BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 9 1937

THE HAEMORRHAGIC STATES*

BY

L. J. WITTS, M.D., F.R.C.P.

Professor of Medicine, University of London; Director of the Medical Unit, St. Bartholomew's Hospital

I feel considerable diffidence in opening a discussion on the haemorrhagic states. It is a subject on which there has already been too much writing and talking and too little experiment. Moreover, the time is not ripe for a schematic presentation such as we can employ in discussing the anaemias. Here we are not dealing with a single-cell system, but with the complex and interlocking mechanism of haemostasis, in which the plasma, the platelets, the endothelial lining of the vessels, and the connective tissues all participate. It is convenient to distinguish between haemophilia and related conditions, in which the blood does not clot normally, and purpura or haemogenia, in which the blood clots with normal speed but the bleeding time is prolonged. Even this distinction is not absolute, for there are conditions, such as melaena neonatorum, which combine the features of haemophilia and haemogenia; a defect in the plasma may not only affect the coagulation of the blood but also interfere with the agglutination of the platelets and the opsonization of the endothelium, so giving rise to phenomena more characteristic of purpura. And in some haemorrhagic states, especially those due to inherited fault, the usual clinical and laboratory tests for a haemorrhagic tendency may be negative in the face of a manifest tendency to bleed excessively. For the purpuras I propose to follow the classification recently given by Davidson (1937) into idiopathic or symptomatic as regards their aetiology, and thrombocytopenic or non-thrombocytopenic as regards their morphology. Let us agree that platelet and vessel wall are both concerned in purpura haemorrhagica and eschew controversy on their relative significance. I wish to treat the haemorrhagic states pragmatically and to isolate certain elements in a purely observational and empirical way, hoping thus to simplify the underlying complexity.

Hereditary Haemorrhagic States

I am increasingly impressed by the frequency and diversity of hereditary haemorrhagic diseases and by their resistance to treatment. The study of hereditary diseases in man has been vitiated by premature dogmatism and by the expectation of a constancy in the mode of inheritance which the student of genetics in plants and animals would from the first have thought improbable. Hereditary haemorrhagic states in man are not subject to immutable laws in pattern and pedigree, and it is wiser to think in terms of affected family groups than of specific diseases and laws of heredity. The hereditary haemorrhagic diseases provide some of the most pathetic cases we see; and it is natural that we should strive to

do everything possible to relieve them. Nevertheless their suffering is not lightened by the publication of methods of treatment which time proves to have no curative value. The local application of coagulant snake venoms is the only new treatment whose value has been confirmed. The venom of Russell's viper (1 in 10,000 solution) or of the Australian tiger snake (1 in 5,000 solution) has been chiefly used (Macfarlane and Barnett, 1934; Rosenfeld and Lenke, 1935). Loose clot is washed away from the bleeding point, and tampons or other appropriate dressings soaked in the venom solution are then applied. With the use of snake venom in haemophilia it is now possible to repair wounds or to carry out small operations such as dental extraction which would previously have been fatal.

Other new treatments have already passed into the limbo of discarded things or show signs of passing there, as they have not lived up to the claims made for them. Any curative action of liver or oestrin in haemorrhagic states has by now been abundantly disproved. It will be interesting to hear the results of trials of the Sheffield treatment of haemophilia with an extract of egg albumen (Timperley *et al.*, 1936). Dr. R. G. Macfarlane and I have had no success whatsoever in four haemophiliacs treated by this method. Injections of moccasin snake venom have been recommended for all forms of chronic and recurrent bleeding, especially those of a purpuric type (Peck *et al.*, 1935, 1936). It is difficult to test a remedy which admittedly makes no difference to the platelets, the coagulation time, or the bleeding time. In three cases of hereditary thrombasthenia I have had no success with treatment with moccasin snake venom, and Davidson (1937) records a similar lack of success with this treatment in idiopathic thrombocytopenic purpura. Moccasin snake venom is reported to be more successful in hereditary telangiectasia, and in one case of this disease where I advised its employment there was a temporary remission of symptoms, but it was soon followed by relapse in spite of continuing treatment. Eugenists may derive a melancholy satisfaction from this catalogue of failures in the treatment of the hereditary haemorrhagic states, and there is no doubt that prevention will always be better than cure. All the same, work at present being carried out in Holland (Bendien and van Creveld, 1935, 1936, 1937) and America (Patek and Stetson, 1936; Patek and Taylor, 1937) suggests that a curative treatment for haemophilia may not for ever elude our grasp.

The Platelets and the Spleen

Idiopathic thrombocytopenic purpura stands out more clearly now that we have been able to detach from it the hereditary purpuras, the allergic thrombocytopenic

* Read in opening a discussion at a joint meeting of the Sections of Medicine, and Pathology, Bacteriology, and Immunology at the Annual Meeting of the British Medical Association, Belfast, 1937.

purpuras due to sensitivity to foods and drugs, and the symptomatic thrombocytopenic purpuras due to destruction of the foci of platelet production in the marrow by organic and inorganic poisons. There are no gross changes in the spleen in idiopathic thrombocytopenic purpura, apart from simple hyperplasia, and the only abnormalities in the marrow are some increase in number and decrease in maturity of the megakaryocytes. We still do not know whether the disease is due to a diminished production or an increased destruction of the platelets. The dramatic results of splenectomy are somewhat discounted by the discovery that within an interval of months or years about half the patients relapse, though as a rule symptoms are much less troublesome than before the operation (Pemberton, 1934; Williamson, 1934). This discovery suggests that splenectomy is not a cure for idiopathic thrombocytopenic purpura in the same sense as it is a cure for acholuric jaundice. Remissions of thrombocytopenic purpura after splenectomy, like remissions of pernicious anaemia following this operation, are apparently due to "the lifting of a mysterious restraint which the spleen exercises upon the delivery of immature blood cells by the marrow" (Cornell, 1927), and do not signify any fundamental change in the underlying disease process. In making these reflections on splenectomy—for I do not call them criticisms—I am mindful of the fact that medical treatment is purely symptomatic and its results inferior to those of surgery (Brown and Elliott, 1936). It is true that there has recently been a revival of interest in treatment by x rays (Mettier and Stone, 1936; Rudisill, 1936), but I should like to hear comments on its value, for it is my impression that x-ray failures have not received the same publicity as x-ray successes.

The mortality of splenectomy in acute attacks of idiopathic thrombocytopenic purpura has been greatly reduced by the practice of repeated or massive transfusions, but in view of the frequency of spontaneous recovery, the difficulty of diagnosis from infectious and malignant purpuras, and the inability to promise complete security from relapse, I should like to ask how long we should persevere with medical treatment before asking the surgeon's help. My present opinion is that medical treatment should be tried for seven to ten days. In chronic cases the operative mortality is small, but I should advise restricting splenectomy to patients in whom the disease is really disabling or is subject to acute exacerbations. There are two other matters connected with splenectomy on which I should like to hear people's experiences. The first is the value of tests with adrenaline or protein shock before splenectomy. Does an increase of platelets in the blood after either of these agents indicate that the operation is likely to be successful, and is the reverse also true? The second question is, How often is relapse due to the growth of a spleniculus? I know that this phenomenon has been described, but when we compare the frequency of relapse in idiopathic thrombocytopenic purpura with its rarity in acholuric jaundice we must doubt whether growth of a spleniculus is a common explanation of relapse, and certainly I should hesitate to advise a second operation.

Vitamin C

The outstanding event of the last decade in the haemorrhagic diseases has been the isolation and synthesis of vitamin C or ascorbic acid. It can now so easily be administered in large doses by mouth or by injection that it has been tried in many diseases, and there has been a spate of papers, comparable with those which followed the introduction of insulin and liver extract,

suggesting that ascorbic acid is a panacea for all kinds of haemorrhagic states and extending its range of usefulness even to dropsy and leukaemia. It is fortunate that at the same time methods have been devised for the estimation of vitamin C in the body fluids, and the test of the resistance of the capillaries has been put on a quantitative basis. It has been shown that while overt scurvy is rare in civilized countries subclinical scurvy is not uncommon, especially in patients who are febrile or who take special diets. Vitamin C cures scurvy rapidly and dramatically, but it has no action on haemophilia, thrombocytopenic purpura, Hensch-Schönlein purpura, leukaemia, or other non-scurvitic haemorrhagic states. It may be that patients with these diseases sometimes suffer in addition from subclinical scurvy, and that the removal of this disability may make all the difference to the appearance of symptoms. Unfortunately this has not been my experience, and I have given massive doses of vitamin C by the mouth and by the veins in these diseases without benefit.

Mrs. W., aged 29, had had symptoms of idiopathic thrombocytopenic purpura for at least two months. Her excretion of vitamin C in the urine was normal (26 mg. daily), and she excreted 729 mg. out of an intravenous test dose of 1,000 mg. of ascorbic acid, suggesting that her tissues were well filled with the vitamin. She was treated for a week with ascorbic acid, 300 mg. intravenously every day; but she had menorrhagia, and her haemoglobin level fell from 65 to 50 per cent. She was then submitted to splenectomy, and her symptoms were much improved. Her platelets remained low throughout, never rising above 40,000 per c.mm.

Miss C., aged 32, had a relapse of symptoms of idiopathic thrombocytopenic purpura twelve months after splenectomy. Less than the normal amount of vitamin C was present in the urine (12 to 24 mg. a day) and only a small fraction of a test dose of 600 mg. of ascorbic acid by mouth was excreted. She was treated for sixteen days with a high vitamin C diet plus 300 c.cm. of orange juice daily, but there was no change in the bleeding tendency or in the number of platelets, which fluctuated about 10,000 per c.mm.

Norman T., aged 15, who suffered from hereditary thrombocytopenic purpura, had a low urinary excretion of ascorbic acid (6.6 mg. a day) and required approximately 2,000 mg. of ascorbic acid to attain normal excretion. He was treated with daily intravenous injections, receiving 4,500 mg. in thirteen days without change in the haemorrhagic tendency or in the number of platelets, which remained about 30,000 per c.mm.

Miss A., aged 36, who suffered from non-thrombocytopenic purpura of many years' duration, associated with splenomegaly and chronic infection of the parotid glands, had a high output of ascorbic acid in the urine (47 mg. daily). As might have been expected, intravenous injections of ascorbic acid in amounts varying from 300 to 900 mg. daily had no effect on the purpura.

William B., aged 15, suffered from a hereditary haemorrhagic diathesis—probably thrombasthenia. His excretion of vitamin C in the urine was low (15 mg. daily). After taking 400 mg. of ascorbic acid a day by mouth for three days he still excreted only 143 mg. in twenty-four hours, so his tissues must have been deficient in vitamin C. He was then treated with a high vitamin C diet and orange juice, 300 c.cm. daily, but the experiment was discontinued after five days, as he had a slight fall and sustained excessive bruising of the face and eye.

I have treated three cases of chronic ulcerative colitis with massive doses of vitamin C, by mouth and parenterally, without affecting the number or composition of the evacuations or the condition of the patient; and three cases of acute leukaemia without affecting the haemorrhagic tendency, the oral lesions, the blood picture, or the fatal termination. I therefore feel justified in concluding that vitamin C, by mouth or parenterally, is of no value as a general or non-specific remedy for haemorrhagic states. In purpura haemorrhagica

the excretion of vitamin C may be normal or subnormal according to our present standards, but in either event vitamin C has no effect on the symptoms or the signs of the disease.

Wilbur (1937) comes to the same conclusion in a review of papers published on vitamin C, and it would appear as if those who have reported improvement have paid too little attention to the facts that many haemorrhagic states recover spontaneously and that diseases as serious as acute leukaemia may show temporary remissions. Vitamin C now takes its place with liver extract, iron, thyroid, and pentnucleotide as a remedy which has a well-defined and restricted sphere of action on the blood and its containing vessels. It is not my intention to minimize that sphere of action, as I believe that subclinical and atypical scurvy is a good deal commoner than most of us used to believe. Archer and Graham (1936) and others have shown that many patients with peptic ulcer suffer from subclinical scurvy, and that it is specially important to secure saturation with vitamin C in the face of haemorrhage or operation. Ingalls (1936) regards subclinical scurvy as an important factor in chronic subdural haematoma. Latent scurvy should be suspected whenever unexplained bleeding occurs in patients with alcoholism or with dietetic or digestive abnormalities, and the diagnosis should be clinched by chemical estimation of the vitamin in the body fluids, if possible, and by observation of the effect of treatment on the symptoms and the capillary fragility. In neither of the following two cases was the vitamin C content of the blood or urine estimated, but they nevertheless suggest that avitaminosis C due to defective diet may favour the occurrence of subcutaneous bleeding in hyperpiesia and nephritis. It will save time to state that in both men the blood count, platelets, bleeding time, and coagulation time were normal.

Peter F., aged 55, had been working with a metal drill pressed against his lower abdomen, as he had done many times without incident before. A day or so later his temperature rose, and it was discovered that he had a wide extravasation of blood over the pubes and perineum, passing on to the penis and scrotum. There was also a bruise on the right forearm. He had had dysentery twenty years before, and since that time had avoided fruit and green vegetables. He had had a cloud of albumin in the urine for many years, and the blood pressure was 210/120, though the blood urea was only 23 mg. per 100 c.cm. There were no other abnormal signs, and the temperature returned to normal in ten days. He was treated with a high vitamin C diet, including orange and tomato juice. Two months later there had been no recurrence of the bleeding and the tourniquet test was negative.

Albert C., aged 49, presented himself with a spontaneous large bruise on the right shoulder. He had had gout for eight years, and a year before had had an attack of unconsciousness suggestive of hypertensive encephalopathy. He drank six pints of ale a day, and his meals were hurried and irregular. The urine contained a trace of albumin, the blood urea was 76 mg. per 100 c.cm., and the urea clearance in the urine was only 26 per cent. of the normal. The blood pressure was 185/120 and the tourniquet test was positive. He was treated by restriction of alcohol, a high vitamin diet, atophan three days a week, and ascorbic acid 100 mg. a day by mouth on the other four days. Two months later he had had no more bleeding and the tourniquet test was negative, although the blood pressure had risen to 240/150.

Nutrition and Haemorrhage

Even more important than the isolation of ascorbic acid is the impact of biochemistry on the haemorrhagic states, the ability to reproduce them in animals, and the exchange of fertilizing ideas between ward and laboratory. The bearing of nutrition on the haemorrhagic states is not limited to scurvy and vitamin C. Szent-Györgyi (1936)

and his colleagues were at first disappointed to find the action of pure ascorbic acid limited to scurvy, as they had successfully treated cases of non-thrombocytopenic purpura with impure preparations of vitamin C. They have now isolated from these sources a substance, flavon, which they have called vitamin P, as they believe it influences the permeability of the vessels. Nothing is more difficult than to establish criteria for capillary permeability and its variation in haemorrhagic states, nor is it easy to prepare large quantities of flavon. For these reasons little further progress has been made on these lines.

Fanconi (1928) in his work on intestinal infantilism noted not only scurvy but also a condition resembling haemophilia, due to a defect in the coagulating power of the plasma. Other paediatricians have observed the same phenomenon in undernourished children, and have been able to relieve it by a diet rich in protein (Kugelmass, 1932). Prothrombin is present in abnormally small amounts in the blood of the newborn infant, and it is probable that the haemorrhagic disease of the newly born, melaena neonatorum, is due to depression of prothrombin below a certain critical level (Brinkhous *et al.*, 1937). A disorder characterized by a lack of prothrombin in the plasma has been produced in birds by a defective diet (Dam *et al.*, 1937). Haemorrhagic chick disease is due to deprivation of a fat-soluble vitamin, the Koagulations-Vitamin or vitamin K, which is present in mammalian liver, egg yolk, and certain vegetable substances such as alfalfa. It is doubtful whether haemorrhagic chick disease can be exactly duplicated in mammals. A very similar disorder, the sweet clover disease of the rabbit, is likewise due to lowering of the prothrombin in the plasma, but though it is a dietetic disease it does not appear to be identical with haemorrhagic chick disease, and while it can be cured by extracts of alfalfa the curative fraction is said to have properties different from those of vitamin K (Quick, 1937). At present it is not clear what bearing these discoveries will have on human therapeutics. Liver and vitamin K have no action on hereditary haemophilia, but there remains a wide field for study in the treatment of melaena neonatorum and the haemorrhagic manifestations of malnutrition and disease of the liver.

In the paper from which I have previously quoted, Kugelmass (1932) advised a diet rich in fat and vitamin D to increase the platelets in purpura haemorrhagica. The literature of the use of vitamins A and D in the haemorrhagic states is confusing and contradictory. Vitamin A almost certainly has no haemostatic properties. Vitamin D, calcium, and parathormone form a mysterious trinity whose aid has been invoked in especial against the haemorrhagic symptoms of diseases of the liver, though they have been recommended in all forms of morbid haemorrhage (McNealy *et al.*, 1935; Lowenburg and Ginsburg, 1936). The evidence for any direct action on the platelets, the endothelium, or the coagulation mechanism *in vivo* is not convincing, and it is probable that any lessening of the morbid haemorrhage of jaundice results from the ability of calcium salts to neutralize the effects of cholaemia (Minot and Cutler, 1928). There is now some hope that this confusion may be clarified by the work of Schiff and Hirschberger (1937), who claim to have increased the platelets in normal and thrombocytopenic children by the administration of a fat-soluble factor that is different from vitamins A and D. This substance, which they have called vitamin T, is present in egg yolk and oil of sesame but not in cod-liver oil and olive oil. They suggest that effects have been attributed to vitamins A and D which were really due to the

solvents in which they were administered. These claims should be readily susceptible of proof or disproof.

It is now the duty of clinical research workers to test on human patients the permeability vitamin flavon, the coagulation vitamin K, and the thrombocyte vitamin F. It is much to be hoped that a higher standard will be attained in tests of this kind than was shown in the advocacy of oestrin, liver extract, and vitamin C for haemophilia and purpura haemorrhagica. Acute cases are rarely suitable, as they so rapidly recover spontaneously and it is hard to obtain numbers large enough for proper controls. Chronic cases of a well-defined type are much better, and they should preferably be idiopathic and not symptomatic in origin. There should be an adequate period of observation before treatment is begun. The isolation of insulin was largely due to the development of simple methods of estimating the blood sugar, and the application of liver therapy was much helped by the use of the reticulocyte crisis. In the same way objective criteria should be used in assessing the value of remedies for the haemorrhagic states—the number of platelets, the capillary resistance, the bleeding time and coagulation time, the retraction of the clot, and in special cases the plasma proteins, fibrinogen and prothrombin.

Summary

1. Hereditary haemorrhagic states show considerable diversity in symptoms and mode of inheritance.

2. The local application of coagulant venoms is the only considerable advance of recent years in the treatment of the haemorrhagic diseases. The value of liver, oestrin, moccasin venom, and the Sheffield extract of egg albumen has not been confirmed.

3. Splenectomy remains the most successful treatment for idiopathic thrombocytopenic purpura, but the frequency of relapses suggests that the operation is a temporary stimulus to platelet production rather than a specific cure for the disease.

4. Vitamin C is of value only in scurvy, whether overt or latent. It is not a general or non-specific remedy for haemorrhagic states. Nevertheless the isolation of ascorbic acid is of especial importance, as it marks the impact of biochemistry on the haemorrhagic states and a probable improvement in the technique of investigation.

I am indebted to Messrs. Hoffmann-La Roche for generous supplies of ascorbic acid and sodium ascorbate; to Dr. H. E. Archer for many estimations of vitamin C in the urine; and to the Medical Research Council for a grant for technical assistance.

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THE CLINICAL PATHOLOGY OF HAEMORRHAGIC STATES *

BY

S. C. DYKE, D.M., F.R.C.P.

Pathologist, The Royal Hospital, Wolverhampton

The development of the haemorrhagic state depends upon the escape of the red cells through the unbroken capillary wall; it may result from various causes. For the determination of the prognosis and the initiation of appropriate treatment accurate diagnosis is desirable. In none of the haemorrhagic states can this be made without the assistance of laboratory methods; in few of them, however, can it be established by laboratory methods alone. Usually it calls for the intelligent consideration of both laboratory and clinical data.

The first step in the laboratory investigation of any case of the haemorrhagic state will consist in the examination of the blood picture. This as usually understood comprises an estimation of the haemoglobin percentage, an enumeration of the red and white cells of the blood, a differential count of the white cells, and a report on the morphological characteristics of the formed elements of the blood—the red and white cells and the platelets. For the satisfactory investigation of the blood picture it is highly desirable that the specimens for each of the examinations mentioned should be taken in the appropriate manner straight from the patient. Preparations made from specimens of blood collected for transmission into oxalate or any other anti-coagulant are usually unsatisfactory and often are quite useless.

Bleeding Time

In the act of taking the specimen of the blood valuable information may be gained as to the bleeding time. No satisfactory quantitative method exists for this determination. Using a large-sized, bayonet-pointed surgical needle and making the puncture after slight massage in the lobe of the ear, the bleeding normally stops well within a minute; usually it is necessary to use a little force to express drops of blood after the first two or three minutes. If after the first two or three drops the blood continues to exude the bleeding time may be taken to be prolonged. In certain cases associated with gross platelet deficiency, such as thrombopenic purpura (purpura haemorrhagica), aplastic anaemia, and lymphatic leukaemia, the bleeding from a simple puncture may persist for many minutes—if unchecked, even for hours.

* Communicated to the Sections of Pathology, Bacteriology, and Immunology, and Medicine, at the Annual Meeting of the British Medical Association, Belfast, 1937.