BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 19 1941

PROTHROMBIN DEFICIENCY IN DISEASE OF THE LIVER AND BILE PASSAGES AND ITS TREATMENT WITH SYNTHETIC VITAMIN K

BY

JAMES REID, M.B.

McCunn Research Scholar, University of Glasgow

(From the Gardiner Institute of Medicine, in the University)

Prothrombin deficiency as a cause of haemorrhage in disease of the liver and bile passages has attracted attention in recent years and has resulted in an important therapeutic advance. A brief account of the development of this work may be given before reporting the results of the present investigation. Dam (1934) and Dam and Schönheyder (1934), while working on a problem of fat metabolism, noticed that chicks fed on a fat-free diet soon developed subcutaneous and intramuscular haemorrhages, which they showed were associated with a deficiency of prothrombin in the circulating blood. They observed that cure was obtained by adding green vegetables to the diet, but that it did not follow addition of the known accessory food factors. Thus a new dietary substance was demonstrated which had the power of increasing the amount of prothrombin in the blood when it was deficient. This new factor was found to be fat-soluble, and was named vitamin K by Dam after the initial letter in the Danish word "Koagulation." Quick and his colleagues (1935), working in America, observed prothrombin deficiency in the blood of patients suffering from severe obstructive jaundice. A link between these two observations was soon demonstrated by Butt *et al.* (1938), Brinkhous *et al.* (1938), and Dam and Glavind (1938) when it was shown that prothrombin deficiency and haemorrhage in obstructive jaundice could be prevented by administering ether extracts of alfalfa grass. This work was at once recognized to be of practical value in the surgery of obstructive jaundice, and was confirmed in America by Stewart and Rourke (1939) and in this country by Illingworth (1939a).

Studies on the constitution and properties of vitamin K were undertaken in Denmark and America. It was early recognized that a naphthoquinone group formed part of the molecule (MacCorquodale *et al.*, 1939); hence various naphthoquinone preparations were used in the treatment of prothrombin deficiency in obstructive jaundice. Of these preparations a water-soluble compound, phthiocol (2-methyl-3-hydroxy-1:4-naphthoquinone), given intravenously, was found to have some activity (Butt *et al.*, 1939), but was apparently not so potent as water-insoluble 2-methyl-1:4-naphthoquinone, injected intramuscularly or given by mouth in conjunction with bile salts (Almquist and Klose, 1939; Macfie, Bacharach, and Chance, 1939).

After the active principle of the vitamin had been isolated and its constitution found to be 2-methyl-3-phytyl-1:4-naphthoquinone (Binkley *et al.*, 1939; Fieser, 1939), it was shown that 2-methyl-1:4-naphthoquinone was at least as potent as the vitamin itself (Ansbacher *et al.*, 1939).

Quantitative Estimation of Prothrombin in Blood

Prothrombin is considered to be a pro-enzyme associated with the globulin fraction of the plasma proteins. It is destroyed by heating blood to 60° C., and may be removed from plasma by adsorbing agents (Quick, 1940). It is believed to be formed by the liver, since the amount in the blood diminishes when the liver is severely damaged, as in acute cytolytic necrosis and in chloroform poisoning (Smith *et al.*, 1937), or when it is partially excised in dogs (Warner, 1938). The only known function of prothrombin is the formation of thrombin in the presence of calcium and thrombokinase, the latter being derived from platelets and tissue juice. Thrombin coagulates fibrinogen, forming fibrin. The velocity of this reaction bears a definite relation to the concentration of thrombin present: thus with small amounts of thrombin the coagulation time is prolonged; with large amounts it is shortened. Hence the time taken for the coagulation of a sample of blood in which adequate amounts of calcium, thrombokinase, and fibrinogen are known to be present will be an index of the amount of thrombin and so of the amount of prothrombin originally present. This coagulation time has been termed the "prothrombin time" (Quick, 1935), and is used as a criterion for the quantitative determination of prothrombin in blood. During the coagulation of blood two reactions are considered to occur, and may be represented thus: (1) prothrombin + calcium + thrombokinase → thrombin; (2) thrombin + fibrinogen → fibrin.

The prothrombin time includes both reactions, and objection may be raised that variations in the speed of the first reaction might vitiate the test as an index of the amount of prothrombin present, but in practice this has not caused any difficulty in my work. It is unnecessary to estimate the amount of fibrinogen in each sample of blood, since quantities insufficient for coagulation are seldom encountered.

Method of Determining the Prothrombin Time (Quick *et al.*, 1935, modified).—4.5 c.cm. of venous blood is taken

into a syringe containing 0.5 c.cm. of M/10 sodium oxalate. After centrifuging, 0.1 c.cm. of plasma is added to a 3 in. by 1/2 in. test-tube containing 0.1 c.cm. of lung extract* (used as the source of thrombokinas) and 0.1 c.cm. of M/10 calcium chloride solution (to neutralize the oxalate and leave a slight excess for the mechanism of coagulation). A stop-watch is started immediately on the

FIG. 1.—The coagulometer.

FIG. 2.—Diagram illustrating mechanism of coagulometer. 1: Spring clip. 2: 3 in. by 1/2 in. test-tube. 3: Water-bath. 4: Driving spindle. 5: Motor of "windspeed wiper." 6: Variable resistance for speed control. 7: Transformer and rectifier. 8: Switches. 9: Electric bulb as heat and light source. 10: Bracket to support water-bath. Thermostatic control was found to be unnecessary.

addition of plasma, and the tube, after being shaken gently for a few seconds, is transferred to a water-bath at 38° C. It is propelled in the water through an angle of 170 degrees by the apparatus shown in the photograph. This procedure ensures that the temperature and range of movement given to each sample are uniform, besides producing a sharp end-point. The watch is stopped when coagulation occurs. By this method the prothrombin time in healthy persons was found to average 25 seconds and to vary between 24 and 27 seconds. In jaundiced patients it varied between 25 and 140 seconds. Duplicate estimations were carried out, the average difference being 1 second. Because of slight variations in the lung extract, and in order to compare results obtained from day to day in the same patient and in different patients, the "prothrombin index" (Quick *et al.*, 1935) was determined as follows:

$$\text{Prothrombin index} = \frac{\text{Unknown prothrombin time in secs.}}{\text{Normal control prothrombin time in secs.}} \times 100$$

The normal range is 90 to 110. The results are expressed as a percentage of normal.

* Fresh ox-lung extract was used as a source of thrombokinas and was prepared by the method described by Smith *et al.* (1939). This extract lost much of its potency in two to three days if kept at room temperature. This period was extended to three to five days if stored at 9° C., but if immediately placed in the freezing chamber of the refrigerator it retained its activity at least four weeks after preparation. By this time the stock had usually been exhausted. The lung extract, in saline, was stored in fifty small glass tubes of about 1.5 c.cm. capacity, sealed, and immediately frozen. A tube was taken from the refrigerator before it was required to carry out a test.

Personal Observations

This paper describes an investigation of prothrombin deficiency and haemorrhage in obstructive jaundice, biliary fistula, catarrhal jaundice, and cirrhosis of the liver; and the treatment of prothrombin deficiency in some of the patients with a new water-soluble preparation. Finally the possibility of a liver function test based on prothrombin estimations is briefly discussed.

Thirty-five patients have been studied, and repeated determinations of the prothrombin index and quantitative van den Bergh reactions were made in all, and in addition the platelet count (Gram's method modified, Reid, 1940), the bleeding-time (Duke, 1915), the capillary resistance test (Göthlin, 1937), and the coagulation time (recalcifying oxalated blood, Quick *et al.*, 1935) were carried out in three patients with post-operative haemorrhage. In 16 cases definite prothrombin deficiency was found, and these were selected for treatment with synthetic naphthoquinone preparations in order that the efficiency of the drug could be determined. Of these patients 8 received 2-methyl-1:4-naphthoquinone† in peanut oil by intramuscular injection, and 8 were given the new 2-methyl-1:4-naphtho-hydroquinone disuccinate‡ by intravenous injection. Daily prothrombin estimations were carried out three to five days before and seven to ten days after treatment, and samples of blood were also taken four hours after giving the drug in order to determine how quickly it acted. For convenience of description the patients have been grouped as follows:

1(a) Obstructive Jaundice due to Neoplasm

Fifteen patients have been studied—seven males and seven females. The age range of the patients was 29 to 74 years, with the maximum age distribution about the sixty-fifth year. The duration of jaundice before investigations were carried out was two to twenty-two weeks, and the degree of jaundice varied between 11 and 32 mg. of bilirubin per 100 c.cm. plasma.

Before Operation.—The prothrombin index in patients before operation ranged from 31 to 100%, and averaged 65%. Slight prothrombin deficiency was occasionally found when the plasma bilirubin was below 20 mg./100 c.cm., but in most of these patients the prothrombin index was within normal limits. When the amount of bilirubin exceeded 25 mg./100 c.cm. plasma, prothrombin deficiency was always found, and was more pronounced the more the bilirubin in the blood increased above this level—i.e., the more complete the biliary obstruction became and the smaller the quantity of bile entering the intestine. The patients on whom these investigations were carried out were all taking satisfactory diets, including green vegetables, so the dietary intake of fat-soluble vitamin K might be assumed to be adequate. Further, it was found by the American workers and Illingworth that vitamin K concentrates and 2-methyl-1:4-naphthoquinone given by mouth had no effect on the low prothrombin levels in obstructive jaundice and biliary fistula unless bile salts were given by mouth at the same time. Hence the correlation between the degree of prothrombin deficiency and the lack of bile entering the intestine supports the view of the above workers that entry of insufficient bile salts into the intestine, with consequent deficient absorption of vitamin K, is the main cause of the fall in the prothrombin level in obstructive jaundice and biliary fistula.

After Operation.—Marked prothrombin deficiency was encountered in patients after operation, in association with

† 2-methyl-1:4-naphthoquinone supplied by Glaxo Laboratories Ltd. under the trade name kapilon.

‡ 2-methyl-1:4-naphthohydroquinone disuccinate supplied by Roche Products Ltd.

much slighter degrees of obstructive jaundice (e.g., 10 mg. bilirubin per 100 c.cm. plasma). This always occurred, whether it was an exploratory laparotomy or an operation to relieve biliary obstruction. In seven such patients a pronounced prothrombin deficiency developed from the second to the sixth day, the prothrombin index being reduced from 5 to 25% in the first twenty-four hours and from 20 to 50% between the second and the sixth day. (These figures tend to under-estimate the actual results, since treatment was not long delayed after the prothrombin index fell below 50%.) Four possible factors which might account for this considerable post-operative fall require consideration: (1) utilization of prothrombin for coagulation of blood during and immediately after operation; (2) a toxic effect of the anaesthetic on the liver; (3) lack of vitamin K, due to defective absorption from the intestine; (4) deficiency of the vitamin in the post-operative diet.

The first of the above factors was shown to be unimportant, because equally low figures were obtained just before and one to three hours after operation. With regard to the second factor, the seven patients showing the marked post-operative fall responded immediately to treatment with naphthoquinone preparations and the prothrombin index rapidly returned to normal; hence liver damage, while it may be a contributory factor, does not appear to play an important part in producing post-operative deficiency. The third factor—interference with the absorption of vitamin K through the absence of bile salts from the intestine—has just been discussed as a cause of prothrombin deficiency. Four of the seven patients referred to above underwent anastomotic operation for the relief of biliary obstruction. The stools were fairly well coloured before operation, but were even darker on the second and third days afterwards. The maximum fall in the prothrombin index occurred on an average on the fourth day, so that if bile salts were being excreted along with the pigment failure of absorption of vitamin K would not be due to this cause. The fourth factor, deficiency of vitamin K in the post-operative diet—so far as it may be assessed at present—was found to exist, since green vegetables (the only known source rich in the vitamin) were not taken for at least one week.

It would therefore appear that a deficient intake of vitamin K may be important in causing the pronounced post-operative fall in the prothrombin index, but a definite statement on the question must await further investigation.

1(b). Non-malignant Obstructive Jaundice

Eight patients, 7 females and 1 male, have been studied. Their ages ranged from 38 to 75 years. Six had chronic cholecystitis with gall-stones, 1 had a post-operative stricture of the common bile duct, and 1 had chronic pancreatitis. All were jaundiced, but not deeply (3 to 7 mg. bilirubin/100 c.cm. plasma), when observations were made.

Before operation the prothrombin index was never below 75%; in 7 it ranged between 80% and 95%. Six patients underwent operation: 4 for removal of gall-stones, 1 for stricture of the common bile duct, and 1 had an exploratory laparotomy. In 4 the prothrombin index ranged between 75% and 80% in the first two days after operation, but thereafter normal values were found. In another patient it fell to 57% on the fourth day, and in the sixth patient it fell to 25% after one week, when haemorrhage from the wound was observed.

Prothrombin deficiency was considered to be due to the causes discussed in dealing with the malignant obstructive jaundice group.

2. Biliary Fistula

There were two patients in this group; their cases are here recorded.

Case 1.—A married woman aged 59 had a cholecystectomy performed for chronic cholecystitis with gall-stones. A complete biliary fistula developed after this operation. Her diet

was satisfactory, but the prothrombin index was only 52% after the fistula had been present for ten weeks. On the day following an operation to close the fistula it fell to 36%; 15 mg. of the intravenous preparation was given, and within twenty-four hours the prothrombin index had risen to 88%.

Case 2.—A married woman aged 52 developed a biliary fistula following cholecystectomy for chronic cholecystitis. A repair operation four months after removal of the gall-bladder failed, and a fistula developed, associated with slight obstructive jaundice (immediate direct van den Bergh and 5 mg. bilirubin/100 c.cm. plasma). The stools were light in colour and bile was present in the urine. The prothrombin index was 80% after the condition had been present for eight months, and showed little variation over a period of three weeks. Two days after intramuscular injection of 15 mg. of 2-methyl-1:4-naphthoquinone the prothrombin index was 103%. A second repair operation was successfully undertaken, further treatment having been given the previous day. Despite the fact that the patient was unable to take anything but fluids for the week following operation the prothrombin index never fell below 90%.

No haemorrhage occurred in either of these patients. In the first a biliary fistula prevented sufficient bile salts entering the intestine, with the result that adequate amounts of vitamin K, though present in the diet, were not absorbed, hence the low prothrombin values. The second had a partial fistula and slight obstructive jaundice, but enough bile salts entered the intestine to prevent serious prothrombin deficiency developing. Pre-operative treatment prevented the usual fall in the prothrombin index after operation.

3. Catarrhal Jaundice

Six patients with catarrhal jaundice were subjects of investigation. There were 3 males and 3 females, and the ages ranged from 19 to 30 years. Two suffered from a mild, 3 from a moderate, and 1 from a severe attack of the disease. The prothrombin index was never below 90% and the plasma bilirubin was 5 and 10 mg. per 100 c.cm. respectively in the 2 patients with the mild form of the disease. In the patients with the moderate attack the lowest prothrombin indices were 80%, 72%, and 65%, and the plasma bilirubin was 18, 9, and 7 mg./100 c.cm. respectively. The prothrombin index was 20% and the plasma bilirubin 35 mg./100 c.cm. at the height of the disease in the patient with severe clinical manifestations. He also had extensive subcutaneous haemorrhages and haematomata on the arms, legs, and abdomen, though external haemorrhage did not occur. His diet was good and the rapid improvement in the prothrombin index (20% to 90% in three days) without extraneous vitamin K therapy coincided with the appearance of bile in the stools, though the plasma bilirubin was still 32 mg./100 c.cm.

The prothrombin deficiency in patients with slight jaundice may be due to a toxic effect on the liver, since they were taking a satisfactory diet and bile was known to be entering the intestine. In the patient with marked prothrombin deficiency failure to absorb vitamin K appeared also to be important, since the prothrombin index rose rapidly after the stools were coloured.

4. Cirrhosis of Liver

Investigations were carried out on 4 patients—2 males and 2 females. Their ages ranged from 46 to 65 years. Slight icterus (2 to 4 mg. bilirubin/100 c.cm. plasma) was present in 3, and the stools were well coloured in all 4. The amount of prothrombin in the blood was always moderately reduced, and the prothrombin index ranged from 65% to 80%. On an ordinary mixed diet the level tended to fluctuate between these figures over a period of 3 to 6 weeks. Normal values were never reached, and there was practically no response to parenteral administration of the vitamin K preparation (see Fig. 4).

Post-operative Haemorrhage

Three patients with obstructive jaundice developed post-operative haemorrhage from their wounds. There was no bleeding into the skin or from mucous membranes. A brief clinical outline of their conditions will be given.

Case 3.—A man aged 27 complained of abdominal pain and vomiting after food for ten weeks, and jaundice for two weeks. He was poorly nourished and a mass was palpable in the epigastrium. The stools were light in colour and the urine contained bile. The plasma gave an immediate direct van den Bergh reaction, with 11.5 mg. bilirubin/100 c.cm. On the day before an exploratory laparotomy the prothrombin index was 76%. At operation an inoperable retroperitoneal sarcoma was found, and the wound was carefully closed. Throughout the day after operation he suffered from marked abdominal discomfort and vomiting, resulting in restlessness. In the evening of the same day it was noticed that his dressing was blood-stained and that a general ooze was coming from the wound. After changing the dressing the haemorrhage stopped until the afternoon of the second day, when the prothrombin index was 50%. The platelet count, the bleeding-time, and the capillary resistance test were normal. The coagulation time was slightly prolonged. Ten mg. of 2-methyl-1:4-naphthoquinone was given intramuscularly, and twenty-four hours later, though he was still restless and vomiting, the haemorrhage had stopped and the prothrombin index was 94%. He died on the fourth day after operation. A post-mortem examination was not carried out.

Restlessness, retching, and vomiting, by putting an extra strain on the wound, was probably the main factor in causing the early onset of haemorrhage, and the fact that it was intermittent is probably a reflection on the slight prolongation of the coagulation time.

Case 4.—A man aged 67 complained of jaundice of three days' duration. He was well nourished and took his food well. The stools were brown in colour and the urine contained bile. The plasma gave an immediate direct van den

FIG. 3.—Showing the onset of haemorrhage after the post-operative fall in the blood prothrombin and the immediate response to treatment with synthetic vitamin K.

Bergh reaction and contained 8.5 mg. bilirubin/100 c.cm. Before operation the prothrombin index was normal (90 to 96%). A cholecystoduodenostomy was performed for a carcinoma of the head of the pancreas, and twenty-four hours after operation the prothrombin index was 75%. It gradually fell until the fifth day, when it was 55%, and the coagulation time was moderately prolonged. The platelet count, the bleeding-time, and the capillary resistance test were normal. On the evening of this day haemorrhage from the wound was noticed, and later his extremities were cold and he became collapsed. Haemorrhage was more or less continuous for

forty-eight hours. The haematocrit reading before the haemorrhage was 40%; afterwards it was 32%, so that probably at least one-fifth of the red cells were lost. The response to treatment is shown in Fig. 3. Satisfactory progress was made until the tenth day; then he became drowsy and dehydrated, and died on the fifteenth day after operation. A post-mortem examination was not performed.

Case 5.—A woman aged 46 complained of intermittent attacks of pain in the right hypochondrium, shivering, and jaundice for the past twelve years. Bile was present in the urine, but the stools were well coloured. The van den Bergh test gave an immediate direct reaction of 6 mg. bilirubin/100 c.cm. plasma. A diagnosis of chronic cholecystitis with obstructive jaundice due to gall-stones was made. A hypochromic anaemia was also present (Hb, 52%; R.B.C., 3,470,000/c.mm.; C.I., 0.73; haematocrit, 30%; W.B.C., 7,200/c.mm.), which was treated successfully with iron. Before operation the prothrombin index was 75%; the platelet count, the bleeding-time, the capillary resistance test, and the coagulation time were normal. A stone was removed from the common bile duct and the gall-bladder was drained. Late in the evening of the sixth day after operation a slow ooze from the wound was first noticed; this continued overnight, and by 10.15 the next morning the patient's extremities were cold and she was collapsed. The prothrombin index was 25% and the coagulation time was much prolonged. The bleeding-time and capillary resistance test were normal. At 10.30 a.m. she was given 15 mg. of 2-methyl-1:4-naphthoquinone intramuscularly, and four hours later the prothrombin index was 75%, the coagulation time was normal, and the haemorrhage had ceased. On the eighth day the prothrombin index was 94%. The subsequent course was uneventful.

Haemorrhage and Prothrombin Deficiency

Haemorrhage associated with prothrombin deficiency has been described in newborn infants, in idiopathic steatorrhoea (Kark *et al.*, 1940), and in hepatic and biliary disease. It may be manifested by ecchymoses, haematomata, and haemorrhage from mucous membranes and even into joints, but it occurs most often from operation wounds (Illingworth, 1939b).

When haemorrhage began in the three cases just described the prothrombin index was 50%, 55%, and 25% respectively. Three patients with obstructive jaundice and one with a biliary fistula showed prothrombin indices of 24%, 26%, 27%, and 36% after operation and yet no haemorrhage occurred. It would therefore appear that there is no constant relation between the degree of prothrombin deficiency and the occurrence of haemorrhage from the operation wound. This statement may be explained by considering that before any serious capillary haemorrhage can occur two conditions must be fulfilled: (1) rupture of the vessels; and (2) an upset in the mechanism for securing haemostasis. Prothrombin deficiency, by interfering with the coagulation of blood (a process of importance in stopping haemorrhage), will thus not necessarily result in haemorrhage, but if rupture of the vessels occurs this interference with the coagulation mechanism will prolong the bleeding. Trauma is suggested as the most frequent cause of rupture of the vessels, since no defect in the capillaries was found, as judged by the frequency of haemorrhage from the operation wound, which is a "weak spot" and so more liable to bleed from minor injury.

A Comparison of Haemorrhage in Jaundice and Haemophilia

Four patients with haemophilia were studied. The platelet count, the bleeding-time, the capillary resistance test, and the prothrombin index were normal and the coagulation time was prolonged (4 to 8 times normal).

In the three patients with obstructive jaundice who developed haemorrhage the platelet count, the bleeding-

time, and the capillary fragility test were normal. The prothrombin index was subnormal and the coagulation time was prolonged in proportion to the degree of prothrombin deficiency—e.g., it was four times normal when the prothrombin index was 25%.

It is suggested, from these observations and the clinical manifestations of haemorrhage in the two conditions, that there is a close analogy between haemophilia and haemorrhage in jaundice. A defect in the coagulation of blood exists in both and trauma is the usual determining cause of haemorrhage. The essential difference between the conditions rests in the particular upset in the coagulation mechanism—in the one a prothrombin deficiency and in the other an unknown congenital defect.

Treatment of Prothrombin Deficiency

The object of treatment is to raise the prothrombin index to the normal level of 90% to 110% in order to correct the defect in the coagulation of the blood. The results are shown in the accompanying table. All the

Table showing Effect of Treatment on the Prothrombin Index

Condition	Preparation and Dose	No. of Cases	Prothrombin Index		
			Before Therapy	4 Hours after Therapy	Time to Reach Normal (Days)
Obstructive jaundice due to neoplasm	I.M. 10 mg.	6	27-64	}*	3
	I.V. 10 mg.	6	24-58		2
Non-malignant obstructive jaundice	I.M. 10 mg.	1	57		1
	I.V. 15 mg.	1	25	75	1
Biliary fistula	I.M. 15 mg.	1	88	—	2
	I.V. 15 mg.	1	36	62	1
Cirrhosis of liver	I.M. 10 mg.	2	60 & 71	62 & 70	No significant change after 7 days
	I.V. 10 mg.	2	70 & 80	71 & 82	

I.M. = Intramuscular. I.V. = Intravenous.

* Six patients had prothrombin indices under 40% before treatment. In three of them an increase of 15 to 30% was observed four hours after giving the intramuscular preparation, and in the others an increase of 25 to 30% four hours after the intravenous preparation.

FIG. 4.—Illustrating the rapid improvement in the prothrombin index, after synthetic vitamin K, in two patients with obstructive jaundice due to carcinoma of the head of the pancreas and the insignificant response in a patient with cirrhosis of the liver. A = Carcinoma of head of pancreas: 10 mg. vitamin K intramuscularly. B = Carcinoma of head of pancreas: 10 mg. vitamin K intravenously. C = Cirrhosis of liver: 10 mg. vitamin K intravenously.

patients except those with cirrhosis of the liver responded to treatment (Fig. 4). The marked activity of 2-methyl-

1:4-naphthoquinone in increasing the amount of prothrombin in the blood has been confirmed, and it may be concluded that the new intravenous preparation is at least as potent as this drug. The intravenous drug appears to be more rapid in its action than the intramuscular one, but for a prolonged action the latter is probably to be preferred. Definite conclusions on the dosage and the time for the maximum response could not be made, but the results suggest that a more rapid increase in the prothrombin index occurs when the larger doses are given. No toxic effects were encountered with either of these preparations, but two patients complained of pain at the site of intramuscular injection.

In preparing a jaundiced patient for operation prothrombin estimations will decide whether treatment is necessary or not. If these estimations are not carried out during the first week after operation it would seem advisable to administer some active form of vitamin K as a routine in view of the marked fall in the amount of prothrombin which may occur during this dangerous period. For this purpose a depot dose of 15 to 20 mg. of 2-methyl-1:4-naphthoquinone intramuscularly on the day of operation is suggested.

Blood Prothrombin Levels and Liver Efficiency

Suggestions have been made that the amount of prothrombin in the blood may be used to assess liver function, and recently Wilson (1940) has reported a relation between the hippuric acid liver-function test and blood-prothrombin levels. The failure of the patients with cirrhosis of the liver to respond to treatment (see table) may be ascribed to liver inefficiency, since, as previously mentioned, the only known conditions affecting man in which prothrombin deficiency does not respond to vitamin K therapy are associated with severe liver damage. Similar results have been reported by Butt *et al.* (1940) in three patients with cirrhosis.

Laevulose-tolerance tests carried out on three of the four patients in whom the above investigations suggested liver inefficiency were normal. Later two of these patients died, and post-mortem examination revealed advanced cirrhotic changes. Thus it may be that the failure of naphthoquinone preparations to increase the subnormal amounts of prothrombin in the blood in patients suffering from chronic hepatic disease such as cirrhosis may prove to be a valuable index of liver inefficiency. This matter is being investigated, and it is intended to make it the basis of a subsequent communication.

Summary

The importance of vitamin K in the prevention and treatment of haemorrhage in hepatic and biliary diseases associated with jaundice has now been fully recognized. The present investigations support previous work indicating that defective absorption of vitamin K due to absence of bile salts in the intestine is chiefly responsible for prothrombin deficiency in obstructive jaundice and biliary fistula prior to operation.

It is suggested that prothrombin deficiency after operation in these conditions—a deficiency which is often pronounced—may be due to a deficient intake of vitamin K in the restricted post-operative diet. Routine pre-operative administration of vitamin K is recommended.

The prothrombin deficiency in cirrhosis of the liver is considered to result from imperfect utilization of vitamin K by the liver.

Prothrombin deficiency is not, even when severe, always associated with haemorrhage. It is considered to be responsible only for the prolongation of haemorrhage after it has been caused by other factors, especially injury.

A new water-soluble preparation (2-methyl-1:4-naphthoquinone disuccinate), injected intravenously, has been found

to be as efficient as 2-methyl-1:4-naphthoquinone in increasing the amount of prothrombin in the blood when there is a deficiency. Moreover, the action of this preparation appears to be more rapid though less sustained than the latter. It has one minor disadvantage in that it is not stable for long in aqueous solution, and so has to be dissolved in water immediately before use.

A close analogy between haemorrhage in jaundice and haemophilia has been made. In both an upset in the coagulation mechanism exists, which is due in the one to prothrombin deficiency and in the other to an unknown congenital defect.

The failure of the patients with cirrhosis of the liver to respond to naphthoquinone preparations suggests that prothrombin estimations may form the basis of an additional test of hepatic insufficiency. This possibility is being explored.

A simple apparatus for determining the coagulation time and prothrombin time has been illustrated and a method of preserving lung extract, used as a source of thrombokinase, has been described.

I wish to thank Profs. J. W. McNee and C. F. W. Illingworth for advice and criticism, the physicians and surgeons of the Western Infirmary for permission to examine and treat the patients under their care, and Glaxo Laboratories Ltd. and Roche Products Ltd. for supplies of vitamin K.

REFERENCES

- Almquist, H. J., and Klose, A. A. (1939). *J. biol. Chem.*, **130**, 787.
 Ansbacher, S., and Fernholz, E. (1939). *J. Amer. chem. Soc.*, **61**, 1924.
 Binkley, S. B., Cheney, L. C., Holcomb, W. F., McKee, R. W., Thayer, S. A., MacCorquodale, D. W., and Doisey, E. A. (1939). *Ibid.*, **61**, 2558.
 Brinkhous, K. M., Smith, H. P., and Warner, E. D. (1938). *Amer. J. med. Sci.*, **196**, 50.
 Butt, H. R., Snell, A. M., and Osterberg, A. E. (1938). *Proc. Mayo Clin.*, **13**, 74.
 ——— (1939). *Ibid.*, **14**, 497.
 ——— and Bollman, J. L. (1940). *Ibid.*, **15**, 69.
 Dam, H. (1934). *Nature*, **133**, 909.
 ——— and Glavind, J. (1938). *Lancet*, **1**, 720.
 ——— and Schönheyder, F. (1934). *Biochem. J.*, **28**, 1355.
 Duke, W. W. (1915). *J. Amer. med. Ass.*, **65**, 1600.
 Ficser, L. F. (1939). *J. Amer. chem. Soc.*, **61**, 2559.
 Göthlin, G. F. (1937). *Lancet*, **2**, 703.
 Illingworth, C. F. W. (1939a). *Lancet*, **1**, 1031.
 ——— (1939b). *Edinb. med. J.*, **46**, 762.
 Kark, R., Souter, A. W., and Hayward, J. C. (1940). *Quart. J. Med.*, n.s., **9**, 247.
 MacCorquodale, D. W., Binkley, S. B., Thayer, S. A., and Doisey, E. A. (1939). *J. Amer. chem. Soc.*, **61**, 1928.
 Macfie, J. M., Bacharach, A. L., and Chance, M. R. A. (1939). *British Medical Journal*, **2**, 1220.
 Quick, A. J. (1935). *J. biol. Chem.*, **109**, Proc. lxxiii.
 ——— (1940). *Amer. J. med. Sci.*, **199**, 118.
 ——— Stanley-Brown, M., and Barcroft, F. W. (1935). *Ibid.*, **190**, 501.
 Reid, J. (1940). *Lancet*, **2**, 584.
 Smith, H. P., Warner, E. D., and Brinkhous, K. M. (1937). *J. exp. Med.*, **66**, 801.
 ——— Ziffren, S. E., Owen, C. A., and Hoffman, G. R. (1939). *J. Amer. med. Ass.*, **113**, 380.
 Stewart, J. D., and Rourke, G. M. (1939). *Ibid.*, **113**, 2223.
 Warner, E. D. (1938). *J. exp. Med.*, **68**, 831.
 Wilson, S. J. (1940). *J. lab. clin. Med.*, **25**, 1125.

The committee of the Royal Melbourne Hospital has accepted responsibility for the erection of a new building for the Walter and Eliza Institute of Research in Pathology and Medicine, now in its twenty-first year. The building will provide additional laboratory space and greatly improved facilities. Meanwhile the annual report of the Institute chronicles a large amount of work, some of it routine investigation and some of it called for by the special demands of the war, in the virus department, the biochemical department, and the departments of clinical and neuropathological research. Much of the work has already been published in Australian journals. Last year the Institute started a blood bank, the only one so far established in Melbourne, to meet emergency blood transfusion requirements. A considerable part of the Institute's work has been the determination of the blood groups of nearly 13,000 troops of the A.I.F. in camp in Victoria. Research has also been undertaken on changes observed during storage of blood, and on the treatment of anuria following incompatible blood transfusions. Endeavours have been made to find a solution which, when injected intravenously in small amounts, will cause rapid alkalization of the urine. A dose of 20 c.cm. molar sodium lactate solution shifts the pH of urine to the alkaline side and maintains it there for half an hour, and it is thought that it may be possible to produce more significant effects with larger doses or more concentrated solutions.

EXPERIENCES IN THE RECEPTION AND TREATMENT OF AIR- RAID CASUALTIES

BY

JOHN ROBERT LEE, M.D., B.S., F.R.C.S.

These notes cover a period of two months when intensive enemy air raids occurred over London. During this period 227 patients came under my care and supervision. Many of us have seen and treated badly injured civilians brought to hospital as the result of road, railway, or works accidents in peacetime. It seems to me, however, that only those who have had to deal with victims of air raids can conceive the appalling condition and appearance of many of these patients on their arrival in hospital. A sight which must be seen to be appreciated fully is the almost indescribably filthy condition of many who evidently had been clean and well clad. A patient is brought to the receiving ward with her clothes cut and torn to shreds, her hair singed, filled with dirt, and matted with blood and cement dust, her body and limbs covered with grit and oil, her face blackened, bruised, and bleeding, her eyes, nose, lips, and ears filled with dirt, her head bandaged, and her limbs immobilized by improvised splints at the first-aid post. Truly it is a picture not easy to forget. Most badly injured patients had been given 1/4 grain to 1/2 grain of morphine; the latter seemed too big a dose. Their ages varied from an infant a few hours old, born and bombed on the same day, to a man aged 92. There were twelve children under 14 years and twenty-six patients over 70. Thirty-six patients were dead or moribund on arrival in the receiving-room. The other patients were classified as follows:

Group 1 consisted of those so terribly injured that they died within an hour of arrival.

Group 2 patients were a few so badly hurt and shocked that they died notwithstanding most prompt measures taken for their resuscitation. Two of these were in so much pain that morphine and other usual sedatives failed to relieve. The administration of repeated short inhalations of chloroform was found to be the only way to calm these patients and to relieve their agony.

Group 3 was made up of those suffering from severe shock and loss of blood. These responded to blood transfusion, other resuscitation measures, and good nursing. After some hours—up to twenty-four—they were in a fit condition to be operated on, and made a good recovery. Some in this group had shattered limbs or had lost part of a limb. Others had head injuries with open or closed fracture of the skull. Three had protrusion of brain substance. All three recovered. Four patients had fractured spine. Two had penetrating abdominal wounds. Others suffered from severe burns.

Group 4 included patients less severely injured. They had large lacerated wounds or open or closed fractures, but shock was not so marked.

Group 5 comprised patients suffering with multiple small cuts, abrasions, and bruises.

Our Routine

Faced for the first time with conditions as described, we evolved and adopted the following routine plan. The patient was at once assured he would be safe and well cared for; those who were distressed because they could not see owing to dirt, swelling, or eye injury were told not to fear going blind. Their eyes were thoroughly cleansed and castor-oil instilled at once, and their lips and mouths were also cleaned. The patients then had a