiol. - 138: 415, 1942-43.

91. Hahn, P.F., Donald, W.D. & Grier, R.C. Jr. The Physiological Bilaterality of the Portal Circulation Stream Line Flow of Blood into the Liver as Shown by Radio-active Phosphorus. Am. J. Physiol. - 143: 105, 1945.

92. Hallet, E.B., Holton, G.W., Paterson, J.C.S. & Schilling, J.A. Liver Blood Flow, Hepatic Glucose Production and Splanchnic Oxygen Consumption in Normal Dogs and Following Eck Fistula: liver blood flow before and after splenectomy. Surg., Gyn., Obst. - 95:401, 1952.

93. Hardy, E.G., Morris, G.C., Yow, E.M., Haynes, B.W., & DeBakey, M.E. Studies in the Role of Bacteria in Irreversible Haemorrhagic Shock in Dogs. Ann. Surg. - 139: 282, 1954.

94. Hausner, E., Essex, H.E.& Mann, F.C. Roentgenologic Observations of the Spleen of the Dog under Ether, Sodium Amytal, Pentobarbital Sodium and Pentothal Sodium Anaesthesia. Am. J. Physiol. - 121: 387, 1938.

95. Hay, E.B. & Webb, J.K. Effect of Increased Arterial Blood Flow to Liver on Mortality Rate Following Haemorrhagic Shock. Surgery - 29: 826, 1951.

96. Hevesy, G. & Zerahn, K. Determination of Red Corpuscle Content. Acta Physiol. Scand. - 4: 376, 1942.

97. Hoffbauer, F.W., Bollman, J.L. & Grindlay, J.H. Factors Influencing Pressure in the Portal Vein as Measured in the Intact Animal. J. Lab. & Clin. Med. - 32: 1401, 1947.

98. Holmes, R.O. & Lovitt, W.V. Studies of the Portal Venous System by Injection Technique. Gastroenterology - 17: 209 1951.

99. Huggins, C. & Post, J. Experimental Subtotal Ligation of the Arteries Supplying the Liver. Arch.Surg.-35:878, 1937.

100. Huizenga, K.A., Brofman, B.L. & Wiggers, C.J. The Ineffectiveness of Adrenal Cortex Extracts in Standardized Haemorrhagic Shock. J. Pharmacol. & Exper. Therap. - 78: 139, 1943.

101. Ingraham, R.C., Goldberg, H., Roemhild, F. & Wiggers, H.C. Influence of Sodium Pentobarbital upon Course of Events in Experimental Haemorrhagic Shock. Am. J. Physiol. - 162: 243, 1950.

102. Ireneus, C. & Puestow, C.B. Effect of Massive Experimental Haemorrhage in Hepatic Function on Dogs. Arch. Surg. - 49: 100, 1944.

103. Ito, H. & Orni, K. Klinische und experimentelle Beiträge zur chirurgischen Behandlung des Ascites. Deutsche Ztschr. F. Chir. - 62: 141, 1901-02.

104. Jackson, H.C. The Effect of Conditions Upon the Latent Period and Rate of Aseptic Post Mortem Autolysis During the First Ten Hours. J. Exper. Med. - 11; 55, 1909.

105. Jaques, L.B., Fidlar, Feldsted, E.T. & Macdonald, A.G. Silicones and Blood Coagulation. Can. Med. Assoc. J. - 55: 26, 1946.

106. Jarcho, L.W. The Effect of Nembutal and Ether Anaesthesia Upon Blood Concentration. Am. J. Physiol. - 138: 458, 1942.

107. Jefferson, N.C., Proffitt, M.M. & Necheles, H. Collateral Circulation to the Liver of the Dog. Surgery - 31: 724, 1952.

108. Johnson, G.S. & Blalock, A. Experimental Shock. IX - A Study of the Effects of the Loss of Whole Blood, or Blood Plasma and of Red Blood Cells. Arch. Surg. - 22: 626, 1931.

109. Katz, L.N. & Rodbard, S. The Integration of the Vasomotor Responses in the Liver with Those in Other Systemic Vessels. J. Pharmacol. & Exper. Therapeutics - 67: 407, 1939.

110. Kirshner, D., Hooton, T.C. & Shearer, E.M. Production of Experimental Portal Hypertension in Dog. Anatomy of Hepatic Veins in Dogs. Arch. Surg. - 53: 425, 1945.

111. Krieger, H., Storaasli, J.P., Friedell, H.L. & Holden, W.D. A comparative Study of Blood Volume in Dogs. Proc. Soc. Exper. Biol. Med. - 68: 511, 1948.

112. Kunkel, H.G. & Eisenmenger, W.J. Increased Portal Pressure and Ascites in Rats Following Ligation of Portal Vein. Proc. Soc. Exper. Biol. & Med. - 71: 212, 1949.

113. Kuntz, A. & Haselwood, L.A. Cutaneo-visceral Vasomotor Reflexes in the Cat. Proc. Soc. Exper. Biol. Med. - 43: 517, 1940.

114. Laufman, H., Craig, R.L. & Furr, W.E. Jr. Reciprocal Hydrostatic Relationship Between Portal and Caval Systems: its application to problem of ascites. Surgical Forum, Clinical Congress of Am. Coll. Surg., W.B. Saunders - pg. 158, 1951.

115. Laufman, H., Furr, W.E., Ross, A., Craig, R.L. & Bernhard, V. Partial Occlusion of the Portal Vein in Experimental Ascites. A.M.A. Arch. Surgery - 65: 886, 1952.

116. Lautenbach, B.F. On a New Function of the Liver. Medical Times & Register - 7: 387, 1876-77.

117. Lawson, H. The Measurement of Bleeding Volume in the Dog for Studies on Blood Substitutes. Am. J. Physiol. - 140: 420, 1943.

118. Lewis, F.J. & Wangensteen, O.H. Penicillin in Treatment of Peritonitis Due to Liver Autolysis in Dogs. Proc. Soc. Exper. Biol. & Med. - 73: 533, 1950.

119. Loeffler, L. Factors Determining Necrosis or Survival of Liver Tissue after Ligation of Hepatic Artery. Arch. Path. - 21: 496, 1936.

120. Lund, H., Stewart, H.L. & Lieber, M.M. Hepatic Infarction. Amer. J. Path. - 11: 157, 1935.

121. McIndoe, A.H. & Counsellor, V.S. The Bilaterality of the Liver. Arch. Surg. - 15: 589, 1927.

122. McIndoe, A.H. Vascular Lesions of Portal Cirrhosis. Arch. Path. - 5: 23, 1928.

123. McIver, M.A. & Winter, E.A. Deleterious Effects of Anoxia on the Liver of the Hyperthyroid Animal. Arch. Surg. - 46: 171, 1943.

124. McLain, P.L., Ruhe, C.H.W. & Kruse, T.K. Concurrent Estimates of Blood Volume in Animals by Bleeding and Dye Methods. Am. J. Physiol. - 164: 611, 1951.

125. McMichael, J. The Portal Circulation - 1. The Action of Adrenaline and Pituitary Pressor Extract. J. Physiol. - 75: 241, 1932.

126. McMichael, J. The Portal Circulation - 2. The Action of Acetylcholine. J. Physiol. - 77: 399, 1933.

127. McMichael, J. & Smirk, F.H. Effect of Experimental Portal Congestion on Absorption and Excretion of Water. J. Path. & Bact. - 37: 81, 1933.

128. McMichael, J. The Oxygen Supply of the Liver. Quart. J. Exper. Physiology - 27: 73, 1937.

129. Mall, F.P. The Contraction of the Vena Portae and its Influence Upon the Circulation. Johns Hopkins Hosp. Rep. - 1: 111, 1896.

130. Mallet-guy, P., Devic, G. & Gangolphe, M. Sudden Experimental Interruption of Portal Vein. Lyon Chirurgical - 45: 929, 1950.

131. Mann, F.C. & Magaths, T.B. The Production of Chronic Liver Insufficiency. Am. J. Physiol. - 59: 485, 1922.

132. Mann, F.C. Personal Communications to Mason, 1925, and to Markowitz, 1949.

133. Mann, F.C., Fishback, F.C., Gay, J.G. & Green, G.F. Experimental Pathology of the Liver - III, IV & V. Arch. Path. - 12: 787, 1931.

134. Mann, F.C. The Portal Circulation and Restoration of the Liver after Partial Removal. Surgery - 8: 225, 1940.

135. Mann, F.C. The Circulation of the Liver. Quart. Bull. Indiana Univ. Med. Centre - 4: 43, 1942.

136. Mann, F.C. The Gastro-intestinal Tract and Liver. J.A.M.A. - 121: 720, 1943.

137. Markowitz, C. and Mann, F.C. Studies on Physiology of Liver; Role of Liver in Formation of Lymph. Am. J. Physiol. - 96: 709, 1931.

138. Markowitz, J. Experimental Surgery. Williams & Wilkins Co., Baltimore, 1949.

139. Markowitz, J., Rappaport, A. & Scott, A.C. Prevention of Liver Necrosis Following Ligation of Hepatic Artery. Proc. Soc. Exper. Biol. & Med. - 70: 305, 1949.

140. Markowitz, J. & Rappaport, A. The Hepatic Artery. Physiol. Rev. - 31: 188, 1951.

141. Martin, G.H., Bunting, C.H. & Loevenhart, A.S. The Morphological Changes in the Tissues of the Rabbit as a Result of Reduced Oxidations. J. Pharmacol. - 8: 112, 1916.

142. Mason, E.C. & Davidson, E.C. Tissue Autolysis in Vivo - I. Blood Changes, Physical and Chemical. J. Lab. & Clin. Med.- 10: 622, 1924-25.

143. Mason, E.C. & Davidson, E.C. II. Pharmacological Study of Toxic Material. J. Lab. & Clin. Med. - 10: 906, 1924-25.

144. Mason, E.C. & Davidson, E.C. III. Observations Using the Spleen. J. Lab. & Clin. Med. - 10: 997, 1924-25.

145. Mason, E.C. & Hart, M.S. The Welch-like Bacillus in the Human Liver. J. Lab. & Clin. Med. - 25: 835, 1940.

146. Michels, N.A. Collateral Arterial Pathways to the Liver after Ligation of the Hepatic Artery and Removal of Coeliac Axis. Cancer - 6: 708, 1953.

147. Milnes, R.F. & Child, C.G. Acute Occlusion by Ligation of the Portal Vein in Macacus Rhesus Monkey. Proc. Soc. Exper. Biol. & Med. - 70: 332, 1949.

148. Milnes, R.F. Hepatic Artery Ligation in Rabbits Followed by Thoracic Caval Constriction. Proc. Soc. Exp. Biol. & Med. - 77: 653, 1951.

149. Milnes, R.F. An Evaluation of Hepatic & Splenic Artery Ligation in Dogs with Experimental Ascites. Surgery - 32: 704, 1952.

150. Morris, A.N. & Miller, H.H. Chronic Portal Vein Occlusion & Portal Hypertension in the Dog. Surgery - 30: 768, 1951.

151. Mosselman & Liénaux. Sur la cause de la mort après la ligature de la veine porte. Ann de Méd. vétérinaire - 34: 467, 1885.

152. Myers, J.D. & Hickham, J.B. Estimation of Hepatic Blood Flow and O_2 Consumption in Heart Failure. J. Clin. Invest. - 27: 620, Sept. 1948.

153. Myers, J.D. & Taylor, W.J. The Estimation of Portal Venous Pressures by Occlusive Catheterization of an Hepatic Venule. J. Clin. Invest. - 30: 662, 1951.

154. Naegeli, T. & Derra, E. Effect of Ligation of Portal & Splenic Veins on Blood Gases & Blood Volume. Schweiz. Med. Wchnschr.- 65: 86, 1935.

155. Nelson, R.M. Metabolic Effects of Paracolon Bacteremia. Ann. Surg.- 134: 885, 1951.

156. Nelson, R.M. & Noyes, H.E. Blood Culture Studies in Normal Dogs and in Dogs with Haemorrhagic Shock. Surgery - 35: 782, 1954.

157. Netter. Arch. Gén. de Méd. - 1884.

158. Neuhof, H. Experimental Ligation of the Portal Vein: its application to the treatment of suppurative pylephlebitis. Surg., Gyn., Obst. - 16: 481, 1913.

159. Nylin, G. & Mahn, M. Concentration of Red Blood Corpuscles Containing Labelled Phosphorus Compounds in the Arterial Blood after the Intravenous Injection. Am. J. Med. Sc. - 207: 743, 1944.

160. Nylin, G. Circulatory Blood Volume of Some Organs. Am. Heart J. - 34: 174, 1947.

161. Oré. Influence de l'obliteration de la veine porte sur la secretion de la bile et sur la fonction glycogenique du foie. Compte rendu Acad. Royal d. Sc. - 43: 463, 1856.

162. Paton, A., Reynolds, T.B. & Sherlock, S. Assessment of Portal Venous Hypertension by Catheterization of Hepatic Vein. Lancet - 264: 918, 1953.

163. Peck, M.E. & Grover, R.F. Cardiovascular Responses to Acute Ligation of Portal Vein. A.M.A. Arch. Surg. - 64: 665, 1952.

164. Pick, L. Ueber totale hämangiomatose Obliteration des Pfortaderstammes und über hepatopetale Kollateralbahnen. Virchow's Arch. f. path. Anat. Berl. - 197: 490, 1909.

165. Popper, H.L., Jefferson, N.C. & Necheles, H. Interruption of All Arterial Blood Supply to Liver not Compatible with Life. Am. J. Surgery - 84: 429, 1952.

166. Popper, H.L., Jefferson, N.C. & Necheles, H. Liver Necrosis Following Complete Interruption of Hepatic Artery and Partial Ligation of Portal Vein. Am. J. Surgery - 86: 309, 1953.

167. Raffuci, F.L. & Wangensteen, O.H. Tolerance of Dogs to Occlusion of Entire Afferent Vascular Inflow to Liver. "Surgical Forum" American College of Surgeons. W.B. Saunders Co., Philadelphia, 1951. Pages 1-5, 1951.

168. Raffuci, F.L. The Effects of Temporary Occlusion of the Afferent Hepatic Circulation in Dogs. Surgery - 33: 342, 1953.

169. Rappaport, A.M. Experimental Ischaemia of Liver and Hepatic Coma. "Liver Injury" Conference Josiah Macy Jr. Found - page 146, 1951.

170. Rappaport, A.M., Clarke, D.W. & Stewart, M. Effect of Liver Ischaemia on Plasma in Dogs, as Measured by Electrophoresic Analysis. Proc. Soc. Exper. Biol. & Med. - 80: 585, 1952.

171. Reeve, E.B. & Veall, N. A Simplified Method for the Determination of Circulating Red Cell Volume with Radioactive Phosphorus. J. Physiol. - 108: 12, 1949.

172. Roberts, G.M. & Crandall, L.A. Jr. Role of Portal System in Regulation of Circulating Blood Volume. Am. J. Physiol. - 106: 423, 1933.

173. Roberts, L.N., Smiley, J.R., Sears, G.A. & Manning, G.W. Plasma Volume Measured by Iodinated Albumin and T.1824. Canad. M.A.J. - 69: 510, 1953.

174. Rolleston, H. & McNee, J.W. Diseases of the Liver, Gall Bladder and Bile Ducts. 3rd Ed. London, MacMillan & Co. Ltd. Page 22, 1929.

175. Romieu, C. & Brunschwig, A. A Bacteriologic Study of the Human Liver. Surgery - 30: 621, 1951.

176. Roome, N.W., Keith, W.S. & Phemister, D.B. Experimental Shock, The Effect of Bleeding After Reduction of Blood Pressure By Various Methods. Surg., Gyn., Obst. - 56: 161, 1933.

177. Rous, P. & Larrimore, L.D. Relation of Portal Blood to Liver Maintenance. J. Exper. Med. - 31: 609, 1920.

178. Rous, P., Gilding, H.P. & Smith, M.B. The Gradient of Vascular Permeability. J. Exp. Med. - 51: 807, 1930.

179. Salzberg, A.M. & Evans, E.I. Blood Volumes in Normal and Burned Dogs. Ann. Surg. - 132: 746, 1950.

180. Sancetta, S.M. Dynamic & Neurogenic Factors Determining the Hepatic Arterial Flow after Portal Occlusion. Circ. Res. - 1: 414, 1953.

181. Sappey, C. Memoire sur les veines portes accessoires. J. Anat. et Physiol. - 19: 517, 1883.

182. Sborov, V.M., Morse, W.C., Giges, B. & Jahnke, E.J. Bacteriology of the Human Liver. J. Clin. Invest. - 31: 986, 1952.

183. Schafer, P.W. & Kozy, J.S. Radical Pancreatoduodenectomy with Resection of Patent Portal Vein: experimental study. Surgery - 22: 959, 1947.

184. Schiff, M. Centralbl. f. d. Med. Wissensch. - 8: 115, 1863.

185. Schilling, H., McKee, F.W. & Wilk, W. Experimental Hepatic Portal Arterio venous Anastomosis. Surg., Gyn., Obst. - 90: 473, 1950.

186. Schmiedel, G.C. De varietations vasorum magni pleurumque momenti, 1744.

187. Schocken, K. The Physical Principles of Blood Circulation. Exp. Med. Surg. - 2: 73, 1953.

188. Schwiegk, H. Untersuchungen über die Leberdurchblutung und den Pfortaderkreislauf. Arch. F. exper. Path. u. Pharmakol. - 168: 693, 1932.

189. Seavers, R. & Price, P.B. Effects and Fate of Blood Transfusions in Normal Dogs. Arch. Surg. - 59: 275, 1949.

190. Segall, H.N. Experimental Anatomical Investigation of Blood and Bile Channels of the Liver; compensatory arterial circulation of the liver in its relation to surgical ligation of hepatic artery; report of a case of arteriosclerotic aneurysm of gastroduodenal artery. Surg., Gyn., Obst. - 37: 152, 1923.

191. Selkurt, E.E., Alexander, R.S. & Patterson, M.B. The Role of the Mesenteric Circulation in the Irreversibility of Haemorrhagic Shock. Am. J. Physiol. - 149: 732, 1947.

192. Seneviratne, R.D. Physiological and Pathological Responses in the Blood Vessels of the Liver. Quart. J. Exper. Physiol.- 35: 77, 1950.

193. Serege. Contribution a l'etude de la circulation du faug porte dans le foie at des localisations lobaires hépatiques. J. de Méd. de Bordeaux - 31: 371, 291, 312, 1901.

194. Shorr, E., Zweifach, B.W., Furchgott, R.F. & Baez, S. Hepato-renal Factors in Circulatory Homeostasis. Circulation - 3: 42, 1951.

195. Simonds, J.P. & Arey, L.B. The Relation of the Smooth Muscle in the Hepatic Veins to Shock Phenomena. Anat. Rec. - 18: 219, 1920.

196. Simonds, J.P. & Brandes, W.W. The Effect of Obstruction of the Hepatic Veins in the Systemic Circulation. Am. J. Physiol. - 72: 320, 1925.

197. Simonds, J.P. & Brandes, W.W. I Anaphylactic Shock and Mechanical Obstruction of the Hepatic Veins in the Dog. II The Effect of Mechanical Obstruction of the Hepatic Veins upon the Outflow of Lymph from the Thoracic Duct. J. Immunol. - 13: 1, 1927.

198. Simonds, J.P. & Brandes, W.W. The Effect of Peptone Upon the Hepatic Veins in the Dog. J. Pharm. & Exper. Therap. - 35: 165, 1929.

199. Simonds, J.P. & Calloway, J.W. Anatomical Changes in the Livers of Dogs Following Mechanical Constriction of the Hepatic Veins. Amer. J. Path. - 8: 159, 1932.

200. Simonds, J.P. & Jergesen, F.H. Late Changes in the Liver Induced By Mechanical Obstruction of the Hepatic Veins. Arch. Path. - 20: 571, 1935.

201. Smith, H.P., Arnold, H.R. & Whipple, G.H. Blood Volume Studies: VII Comparative Values of Welcker Carbon Monoxide Determinations; accurate estimation of absolute blood volume. Am. J. Physiol. - 56: 336, 1921.

202. Smythe, C.M., Fitzpatrick, H.F. & Blakemore, A.H. Studies of Portal Venous Oxygen Content in Unaesthetized Man. J. Clin. Invest. - 30: 674, 1951.

203. Solowieff. Arch. Path. Anat. - 62: 195, 1875.

204. Stopford, J.S.B. The Portal Systemic Anastomoses. Medical Chronicle - 61: 12, 1915.

205. Tanturi, C., Swigart, L.L. & Canepa, J.F. Prevention of Death from Experimental Ligation of the Liver (hepatic proper) Branches of the Hepatic Artery. Surg., Gyn., Obst. - 91: 680, 1950.

206. Tappeiner, H. Ueber den Zustand des Blutstromes nach Unterbindung der Pfortader. Arbeit. a. d. physiol. Anst. z. Leipzig. 1873.

207. Thomas, W.D., & Essex, H.E. Observations on the Hepatic Venous Circulation with Special Reference to the Sphincteric Mechanism. Am. J. Physiol. - 158: 303, 1949.

208. Tonolli, G. Oberti. Experimental Sudden and Total Ligation of Portal Vein in Relation to Genesis of Ascites. Boll. Soc. Ital, biol. sper. - 23: 1233, 1947.

209. Trusler, H.M. & Reeves, J.R. Significance of Anaerobic Organisms in Peritonitis due to Liver Autolysis. Arch. Surg. - 28: 479, 1934.

210. Trusler, H.M. & Reeves, J.R. & Martin, H.E. Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis. Arch. Surg. - 30: 371, 1935.

211. Trusler, H.M. & Martin, H.E. The Cause of Death in Liver Peritonitis. Surgery - 1: 243, 1937.

212. Tschernikoff, A.M., Malenjuk, W.W., Jakubovitsch, M.E. & Klantaroff, M. Ch. Arch. f. d. Physiol. - 227: 85, 1931.

213. Volwiler, W., Grindlay, J.H. & Bollman, J.L. The Relation of Portal Vein Pressure to the Formation of Ascites - an experimental study. Gastroenterology - 14: 40, 1950.

214. Wakim, K.G. & Mann, F.C. The Intrahepatic Circulation of Blood. Anat. Rec. - 82: 233, February 1942.

215. Wakim, K.G. Effects of Adrenalin and Nembutal Anaesthesia on Blood Constituants Before and After Splenectomy. J. Lab. & Clin. Med. - 31: 18, 1946.

216. Wang, C.I. & Walcott, W.W. Effects of Anaesthesia on Bleeding Volume in the Dog. Am. J. Physiol. - 170: 143, 1952.

217. Wermuth, E.G. Anastomoses Between Rectal and Uterine Veins Forming a Connexion Between the Somatic and Portal Venous System in the Recto-uterine Pouch. J. Anat. - 74: 116, 1939-40.

218. Wiggers, C.J. Present Status of the Shock Problem. Physiological Reviews - 22: 74, 1942.

219. Wiggers, C.J., Opdyke, D.F. & Johnson, J.R. Portal Pressure Gradients Under Experimental Conditions, Including Haemorrhagic Shock. Am. J. Physiol. - 146: 192, 1946.

220. Wiles, C.E., Schenk, W.G. & Lindenberg, J. Influence of Hepatic Artery Ligation on Regeneration of Liver Tissue in the Rat. A.M.A. Arch. Surg. - 64: 783, 1952.

221. Winternitz, M.C. The Effect of Occlusion of the Various Hepatic Vessels Upon the Liver. Bull. Johns Hopkins Hosp. - 22: 396, 1911.

222. Wolbach, S.B. & Saiki, T. A New Anaerobic Sporebearing Bacterium Commonly Present in Liver of Health Dogs. J. Med. Res. - 21: 267, 1909.

223. Wu, P.P.T. The Maximal Volume of the Human Spleen. Surg., Gyn., Obst. - 77: 74, 1943.

224. Zanetti, M.E. Significance of Elevated Portal Vein Pressure in Etiology of Haemorrhagic Shock. Am. J. Physiol. - 171: 538, 1953.

225. Zimmerman, H.M. Infarcts of the Liver and the Mechanism of Their Production. Arch. Path. - 10: 66, 1930.

226. Zweifach, B.W., Hershey, S.G., Rovenstine, E.A., Lee, R.E. & Chambers, R. Anaesthetic Agent a Factor in Circulating Reaction Induced by Haemorrhage. Surg. - 18: 48, 1945.