RECENT ADVANCES IN THE TREATMENT OF OBSTRUCTIVE JAUNDICE

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In addition to the hazards incident to all surgery of the upper abdomen, operations on the biliary tract, performed in the presence of obstructive jaundice, are associated with special risks arising as the result of the biliary obstruction. The danger of secondary hemorrhage, of liver failure, and of the development of cholangeitis is always present in these operations. In the past year, however, certain advances in the prophylaxis and treatment of these complications have been made and we have good reason to believe that a striking reduction in the postoperative mortality rate of jaundiced patients will soon be observed.

The liver is invariably damaged by long-standing obstruction of the biliary tract. A marked hemorrhagic tendency is often present in patients with this condition and they are in poor condition to withstand a major surgical procedure. It is therefore not surprising to find the surgical mortality higher in patients with obstructive jaundice than in unjaundiced patients subjected to similar surgical procedures.

Hemorrhage is the greatest single cause of death, one-third of all postoperative deaths being attributable to this cause. Other causes of death in the order of their frequency are pneumonia, liver failure, cardiac failure, and a varied assortment of incidental complications (Table 1).

TABLE 1

ANALYSIS OF CAUSES OF DEATH

Cause of Death	*Per Cent*
Hemorrhage	34
Pneumonia	20
Liver failure	14
Heart failure	8
Extensive metastases	6
Peritonitis	3
Duodenal fistula	3
Pyloric obstruction	3
Stricture of common duct	3
Uremia	3
Unknown cause	3
	100

Secondary hemorrhage has been the most common complication following operations on patients with obstructive jaundice. In our experience hemorrhage has occurred most frequently on the first day, nine of the patients in this series of 100 cases having bled in the first 24 hours after operation. Three patients bled on the third day, and one each on the fourth, fifth, sixth, eighth, tenth, eleventh, twelfth, and nineteenth days.

Another troublesome complication following operations for obstructive jaundice has been the development of cholangeitis. This occurred to some extent in 29 per cent of the operations in which anastomoses between the biliary and gastro-intestinal tracts were performed. There were, however, no postoperative hospital deaths attributable to cholangeitis.

Liver failure has been a rare but more serious complication following operations on the biliary tract in jaundiced patients. This complication occurred in 6 per cent of all the cases. Liver failure was observed most frequently following operations for carcinoma of the pancreas and when it occurred it usually was fatal.

The Bleeding Tendency in Jaundice

Until recently, the fear of postoperative hemorrhage has handicapped the surgeon in his attempts to relieve patients with obstructive jaundice. However, recent developments in the diagnosis and treatment of this hemorrhagic tendency will unquestionably result in a marked diminution in hemorrhage as a postoperative complication and will open the field for a more radical surgical attack not only on stones in the common bile duct but also on neoplasms of the bile ducts, the ampulla of Vater, and the head of the pancreas.

A review of the physiology of the clotting of blood shows that prothrombin, thromboplastin, and calcium unite to form thrombin. This in turn unites with fibrinogen so that fibrin is formed.

$$\left.\begin{array}{l}\text{Prothrombin}\\ \text{Thromboplastin}\\ \text{Calcium}\end{array}\right\rangle \quad \text{Thrombin} + \text{Fibrinogen} = \text{Fibrin}$$

It has been well established that the cause of the hemorrhagic tendency in jaundice is a deficiency in prothrombin. A prothrombin deficiency likewise occurs in animals having complete external biliary fistulae. Thus the tendency to bleed is the result of a failure of the gastro-intesinal tract, in the absence of bile, to absorb certain extraneous substances[1]. The older belief that the bleeding was the result of excessive amounts of bile in the blood stream must therefore be discarded.

Hitherto, this bleeding tendency has been difficult to determine before operation. Ordinary tests of the bleeding and clotting time have been unsatisfactory. The bleeding time by the Lee-White method often indicates that a hemorrhagic tendency will occur but this test has not been very satisfactory. By the Lee-White method, venous blood is used, the blood is placed in tubes, and the time of clotting is recorded. Any time over eight minutes is considered to be abnormal. The Lee-White coagulation time is prolonged in only about one-third of the cases in which a hemorrhagic tendency exists.

Ivy[2] has recently reported a technic for bleeding time which is alleged to be of value in the study of the hemorrhagic tendency in jaundice. By this method a tourniquet is applied to the arm in order to overcome capillary resistance. The bleeding time is then measured in the usual way. It is quite true that the bleeding time by this method is almost always prolonged in deep jaundice but the bleeding time tends to be prolonged in proportion to the severity of the jaundice rather than in relation to the tendency of the patient to bleed. This test, therefore, gives very little more information than does the icteric index.

Quick's[3] method for the determination of the prothrombin clotting time has been proved to be a valuable aid in the diagnosis of a hemorrhagic tendency. In this test all the factors which are necessary for the coagulation of the blood are added in excess and a specimen of blood plasma is then added and the time for clotting is recorded. Specifically, the blood is oxalated and the plasma obtained. The plasma is then mixed with an emulsion of dried rabbit brain to supply an excess of thromboplastin. Calcium chloride is added to this mixture. The number of seconds that it takes at a temperature of 37.5° C. for a clot to form is recorded as the prothrombin time. Normal values are about 20 seconds and bleeding tendencies in the presence of jaundice are not apparent when the prothrombin clotting time is less than 40 seconds. More accurate information as to the presence of a latent hemorrhagic tendency in patients who have a prothrombin clotting time of less than 40 seconds can be obtained by diluting the serum by half and then determining if there will be a further prolongation of the prothrombin clotting time.

A bleeding tendency does not occur until the prothrombin level reaches approximately 20 per cent of normal. It is thus apparent why a jaundiced patient who has an apparently normal prothrombin clotting time will suddenly begin to bleed after an operation. If the amount of prothrombin in the blood was above the critical level before operation, dilution of the prothrombin as a result of blood loss at the time of operation may result in a diminution of the prothrombin below the critical level and in the appearance of a hemorrhagic tendency.

Naffziger and Carr[1] have conducted some interesting investigations on the influence of high protein diets in jaundice. They find that in the presence of jaundice a high protein diet results in an elevation of the sulfur content of the blood to nearly double its normal level. They have also noticed that when jaundiced dogs are fed on a meat diet, hemorrhage and death occurs promptly, but if a similar group of dogs is fed on a high carbohydrate diet, life is prolonged approximately three times.

Walters[5] and others have suggested that bleeding tendencies can be diminished by the administration of calcium chloride or calcium gluconate intravenously. Although calcium in vitro seems to diminish the clotting time of the blood in jaundiced patients, clinically the administration of calcium has not proved to be of much value except to alleviate the troublesome pruritus.

The most promising treatment of the hemorrhagic tendency in jaundice is that recently reported by Butt, Snell, and Osterberg[6] of the Mayo Clinic. This group became interested in the reports of Dam and his coworkers[7] on the hemorrhagic tendency which developed in chicks fed on a diet deficient in certain fat soluble compounds but adequate in respect to vitamins A, B_1, B_2, C, and D and in total fat and cholesterol. Dam was able to demonstrate that the hemorrhagic tendency was promptly corrected by the administration of a substance found in the unsaponifiable non-sterol fraction of hogs' liver fat and in alfalfa. This substance he designated as vitamin K.

Heymann and his coworkers[8] have shown that fats and sterols are not absorbed from the intestines of a dog in the presence of an external biliary fistula and Heymann was able to show that viosterol was not absorbed after experimental ligation of the common duct. It is probable, therefore, that the hemorrhagic tendency in obstructive jaundice is due to a failure to absorb the anti-coagulation vitamin designated as K.

A third interesting piece of experimental work has been done by Roderick[9] who has shown that animals fed on spoiled sweet clover hay developed a hemorrhagic tendency. As yet the exact cause of this tendency has not been determined, although it is known that it is the result of a prothrombin deficiency. Whether the spoiled hay interferes with the absorption of vitamin K, or whether the formation of vitamin K is interfered with by damage to the liver from some agent present in the spoiled hay, is not known.

Snell[10] states that we are justified in concluding, "(1) that the hemorrhagic state in jaundice is attributable to a deficiency of prothrombin which in turn is due to failure of absorption or utilization of some substance normally present in the diet which requires bile for its absorption; (2) that this substance may be the hypothetical coagulation vitamin

(vitamin K), and (3) that additional toxic factors may deplete the supply of prothrombin, as in sweet clover disease and necrosis of the liver caused by chloroform." Theoretically, 20 mg. of vitamin K should be an adequate daily dose for man, but ten times this dose, approximately 200 mg. daily, is the dose that Butt and Snell have been using.

Greaves and Schmidt[11] demonstrated that bile salts serve as a carrier for fat-soluble vitamins and therefore in cases in which bile is not entering the intestinal tract it is essential to administer them along with the vitamin K in order to insure its absorption.

Through the courtesy of Dr. Butt of the Mayo Clinic, we were able to obtain a supply of vitamin K and have confirmed his observations on its efficacy in the control of hemorrhage in jaundiced patients. In one case, a deeply jaundiced patient on Dr. T. E. Jones' Service, there had been profuse bleeding from the uterus, the mucous membranes, and the incision. The prothrombin clotting time was 60 seconds and the patient's condition was critical. Within 12 hours after the administration of 200 mg. of vitamin K by mouth along with 6 "Kapseals of S-Bile"

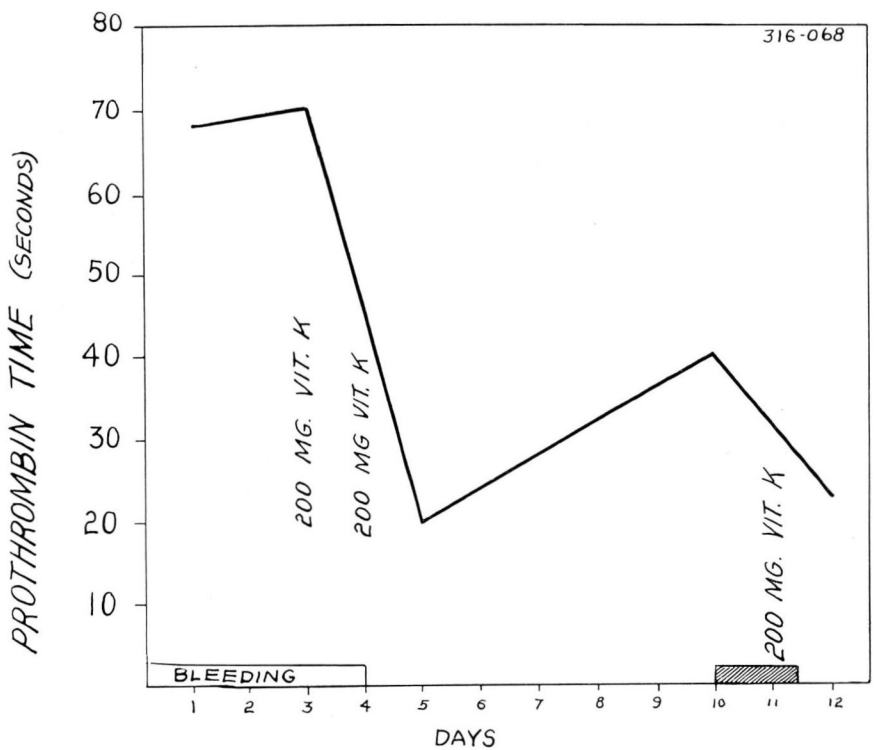

CHART 1: Chart showing the reduction in prothrombin clotting time and cessation of bleeding following the administration of vitamin K.

(Parke, Davis & Co.) all bleeding had stopped. On the following day 200 mg. of vitamin K was again given and the prothrombin clotting time was found to have fallen to normal (Chart 1).

An essential point is that vitamin K will not reduce the prothrombin clotting time unless bile is in the intestinal tract or unless it is given along with bile salts. One of Butt and Snell's charts demonstrates this very clearly, vitamin K having been given alone for one week with no change in the clotting time and then, when bile salts were added to the vitamin K, the prothrombin time promptly fell from 110 to 30.[6]

Blood transfusion has also been a valuable agent in the control of the hemorrhagic tendency in jaundice. Normal blood contains a great excess of prothrombin (approximately 5 times the amount necessary for coagulation) and consequently the administration of one or more blood transfusions may raise the prothrombin level to a point where bleeding will be avoided or stopped. The bleeding is generally not from large vessels and in our experience has occurred most commonly into the incision or into the gastro-intestinal tract. Not infrequently the bleeding may occur from all the mucous membranes. If sufficient blood to make up the prothrombin deficiency can be given, the bleeding should always stop. Inasmuch as the majority of hemorrhages have occurred within the first 24 hours after operation, it is well to give a blood transfusion before and another immediately after the operation. But an equal number of hemorrhages have occurred later in convalescence and therefore a third transfusion should be given about the third or fourth day after the effects of the initial transfusions have worn off. Since the discovery of vitamin K, however, there is less indication for blood transfusion.

Liver Failure

Although liver failure has been directly responsible for a relatively small proportion of the deaths following operations on jaundiced patients, it is not unlikely that many terminal pneumonias and some of the postoperative hemorrhages have been the indirect result of damage to the liver. It is therefore essential that deeply jaundiced patients have a low protein and high carbohydrate diet for some days prior to operation. In cases with marked liver damage glucose should be administered intravenously by the continuous drip method for 24 hours prior to operation and for the first two or three days afterwards or until the patient is again able to assimilate a high carbohydrate diet.

We have demonstrated clearly in hyperthyroidism that glucose given intravenously by the continuous drip method is much more effective in controlling the postoperative thyroid reaction than is the intermittent administration of large quantities of glucose solution. When the glucose is given intermittently it is usually given too rapidly and a great deal of it is eliminated by the kidneys. The same applies in obstructive jaundice and if the maximum assimilation of the glucose is to be obtained and the liver is to be given maximum protection the glucose should be given continuously. In a recent case of obstructive jaundice the patient began to hiccough on the second postoperative day and on the third postoperative day he became confused and delirious. His condition appeared desperate; blood transfusion was given in order to prevent any tendency to bleed, but it was not until a continuous drip of glucose was given intravenously that the delirium cleared, the hiccoughs finally ceased, the liver again began to function and the bile which had been pale and had been excreted through the T-tube in very small amounts rapidly returned to normal quality and quantity. This patient was practically afebrile during the period of his delirium and there was no evidence of pulmonary or intraperitoneal complication. The toxic reaction was certainly the result of liver failure and the dramatic recovery was in all probability directly attributable to the administration of large quantities of glucose intravenously and continuously.

Cholangeitis

A second complication of surgery in the biliary tract is the development of cholangeitis, a complication which has occurred following 29 per cent of the operations in which anastomoses were made between the biliary tract and the gastro-intestinal tract. Hitherto, we have had no logical means by which to combat this type of infection.

It has recently been demonstrated in the experimental laboratory that sulfanilamide is excreted in the bile. External biliary fistulae were made in dogs, large doses of sulfanilamide were given to these animals, and we were able to recover sulfanilamide in the bile in amounts equivalent to that present in the blood. Clinically, we have tried sulfanilamide in several cases of cholangeitis with promising results. In one case an anastomosis between the gallbladder and the jejunum had been performed, a cholecystoduodenostomy or cholecystogastrostomy being rendered impossible by an extensive carcinoma of the stomach which had invaded the common duct and resulted in jaundice. After operation, as is often the case when the lower portion of the intestinal tract is anastomosed to the biliary system, severe cholangeitis with chills, fever, and jaundice developed. The patient was treated with sulfanilamide

and within 48 hours the chills and fever had subsided and the temperature returned to normal. We have since observed similar responses to sulfanilamide in other patients with cholangeitis. It therefore appears that sulfanilamide may be as valuable an antiseptic in the biliary tract as it has proved to be in certain stubborn B. coli infections of the urinary tract.

The Surgical Treatment of Carcinoma of the Pancreas and Bile Ducts

In our experience, the surgical mortality following cholecystogastrostomy or cholecystenterostomy performed to relieve obstruction of the bile ducts by carcinoma of the pancreas has been slightly lower than that of exploratory operations or cholecystostomies performed for the same condition. The incidence of fatal hemorrhage after operation was four times as high in those patients having merely drainage of the gallbladder or exploratory operations and the deaths from liver failure were twice as frequent. In other words, we have evidence to indicate that the more extensive surgical procedures involving anastomosis between the biliary tract and the gastro-intestinal tract carry with them a lower mortality rate than do the palliative operations in which the abdomen is only explored or the gallbladder is drained.

The lower mortality rate associated with the more extensive operations can best be explained by the fact that in an anastomosis operation obstruction of the liver is always removed and with the bile returning to the gastro-intestinal tract the patient's ability to assimilate food is increased and his convalescence is therefore more rapid and complete. To be sure, one must remember that when only exploratory operations were performed they were often on the patients who were in the poorest condition to withstand major surgery. But it is nevertheless clear, in view of the results that have been obtained, that the anastomosis operations are well justified. The pruritus is relieved and in many instances the patients have lived in comfort for from one to two years after operation.

Until Whipple[12] described a radical two-stage operation for carcinoma of the ampulla of Vater and for carcinoma of the pancreas and proved that the external secretion of the pancreas was not necessary for the maintenance of life and health, obstructive jaundice due to malignancy of the head of the pancreas was considered to be hopeless. The main problem had always been the successful reimplantation of the pancreatic ducts into the gastro-intestinal tract. Attempts to anastomose the pancreatic duct to the intestinal tract too often resulted in a pancreatic and intestinal fistula with digestion of the surrounding tissues and event-

ual death of the patient. Successful radical resection of the head of the pancreas was not therefore performed until recent times.

Carcinoma of the pancreas does not necessarily metastasize early. In 60 per cent of the cases in this series there were no demonstrable metastases at the time of operation. Likewise, in 60 per cent of the cases of carcinoma of the bile ducts and in the one case of carcinoma of the ampulla of Vater no demonstrable metastases were present. In many of these cases the carcinoma was apparently limited to the field that could be excised by a radical operation. In other words, a large number of these patients had a possibility of being cured by radical surgery.

Although most autopsy statistics show that only about 10 per cent of all carcinomas of the pancreas fail to show metastasis[13] at the time of the patient's death, a much higher percentage of carcinomas of the ampulla of Vater and of the bile ducts have failed to metastasize by the time the patient died. Moreover, many of these patients died without surgical intervention and should therefore be considered to be later cases than the surgical cases generally seen.

In view of these figures and the success which radical operations on carcinoma of the head of the pancreas are obtaining, I believe we should be less pessimistic in regard to the prognosis in this disease. The least that we can do is to perform an anastomosis between the biliary tract and the intestinal tract so that the patients will obtain relief of their symptoms and so that, in the rare case where the lesion is a pancreatitis rather than a carcinoma, the patients will obtain a permanent cure. One patient in our series lived two years following an anastomosis between the intestinal tract and the biliary tract, ultimately dying of carcinoma of the pancreas but being perfectly well for a year after operation, then having a gastro-enterostomy because of obstruction of the duodenum, and again being well for nearly a year before finally succumbing to carcinoma.

Twelve cases of radical resection of the head of the pancreas have already been reported, six patients have survived operation, and one of these (reported by Whipple) is still alive and well nearly three years after the original operation.

I have recently performed a radical two-stage resection of the head of the pancreas on a patient with a well-differentiated duct type of carcinoma which was apparently limited to the head of the pancreas[14]. The excision of the tumor appeared to be complete. It is now eight months since operation, the patient is back at work, is gaining weight, feels well, and in this case I believe that the prognosis is at least hopeful.

With the recent development of vitamin K to correct the hemorrhagic tendency in jaundiced patients, by means of continuous drip of in-

travenous glucose used to combat liver failure, and with the advent of sulfanilamide in the treatment of cholangeitis, radical surgery of the pancreas and biliary tract will unquestionably receive a new impetus.

Summary

1. Postoperative hemorrhage has been the most common and most serious complication following operations on patients with obstructive jaundice.

2. The hemorrhagic tendency in jaundice is the result of a diminution of the prothrombin content of the blood.

3. The prothrombin clotting time is the most reliable method of determining the presence of a hemorrhagic tendency.

4. The administration of vitamin K and bile salts restores the prothrombin clotting time to normal and corrects the hemorrhagic tendency of jaundiced patients.

5. The most effective protection against liver failure is the *continuous* intravenous administration of large quantities of a 10 per cent solution of glucose both before and after operation.

6. Sulfanilamide has been effective in the control of cholangeitis.

7. It is probable that the indications for radical surgery of the biliary tract and carcinoma of the head of the pancreas will be extended as a result of the recent technical and physiological developments in the field of obstructive jaundice.

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