Recommendations

1. Those with a mental age of less than 10 years should be prevented at the recruiting boards from joining the Army or, if already enlisted, should be discharged.

2. Since those with mental ages between 10 and 12 are often unstable, break down more than the normal under active service conditions, and frequently report sick, they should be sent to a labour corps and receive special consideration at the end of three months' service. Due allowance for a fall in intelligence due to age should be made in the case of older soldiers (I allow a drop of 1 year of mental age for each decade after 25 years in computing the mean score for average older men).

3. To arrive at a rough assessment of the mental age the progressive matrices tests could be used; but the method of assessment is not so important, though there are several reasonably reliable methods. What is really important is that some systematic attempt should be made to eliminate the defectives.

4. Since some people will raise an objection to the idea of "weeding out" defectives it should always be stressed that the task is to keep certain less gifted members of the population at jobs in which they are stable and in which they can be of most use to the national effort.

Summary

The mental defective in the Army—slow to learn, prone to breakdown, a misfit and potential danger—is discussed. Aids in spotting the defective are given. It is pointed out that, though a hindrance in the Army, he may be put to useful work in civil life in wartime. Recommendations are made for handling the problem.

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HYPOPROTHROMBINAEMIA AND AVITAMINOSIS-K IN MAN

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The control of haemorrhage in man is dependent on the "protective" reaction of the vascular tree to trauma and on the ability of the blood to coagulate normally. Although the former defence mechanism is not at all clearly understood, recent studies have demonstrated the validity of the so-called classical theory of blood coagulation (Eagle, 1939), and the majority of workers in this field now subscribe to Schmidt's (1895) original hypothesis, concisely expressed by the following equations:

Despite the fact that very little is known of the chemical nature of any of the organic constituents of the plasma, which react together to form a blood clot, clinical and experimental studies by chemists, biologists, and physicians during the past five years have provided a sound basis for the diagnosis and treatment of previously obscure haemorrhagic diseases. This advance in knowledge is in the first place due to the recent development of methods for the estimation of blood-prothrombin levels (Quick and others, 1935; Brinkhous and others, 1938; Dam and Glavind,

1938), which are more specific than those previously used (Howell, 1914); and, secondly, because Dam and his co-workers in Copenhagen were able to demonstrate that a fat-soluble substance, vitamin K, could restore the marked hypoprothrombinaemia and control the haemorrhagic tendency of experimental dietary "haemophilia" in chickens (Dam and others, 1936).

It is the purpose of this communication to discuss some of the clinical aspects of hypoprothrombinaemia and avitaminosis-K in man in the light of recent knowledge and as a result of personal observation of 178 patients in the Boston City Hospital during the past two years. The majority of these patients suffered from haemorrhagic manifestations and all were suspected of having a diminished blood-prothrombin concentration. Consequently their blood-prothrombin concentration levels were measured by

FIG. 1.—The relation between the prothrombin percentage of human plasma and the Quick prothrombin time in the presence of excess tissue thromboplastin, giving a Quick prothrombin time of 25 seconds for normal control plasma.

Quick's method. The test measures the time taken for a sample of citrated plasma to coagulate, after recalcification, in the presence of an excess of tissue thromboplastin, as compared with the time taken for a sample of normal citrated plasma to clot when treated in the same way. Conversion of these "times" to blood-prothrombin concentration are made by reference to a curve (Fig. 1) constructed according to the method of Kark and Lozner (1939).

The Quick test is extremely simple, and the recent introduction of a stable thromboplastin (Souter and Kark, 1940), requiring only the addition of distilled water before use, would seem to remove the one serious obstacle to the performance of the test in the physician's office, and also enables it to be performed with greater ease elsewhere. The Quick test is performed as follows:

4.5 c.cm. of blood is taken into a saline-washed syringe by means of a clean venepuncture, and mixed with 0.5 c.cm. of 2.5% solution of sodium citrate in a centrifuge tube. The blood is spun at 1,500 r.p.m. for five minutes and the plasma drawn off. The test must be performed on this plasma within the next six hours.

Thromboplastin is prepared by stripping the brain of a freshly killed rabbit of blood vessels and meninges and washing it in tap-water. The brain is then macerated, spread thinly on plate-glass, and dried in an oven at 37° C. for twenty-four to forty-eight hours. To each 0.5 gramme of this dried material 5 c.cm. of a 0.85% solution of sodium chloride is slowly added and thoroughly mixed into a thin paste. The paste is incubated for fifteen minutes in a water-bath at 56° C. and then centrifuged at 2,000 r.p.m. for five minutes. The upper layer of opalescent fluid in the centrifuge tube is used as a source of thromboplastin and retains its activity for from two to four days when kept in the ice-box.

To perform the test, 0.1 c.cm. of thromboplastin solution is pipetted into a 75 by 19 mm. tube, together with 0.1 c.cm. of plasma; such a clot forms within twenty to twenty-five seconds. Chloride solution, containing 0.277 grammes of calcium chloride per 100 c.cm. distilled water, is then added. The stop-watch is started and the tube is agitated for fifteen seconds in the water-bath. The tube is then removed from the water-bath and tilted gently up and down once or twice a second. The end-point is sharp, and occurs when the mixture suddenly ceases to flow smoothly and a clot is formed. In normal plasma such a clot forms within twenty to twenty-five seconds, depending on the batch of thromboplastin used.

It is extremely important to check each new thromboplastin solution against a normal control plasma before making observations on the plasma of patients suspected of having hypoprothrombinaemia.

Clinical Manifestations of Hypoprothrombinaemia in Man

A haemorrhagic state consequent on a reduction of active prothrombin in the circulating blood does not arise unless the blood-prothrombin level has dropped considerably. Although there is a wide margin of safety, personal observations indicate that the critical level for bleeding is somewhat higher than the 15 to 20% of normal which Quick (1938) originally postulated.

Of the 178 patients studied 53 had a haemorrhagic condition which was directly consequent on a marked hypoprothrombinaemia and which, in most instances, was controlled by vitamin K therapy. This condition, which we have termed haemorrhagic hyperprothrombinaemia (Kark and others, 1940), may be divided into two classes—latent haemorrhagic hypoprothrombinaemia and spontaneous haemorrhagic hypoprothrombinaemia.

Latent Haemorrhagic Hypoprothrombinaemia

When the patient's blood-prothrombin level has fallen to about 35% of normal, haemorrhagic manifestations occur at the sites of *obvious* trauma; bleeding starts from recent operation wounds or where the gums have been damaged by too vigorous brushing of the teeth. Below this level, too, dangerous haemorrhage occurs from intestinal ulcerations, if they are present. One physical sign especially gives evidence of the marked reduction in the blood prothrombin. In all patients in whom the prothrombin level had dropped to below 35% of normal, haematomata became evident at the site of venepuncture or where the skin had been punctured for bleeding-time estimations. These "*needle-puncture haematomata*" were often the only outward clinical evidence of a dangerous tendency to bleed.

Spontaneous Haemorrhagic Hypoprothrombinaemia

A spontaneous haemorrhagic diathesis becomes apparent when the blood-prothrombin level has fallen to from 15 to 20% of normal. This condition is seen especially in newborn infants and occasionally in patients suffering from idiopathic steatorrhoea (Kark and others, 1940), obstructive jaundice, or severe parenchymatous hepatic disease.

The condition may manifest itself by the spontaneous appearance of large haematomata on the back, thighs, or other sites of pressure. Dramatically, haemarthrosis, severe haematemesis, epistaxis, haematuria, or melaena may be the presenting symptom. Menorrhagia and intracranial and retinal haemorrhages have been noted. Intractable haemorrhage may occur from trivial skin wounds or, in infants, from the umbilical cord. Although the gums may bleed they do not show the purple sponginess characteristic of scurvy, and perifollicular haemorrhages of the skin are not a feature of this condition. Laboratory studies are striking. The blood-coagulation time is prolonged, but not to the same extent as it may be in haemophilia. No abnormalities are noted in clot retraction either in clotted whole blood or in recalcified plasma. The bleeding time, though usually

normal, is occasionally prolonged.* The capillary fragility is unaltered, as is the blood-platelet count. Marked prolongation of Quick's prothrombin time is present, and is the crucial finding.

The main features of haemorrhagic hypoprothrombinaemia are as follows:

"Needle-puncture" haematomata; continued and prolonged wound haemorrhage; subcutaneous haematomata, especially at pressure points; haemarthroses, epistaxis, haematemesis, melaena, haematuria, retinal haemorrhages, menorrhagia. No gum changes; no perifollicular haemorrhages.

Laboratory Data.—Blood—prothrombin concentration markedly reduced; prolonged coagulation time; occasionally increased bleeding time; normal capillary fragility; clot retraction normal; platelets normal.

Clinical Causes of Hypoprothrombinaemia in Man

The development of hypoprothrombinaemia in man is usually associated with evidence of florid pathological disturbances of the bile ducts, intestine, or liver. Although the precise interrelationship between these organs, vitamin K, and prothrombin is not understood, the broad outlines of the physiological processes which maintain an adequate concentration of prothrombin in the blood have been clearly drawn. Experimental evidence has shown that prothrombin is formed by the liver (Smith and others, 1937; Warren and Rhoads, 1939) if an adequate supply of vitamin K is maintained. Furthermore, the presence of bile salts in the intestinal canal is necessary for the proper absorption of the naturally occurring vitamin, which is an oily substance (Greaves and Schmidt, 1937; Greaves, 1939). Prothrombin is destroyed in the body by passage through the lung (Andrus and others, 1940) and perhaps by a sustained rise in temperature (Wilson, 1939). Thus it is clear that hypoprothrombinaemia may develop as a result of a nutritional deficiency of vitamin K or following a disturbance in the formation or metabolism of prothrombin.

With this in mind the following classification of diseases in which hypoprothrombinaemia is known to occur is suggested:

NUTRITIONAL DEFICIENCY OF VITAMIN K

Restricted or Unbalanced Diet.—Scurvy; pellagra; rickets; idiopathic steatorrhoea; haemorrhagic disease of the newborn.

Defective Absorption from the Intestine.—(1) In the absence of bile salts: Obstructive jaundice; biliary fistula. (2) In the presence of intestinal disease: Regional ileitis; ulcerative colitis; intestinal obstruction; polyposis coli; idiopathic steatorrhoea; neoplasm of the intestine.

METABOLIC DISTURBANCES OF PROTHROMBIN ANABOLISM AND KATABOLISM

Failure of Production of Prothrombin by the Liver.—(1) Degenerative or infective parenchymatous processes: Acute yellow atrophy; infective hepatitis. (2) Infiltrative parenchymatous processes. Generalized carcinomatosis; leukaemia.

Diminished Production of Prothrombin by the Liver.—Chronic hepatoses (Banti's syndrome, alcoholic cirrhosis); catarrhal jaundice; leukaemia; neoplasm of the liver.

Increased Destruction of Prothrombin.—Artificial fever therapy; prolonged fever.

In many conditions hypoprothrombinaemia results from a combination of pathological disturbances. This is especially true in intestinal diseases. Here, besides absorptive difficulties, there may be loss of vitamin K, and possibly of prothrombin, by excessive vomiting, diarrhoea, or the removal of succus entericus by a Wangenstein drainage tube. To this loss may be added the restricted dietary intake

* Preliminary investigations would suggest that when this latter finding is present it may be due to coexisting scurvy.

common in these patients and destruction of prothrombin by long-continued fever. Case 1, below, illustrates such a combination of circumstances.

When ulcerative conditions of the bowel are present and hypoprothrombinaemia develops, continuous haemorrhage from the lesion will occur when the prothrombin level has decreased to about 35% of normal. This is true of ulcerative colitis and regional ileitis, and possibly explains the intestinal haemorrhage seen in enteric fever. When the mucosa is intact, however, no melaena or haematemesis will become evident until the blood-prothrombin level has dropped to the spontaneous haemorrhagic level of from 15 to 20%. Such a condition is especially common in haemorrhagic disease of the newborn and is sometimes found associated with idiopathic steatorrhoea.

Dietary deficiency *per se* rarely causes a haemorrhagic hypoprothrombinaemia (Kark and Lozner, 1939). We have, however, observed an infant with rickets of dietary origin who developed a spontaneous subarachnoid haemorrhage; the blood-prothrombin level was extremely low, being 20% of normal. The prothrombin level was rapidly restored to normal by therapy with synthetic vitamin K parenterally, and the child made an uneventful recovery following craniotomy and evacuation of the blood clot.

In idiopathic steatorrhoea, although a hypoprothrombinaemia does occur as a result of failure of intestinal absorption while a mixed diet is being taken, a haemorrhagic level is not reached unless the patient is on a low-fat diet (Kark and others, 1940). As a result of such a regime fat-soluble vitamins are markedly restricted, and within six months to two years features of spontaneous haemorrhagic hypoprothrombinaemia may appear.

Metabolic Disturbances of Prothrombin Anabolism and Katabolism

The manner in which the production and destruction of prothrombin in the body take place is not clearly understood, and for this reason any classification on the basis of metabolic disturbances of prothrombin formation or breakdown must of necessity be tentative. It has long been known that prothrombin is sensitive to heat and is readily destroyed by a temperature of 40° C. in a water-bath. Prothrombin studies were therefore made on patients undergoing artificial fever therapy. The results obtained were inconclusive. However, Wilson (1939) reported observations on a series of patients undergoing artificial fever therapy who developed a severe haemorrhagic diathesis and pronounced hypoprothrombinaemia. As yet it is not clear whether high pyrexia during the course of a disease is in itself capable of hastening the destruction of prothrombin in the blood, but it would appear that in patients with hypoprothrombinaemia a sudden high fever may accelerate the rate of destruction of prothrombin.

In newborn infants a physiological drop in prothrombin occurs after birth and, reaching a low level four or five days later, gradually returns to normal (Brinkhous and others, 1937; Waddell and Guerry, 1939). When this physiological drop becomes marked, haemorrhagic disease of the newborn develops. Castle (1939) has suggested that this condition is a nutritional disease dependent perhaps on a maternal deficiency or on the deficient synthesis of vitamin K in the newborn before the intestinal bacterial flora becomes established. While this may be true it would seem that other factors may also play a part in the production of haemorrhagic disease of the newborn through over-activity of normal physiological processes which occur after birth. Although Kugelmass and Tritsch (1929) reported low prothrombin concentrations in the blood of a mother whose infant developed haemorrhagic disease of the new-

born, the test they used was not specific for prothrombin. Since the introduction of more specific tests and the consequent revival of interest in blood prothrombin concentration in the newborn no reports have been published of a diminished prothrombin level in mothers of infants suffering with haemorrhagic disease of the newborn, nor have we been able to find any reduction of the prothrombin in the mothers of babies with prothrombin deficiency whom we have studied. It is known that in premature infants the physiological reduction in the prothrombin concentration level is greater, and haemorrhagic disease of the newborn is more common, than in infants born at full term (Shettles and others, 1939; Kato and Poncher, 1940). In a premature infant the general body metabolism is much increased, and it may then perhaps be true that a severe fall in blood prothrombin in a newborn infant is an index of an abnormally raised metabolism, with a consequent increase in the normal physiological process of blood-prothrombin reduction.

Hypoprothrombinaemia and the Prognosis of Patients with Liver Disease

Since Quick and others (1935) first reported the association of hypoprothrombinaemia with various types of jaundice numerous authors (Quick, 1938; Butt and others, 1939; Scanlon and others, 1939) have noted that patients with parenchymatous disease of the liver may have a low blood prothrombin which does not respond to therapy with vitamin K and bile salts. This failure of response is due to total or partial failure of the mechanism by which prothrombin is formed. Preliminary observations (Kark and Souter, 1940) on this phenomenon have shown that patients with liver disease and hypoprothrombinaemia may be divided into two main classes: those whose liver disease is so severe and widespread that they are *totally unable* to manufacture prothrombin; and those with more chronic and less widespread liver damage who are able to manufacture *some* prothrombin. In such patients it was not possible to correct the hypoprothrombinaemia by therapy with natural and/or synthetic vitamin K, supplemented in some cases by transfusion or therapy with large amounts of liver. The first group, with severe liver disease, always developed a haemorrhagic hypoprothrombinaemia; and all the patients in this group died within a short time of their admission to hospital. The second group, who also did not respond to therapy, never developed a haemorrhagic tendency (i.e., the blood-prothrombin concentration always remained above 35%), and were eventually discharged from hospital. Further studies have confirmed these observations, and it is now believed that if a patient with liver disease develops a severe hypoprothrombinaemia (below 35%) which is *resistant* to vigorous treatment with parenteral vitamin K in large doses, then the immediate prognosis is very grave. The immediate prognosis of the second group is good, but since they have been studied only during the nine months before writing this paper it has not been possible to assess their prognosis correctly on the basis of the prothrombin level of their blood. It is likely, however, that the Quick test, used in conjunction with vitamin K therapy, may become a useful liver-function test. The following case is illustrative:

A young boy suffering from acute rheumatic fever and severe congestive failure developed an acute parenchymatous hepatitis during his illness. He was extremely ill with cholaemia, and a severe haemorrhagic tendency became evident. On clinical and laboratory evidence he was given a bad immediate prognosis. His prothrombin level at the height of his illness was found to be 24% of normal. Following injection of synthetic vitamin K the prothrombin concentration rapidly and unexpectedly increased to well above the level for haemorrhage, but

remained between 45 and 50% of normal, despite further treatment. On this basis it was felt that his immediate prognosis, notwithstanding the other observations, was good. At present, six months after the acute episode, he has a chronic hepatitis with ascites, and his prothrombin level has not yet returned to normal.

In this patient it is probable that a moderate metabolic disturbance in the manufacture of prothrombin was accompanied by a failure of absorption of vitamin K from the gut because of obstructive jaundice due to hepatic cell swelling, with subsequent pressure on the intrahepatic ducts.

Hypoprothrombinaemia and the Diagnosis of Obstructive Jaundice.—When the patient with intense jaundice and acholic stools presents a problem in differential diagnosis the rapid return of a lowered prothrombin concentration to a normal figure following the administration of adequate doses of parenteral vitamin K is strongly suggestive of obstructive jaundice.

Haemorrhagic Conditions unassociated with Hypoprothrombinaemia.—In patients with haemophilia, purpura haemorrhagica, thrombocytopenia, "idiopathic" menorrhagia, polycythaemia, and other blood dyscrasias the blood-prothrombin levels were within normal limits. When vitamin K was given to some of these patients it was, as anticipated, without effect on their haemorrhagic diatheses. In patients who had bled from peptic ulcers the blood-prothrombin level was but little reduced even when haemorrhage had been severe. This reduction in blood-prothrombin concentration paralleled the amount of prothrombin lost with the blood from the lesion, and was never severe enough to perpetuate the haemorrhage by reason of prothrombin depletion.

Treatment of Hypoprothrombinaemia

The development of synthetic analogues of vitamin K has rendered the use of natural vitamin K, together with bile salts, unnecessary. The synthetic substances are more effective, their dosage is more easily standardized, and they are less expensive to manufacture. Of the numerous known synthetic compounds with vitamin K activity, 2-methyl-1:4-naphthoquinone, described in detail by Ansbacher and Fernholz (1939a), is most active, and it is at least three times as potent as natural vitamin K (Ansbacher and Fernholz, 1939b). This yellow crystalline substance is only slightly water-soluble and is not easily adaptable for parenteral use.

Recently Moore and Kirchmeyer (personal communication) have synthesized a water-soluble compound, 2-methyl-1:4-naphthohydroquinone-3-sodium-sulphonate,* which is made up so that 1 c.cm. of an isotonic solution containing it is equivalent in vitamin K activity to 2 mg. of 2-methyl-1:4-naphthoquinone. This material is potent and easily administered parenterally; no toxic symptoms have been noted referable to its use in the dosage given (Kark and Souter, 1940).

Since the experience in this laboratory has been limited to the use of these two compounds and natural vitamin K no mention will be made of any of the many other synthetic analogues of vitamin K.

Parenteral Therapy

In the treatment of haemorrhage resulting from hypoprothrombinaemia the parenteral compound is most useful, and intravenous administration of the drug is most effective in checking active bleeding; a haemorrhage is controlled within one and a half to three hours after injection, while the blood-prothrombin level rises rapidly and reaches a

normal level within twenty-four to forty-eight hours. A single intravenous injection, however, will not maintain a normal concentration, and the prothrombin level will fall within the succeeding twenty-four hours and may rapidly return to a level at which there is danger of haemorrhage.

A single intramuscular injection, while not so effective in the rapid control of haemorrhage, will, however, maintain a normal level of prothrombin in the blood for some days. It is therefore advisable, in a patient presenting active haemorrhage, to give both intravenous and intramuscular injections of the water-soluble compound in order that the maximum advantage of each route of administration may be utilized in raising the prothrombin concentration of the blood rapidly and in maintaining it at a high level.

When given parenterally, 1 to 3 c.cm. of the water-soluble compound (equivalent to 2 to 6 mg. of 2-methyl-1:4-naphthoquinone) has been found sufficient to control haemorrhagic hypoprothrombinaemia in the presence of a normal liver (see case records and Fig. 3).

In patients with hypoprothrombinaemia who are vomiting actively, or in those patients suffering from gross intestinal absorptive difficulties, one intramuscular injection of 3 c.cm. of the water-soluble compound will usually restore the prothrombin level to normal and maintain it at a high level for from four to six days.

Oral Therapy

The first clinical application of therapy with vitamin K was to treat patients suffering with disease of the biliary passage and hypoprothrombinaemia by the administration of natural or synthetic vitamin K orally in an oily vehicle together with bile salts or bile given by duodenal tube. Many of these patients developed nausea, vomiting, or diarrhoea as a result of taking the bile preparations. Preliminary investigations, however, on a few patients who had complete biliary obstruction (as evidenced by the absence of urobilinogen from their stools) and hypoprothrombinaemia have shown that 2-methyl-1:4-naphthoquinone when made up in tablet form is absorbed from the alimentary canal in the absence of bile salts. In these patients 2 mg. of the material given three times a day will control the hypoprothrombinaemia (see case records and Fig. 4). Smith and Owen (Moore and Kirchmeyer, personal communication) have successfully treated similar cases by administration of a water-soluble naphthol without bile salts.

In patients with nutritional deficiency or in patients with idiopathic steatorrhoea 1 mg. of 2-methyl-1:4-naphthoquinone given daily will usually suffice to control hypoprothrombinaemia or prevent its appearance (Kark and others, 1940).

Prophylaxis

There is good evidence to show that the prothrombin level of babies born of mothers treated with vitamin K before labour is higher than that found in babies of mothers who have not been so treated (Shettles and others, 1939). Ideally, it might be advisable to give pregnant women at least 2 mg. of 2-methyl-1:4-naphthoquinone daily during the last week of their pregnancy, and to feed or inject a similar dose to the baby soon after birth. If the latter therapeutic measure alone were to be adopted as a routine procedure haemorrhagic disease of the newborn would become an extremely rare condition.

It is probable that in the future vitamin K or one of its analogues will be given as a routine pre-operative measure to patients suspected of having hypoprothrombinaemia. It is proper to emphasize at this point that the administration of therapeutic doses of vitamin K or its analogues before operation is not in itself a guarantee that the blood-

* Now known as hykinone, and produced by Abbott Laboratories, N. Chicago, Ill.

prothrombin concentration will be raised to within normal limits. Indeed, in certain patients with liver disease this effect is not accomplished. For this reason it is always necessary to determine the blood-prothrombin concentration immediately before operation, even when vitamin K or one of its analogues has been given in amounts considered adequate. When the prothrombin level is found to be low in spite of such treatment, transfusion of *fresh* blood or plasma is the only known therapeutic measure which can increase the prothrombin concentration of the blood. The indiscriminate administration of vitamin K to patients showing a bleeding tendency without establishing that the condition is one of haemorrhagic hypoprothrombinaemia is to be deplored. Therapeutic failure in such cases may unjustly throw discredit on a valuable and specific remedy.

Illustrative Cases

Case 1 (Fig. 2).—A poorly nourished young girl aged 18 suffering with regional ileitis developed an intraperitoneal abscess

FIG. 2.—Case 1. The effect of intramuscular natural vitamin K (6,000 Dann units) on the blood-prothrombin percentage and haemorrhagic tendency of a patient with regional ileitis.

FIG. 3.—Case 2. The effect of 3 c.c.m. of water-soluble vitamin K on the blood-prothrombin percentage, coagulation time, and haemorrhagic tendency of a patient with stenosis of the common bile duct. (Each cubic centimetre of water-soluble vitamin K is equivalent to 3.2 mg. of 2-methyl-1:4-naphthohydroquinone-3-sodium-sulphonate.)

after a laparotomy. Her post-operative course was extremely stormy. She had hectic fever, diarrhoea, vomiting, and mild dementia. Haemorrhage occurred from the bowel and from the abdominal wound. The blood-prothrombin concentration was markedly reduced, but treatment with 4 c.c.m. of intramuscular natural vitamin K (6,000 Dam units) controlled the haemorrhage and restored the blood-prothrombin level to normal.

Case 2 (Fig. 3).—A woman aged 42 suffering from traumatic stricture of the common bile duct had had recurrent attacks of obstructive jaundice for ten years. During this time she had on many occasions developed a haemorrhagic diathesis, which was uncontrolled by therapy. On her admission to hospital her blood-prothrombin concentration was less than 5% of normal and she was bleeding from her nose and gums. Intramuscular injection of 3 c.c.m. of water-soluble synthetic vitamin K (equivalent to 6 mg. of 2-methyl-1:4-naphthoquinone) controlled the bleeding within one and a half hours, and the blood-prothrombin concentration returned to normal by the next day. Since this time the patient's blood-prothrombin concentration has been maintained at a high level by treatment with injections of the water-soluble compound or by the oral administration of 2-methyl-1:4-naphthoquinone.

Case 3 (Fig. 4).—A woman aged 73, with carcinoma of the pancreas, developed a painless obstructive jaundice which was complete. Marked bruising appeared at the site of a venepuncture and her blood-prothrombin concentration was found to be severely reduced. Oral administration of 2-methyl-1:4-naphthoquinone without the bile salts restored the prothrombin

FIG. 4.—Case 3. The effect of oral administration of 2-methyl-1:4-naphthoquinone without bile salts on the blood-prothrombin percentage of a patient with carcinoma of the pancreas and obstructive jaundice. (Each small block represents 2 mg. of 2-methyl-1:4-naphthoquinone.)

level to normal, and surgical intervention was successfully accomplished without abnormal haemorrhage. While she remained in hospital she was given 4 mg. 2-methyl-1:4-naphthoquinone each day to maintain her blood-prothrombin concentration at a high level.

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