HAEMORRHAGIC STATES*

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The haemorrhagic disorders have afforded interesting problems in medicine and surgery for thousands of years. More advances have been made in our knowledge of these conditions since the turn of the century than in any previous half-century since probable haemophilia was described in the Jewish Talmud in the second century A.D. It is impossible to detail the whole field here, but some of the diagnostic and therapeutic problems which have been of special personal interest for many years will be given more fully. Elsewhere in this issue haemophilia and platelet function are made special topics.

Diagnosis of a Haemorrhagic State

Points in favour of such a condition include haemorrhage from different parts of the body and abnormal bleeding since childhood or for many years. Study of a complete family tree may supply invaluable evidence of a similar state in blood relatives, while local bleeding from mucosae without a demonstrable organic lesion and haemorrhage into deep tissues and/or joints without a history of severe trauma are supportive. The necessity for blood transfusion after tonsillectomy and/or dental extraction, and haemorrhage for more than 24 hours after nose and throat operations, are suggestive. Abnormal haemorrhage is a not uncommon event in dental practice today. Thus, for example, 183 cases were treated at the Royal Hospital, Sheffield, during an eight-month period in 1957 (Rastall, 1958). Some 10 of these patients who bled for more than 48 hours after dental extraction had haemorrhagic disorders, the rest being due to sepsis and trauma.

Main Type of Haemorrhagic State

The fundamental defect(s) may be of (1) capillary and/or platelet origin and/or (2) coagulation abnormalities. Spontaneous petechiae or intradermal ecchymoses, spontaneous bleeding from mucosae and the presence of a disease known

to be associated with a platelet and/or capillary defect such as leukaemia, carcinomatosis, myelomatosis and aplastic anaemia favour the former group. Haemorrhage which is not limited to skin and mucous membranes and that usually related to trauma (deep haematomata, haemarthroses), favour a coagulation defect, as does slow persistent oozing from the skin and/or mucosae.

Tests for Capillary and/or Platelet Abnormalities

These include capillary resistance tests of tourniquet and negative pressure types, the bleeding time, platelet count and morphology, microscopy of the nail-fold capillaries, and bone marrow examination.

Haemorrhage due to Capillary Defects *Symptomatic*

Infections including bacterial endocarditis, influenza, nephritis, scarlet and typhoid fevers, and meningococcal septicaemia may also be associated with thrombocytopenia in the severer phases. Drugs and poisons causing this type of purpura include quinine, largactil, belladonna and snake venom. Scurvy, metabolic states (anoxia, hypertension, diabetes mellitus, uraemia—there may also be thrombocytopenia and/or thrombocytopathy here too—hypothyroidism), and mechanical trauma (convulsions, whooping cough, etc.) may be responsible. Finally, senility is a not uncommon cause of purpura, especially on the backs of hands and wrists.

Allergic Purpuras and Sneddon's Purpura

Henoch and Schönlein purpuras and purpura simplex constitute the main group. Here the purpura is due to protein sensitivity and may be precipitated by a food, e.g. tomato or by an infection, especially streptococcal, or there may be no such apparent factor. It is probable that there is a close connection with rheumatic fever and acute nephritis.

Attacks of fine purpura, accompanied by malaise, occur especially on the limbs in purpura simplex.

*Based on a lecture given to Sheffield Medical-Chirurgical Society on November 14, 1957.

In severer cases urticaria may be seen and there are all gradations of severity between this and visceral and joint involvement. Henoch's purpura typically presents with abdominal colic and melaena due to an effusion of blood and serous fluid into the wall of the intestine. Occasionally intussusception is seen, also numerous scars of abdominal operations. Painful periarticular swellings without haemorrhage into the joint occur in the Schönlein type of purpura. Any combination of the three main groups may be seen, and haemorrhages may occur into muscles, or the central nervous system, while haemorrhagic nephritis is another relatively rare complication. Relapses are common. Severer cases show a polymorph leucocytosis, the tourniquet test may be positive and abnormal nail-fold capillaries may be seen. There are no other relevant haematological changes.

Treatment consists of bed rest and the elimination of septic foci and dietetic factors with desensitization if indicated. Antihistamines and adrenalin may give symptomatic relief, also steroid hormones, and especially ACTH, but relapses are common although the prognosis for life seems to be good.

Sneddon (1957), in his review of purpuras as seen by the dermatologist, describes an entity of generalized purpura with increased capillary fragility complicating orthostatic or varicose purpuric eruptions. A theory is advanced that generalized capillary damage may be a result of a phenomenon similar to auto-sensitization eczema. One has been privileged to see these and other similar cases. Apart from a positive tourniquet test and abnormal capillaries on microscopy, the usual screening haematological tests have been normal.

Hereditary Haemorrhagic Telangiectasia

Localized collections of non-contractile capillaries which blanch under pressure constitute this hereditary condition which is transmitted as a non-sex-linked Mendelian dominant. The telangiectases occur most obviously in the nose, on the lips, tongue, face, fauces, and round the nails of fingers and toes. However, they may be widespread and give rise to haematemesis, melaena, haematuria, and menorrhagia, besides epistaxes. One has seen cases with involvement of the liver, retina, and conjunctiva, while pulmonary arteriovenous aneurysm and other congenital abnormalities occur.

Local treatment, often unsatisfactory, consists of cauterization, application of radium plaques, arterial ligation, and the use of styptics such as topical thrombin or fibrin foam. The author has been impressed with the treatment recommended

by Koch, Escher, and Lewis (1952). Women are given 0.25 mg. of ethinyl oestradiol daily at the outset, and men 0.5 mg. of the same drug plus 5 mg. of methyl testosterone daily. The usual toxic side effects of oestrogen therapy, such as sodium and water retention, and gynaecomastia in the male, and methyl testosterone jaundice, have to be kept in mind. It is possible to reduce the dosage to a maintenance level, e.g. a personal case who developed sensitivity to ethinyl oestradiol as shown by nausea and abdominal discomfort 15 minutes after administration remains free from bleeding so long as he takes 12 mg. of chlorotrianisene once every 10 days.

Ehlers-Danlos Syndrome

This rare condition of abnormal elasticity and fragility of the skin, and abnormal capillary fragility, appears to be inherited in some cases as a simple dominant. It is characterized by abnormal stretching of scar tissue, pouches of skin round the elbows and knees, hyperextensibility of joints, epistaxes, menorrhagia, melaena, large haematomata, pseudo-tumours over bony prominences and nodules beneath the skin, in varying combination. While a degree of pessimism may seem warranted in some cases at the outset, one has been impressed with the satisfactory outcome regarding things which really matter in life, e.g. one patient who had had severe rectal bleeding negotiated pregnancy, delivery and the puerperium in a perfectly normal matter.

von Willebrand's Disease

This state, which is sometimes known as hereditary pseudohaemophilia or constitutional thrombopathy, was first described by von Willebrand in 1926 and 1931. It is usually described as a rare disease and given but scant mention in haematological text-books. In one personal series, however, 88 cases of haemophilia and Christmas disease were seen over the same period of time as 127 cases of von Willebrand's disease. It is a hereditary dyscrasia of capillaries, often, but not always, transmitted as a non-sex-linked Mendelian dominant. In 100 per cent. of personal cases, microscopy of the nail-fold capillaries has shown abnormal tortuosity, calibre variation and usually defective contractility to trauma of some forms, while the bleeding time has been prolonged during bleeding phases and often normal in between these. Similar remarks apply to the capillary resistance tests as to the bleeding time.

The disease resembles haemophilia, in that there may be excessive bruising and bleeding from minor cuts, and persistent bleeding from nose, mouth,

uterus, gastro-intestinal tract and urinary tract. While, typically, there is no associated blood coagulation or platelet abnormality, some cases have an additional deficiency of anti-haemophilic factor (A.H.F.). Personal cases include nine males and three females. Furthermore, another female patient appears to have Christmas factor deficiency in addition to the capillary defect. One wonders how many cases of haemophilia reported in the female are in fact cases of von Willebrand disease plus A.H.F. deficiency. Purpura may be evident, and many personal cases have presented due to haemorrhage after dental surgery or surgery on the nose, mouth and throat. Indeed, official surgery as the above or, for example, vaginal hysterectomy seems particularly liable to give trouble due to haemorrhage, while other types of surgery may be less fraught with hazard. Thus, for example, one patient with severe haemorrhage following dental extractions experienced no such trouble with partial colectomy for neoplasm.

So far as treatment is concerned, the haemoglobin level should be kept above 75 per cent. as anoxia has an adverse effect. Local pressure, haemostatics and palliative therapy may be indicated. Steroid hormones and ACTH in theory should be of assistance, but in fact are usually disappointing. Planned surgery should, ideally, only be performed during phases associated with a normal bleeding time. Local haemostasis is important, e.g. there is much to be said for routine suturing of the gums following dental extractions. If there is an associated A.H.F. or Christmas factor deficiency, treatment must be modified accordingly.

Haemorrhage due to Platelet Defects

Drugs

These are a common cause of purpuric eruptions, and a careful history with persistent leading questions may be necessary. They may act as Sedormid (Ackroyd, 1949a, 1949b, 1951) and quinidine (Bolton, 1956) by the production of a thrombocytolysin, although even here a capillary factor is involved (Ackroyd, 1955). Drugs such as benzol and metals depress megakaryocytic function in the bone marrow. A large variety of drugs may cause purpura, e.g. carbromal, DDT, procaine penicillin, mersalyl, isoniazid, etc., and much depends upon individual sensitivity.

Disease of Bone Marrow

This may be primary or secondary. The former group includes aplastic and hypoplastic anaemia, congenital hypoplastic thrombocytopenia, leukaemia, myelomatosis, and pernicious anaemia, and the latter acute specific fevers, drugs, irradiation effects, secondary carcinomatous deposits, and cachectic states.

Hypersplenism

Hypersplenism may be seen in the Banti and Felty syndromes, Hodgkin's disease, lymphosarcoma, etc. In this group of cases there is a normal or increased bone marrow production of platelets which are destroyed in the spleen.

Idiopathic Thrombocytopenia

This disease, which is commonest in young adults, is characterized by haemorrhages into the skin and mucous membranes, a low platelet count with abnormal forms, a prolonged bleeding time, and increased calibre variation and tortuosity of nail-fold capillaries with defective contractility to trauma. This vascular defect, hypersplenism, the presence of platelet antibodies, endocrine factors and, last but not least, marrow dysfunction causing defective production, maturation or release of platelets probably all play a part in aetiology. The disease may precede frank disseminated lupus erythematosus and, very rarely, it may occur during pregnancy only.

Serious haemorrhage usually responds to relatively fresh blood or platelet transfusions. ACTH and steroid hormones may control and cure the disease, but in very many cases maintenance is necessary. As the results of splenectomy are generally excellent, more now believe that this operation should be performed at the first favourable opportunity in such cases under an ACTH or steroid umbrella.

Very rare diseases somewhat resembling this are hereditary haemorrhagic thrombasthenia, and granulopenic thrombopathy. Both are associated with a normal platelet count, but with abnormal platelet function.

Massive Blood Transfusion

This may cause thrombocytopenia even though the blood be compatible (Krevans and Jackson, 1955).

Thrombotic Thrombocytopenic Purpura

Symmers (1956) has reviewed this rare disease of unknown aetiology, which is characterized by thrombocytopenic purpura, haemolytic anaemia and transient neurological signs and symptoms. Platelet thrombi are found in large numbers in arterioles and capillaries throughout the body.

Haemorrhagic Thrombocythaemia

Elderly males especially suffer from this rare disease which is characterized by increased (functionally defective) platelet production in the bone marrow and by thromboses and haemorrhages,

and sometimes splenomegaly. The author has found splenic irradiation, triethylene melamine, and chlorambucil to be helpful therapeutic agents in this condition.

Haemorrhage due to Defects in Blood Coagulation

These may be divided into those due to (1) a deficiency of plasma factors, (2) circulating anticoagulants, (3) fibrinolysis, and (4) dysproteinaemias. Possible methods of investigation and differentiation are given by Biggs and Macfarlane (1957), to whom the author is greatly indebted, and by Blackburn (1955).

Hereditary Defects

Haemophilia and Christmas disease are inherited typically as sex-linked recessive factors, the male suffering from the disease and the female transmitting it. A non-sex-linked dominant history is found in congenital factor V and factor VII deficiencies, while congenital fibrinopenia is transmitted as a non-sex-linked recessive factor and there is usually a history of cousin intermarriage. Abnormal haemorrhage since early childhood obviously favours a hereditary defect.

Acquired Defects

A negative family history and onset later in childhood or later in life support a diagnosis in this group.

1. DEFICIENCY OF PLASMA FACTORS

Haemophilia is the subject of a separate paper in this journal. It is probably the best-known member of this group of diseases and its separation from the serum (not plasma) deficiency of Christmas disease is largely thanks to the work of Biggs and Douglas (1953) on the thromboplastin generation test (T.G.T.). Since then a number of other and rarer thromboplastin generation deficiencies have come to light, e.g. Stuart clotting defect (Graham, Barrow and Hougie, 1957), Hageman factor deficiency (Jim and Goldfein, 1957), plasma thromboplastin antecedent (P.T.A.) deficiency (Rosenthal, Dreskin and Rosenthal, 1953), P.T.F.-D. deficiency (Spaet, Aggeler and Kinsell, 1954), and Prower factor deficiency (Denson, 1958). These factors seem to be definite entities as shown by cross-correction tests, apart from the Stuart and Prower factors which are probably identical (Dische, 1958). It is particularly interesting to note that Prower factor deficiency interferes with thromboplastin generation, while factor VII deficiency does not do so. Recently Nour-Eldin and Wilkinson (1958) have introduced a stimulating new concept of a clotting inhibitor in haemophilia and Christmas disease plasma, the Bridge

anticoagulant, but it is absent in cases of von Willebrand's disease with A.H.G. deficiency (Wilkinson, Nour-Eldin and Israels, 1958).

We have found the booklet entitled 'Haemophilia. Some Useful Notes and Advice,' 1956, issued by the Ministry of Health and Department of Health for Scotland, to be particularly useful in helping patients and their relatives. I would emphasize the value of sound conservative dental therapy and the closest co-operation between dental surgeon and haematologist. For most dental cases my colleagues at the Charles Clifford Dental Hospital, Mr. R. Rastall, and Professor G. L. Roberts and I find oral antibiotic therapy, fresh frozen plasma given immediately before operation, and efficient dental splinting to be adequate if not more than two teeth (ideally adjacent) are removed at any one time. For larger operations in this and other fields, concentrated human plasma kindly supplied by Dr. W. d'A. Maycock and beef A.H.F. kindly delivered through Dr. Rosemary Biggs, have been used to good effect. Biggs (1957) and Macfarlane and Biggs (1959) review these and other therapies.

Factor V (labile factor) deficiency gives an abnormal 1-stage prothrombin time and a plasma deficiency in the T.G.T. It may be congenital and occurs more commonly in liver disease, leukaemia, carcinomatosis, acute infections, and following massive blood transfusions.

Factor VII deficiency is associated with an abnormal 1-stage prothrombin test, but the T.G.T. is normal. It is usually associated with true prothrombin deficiency in obstructive jaundice, steatorrhoea and treatment with the dicoumarin drugs. Rarely the deficiency may be congenital.

True prothrombin deficiency, in which the 1-stage prothrombin test may be normal or near normal thus requiring a 2-stage test for its demonstration, may be congenital extremely rarely. It occurs in liver disease, during treatment with the dicoumarin group of drugs and in the vitamin K deficiency of the newborn.

Fibrinogen deficiency is very rarely congenital, and may be found in liver disease, tuberculosis, scarlet fever, and fibrinolytic syndromes.

Finally, plasma defects may occur in combination, e.g. factor VII plus Christmas factor deficiency, factor V deficiency plus haemophilia, etc.

2. CIRCULATING ANTICOAGULANTS

These may represent antibodies formed by transfusion or pregnancy. They may interfere with human thromboplastin formation and utilization, or be of heparin type following especially irradiation and other antimitotic therapy. While some cases are idiopathic, others are associated

with collagen diseases and infections such as tuberculosis. Hougie (1955) reviews the field.

3. DEFIBRINATION SYNDROMES

These occur in pregnancy (premature separation of the placenta, intrauterine death, amniotic embolism, hydatidiform mole), following operations on the lung and brain occasionally, and in relation to prostatic disease, especially malignant. Fibrinolysis may also be stimulated by plasma or blood transfusion reactions, and occur in cirrhosis of the liver and in leukaemia. Of the rapid methods for fibrinogen assay, one has found that of Scott (1955) to be particularly useful. The 1-stage prothrombin test and the platelet count may be abnormal too. Treatment with fibrinogen intravenously has dramatic results (Swan, Wood and Daniel, 1957), while fresh blood is needed in associated factor V deficiency, and parenteral calcium with renal damage. Dextran should be avoided as it forms a dextran-fibrinogen complex.

4. DYSPROTEINAEMIAS

Idiopathic hyperglobulinaemia which occurs almost entirely in women, is associated with chronic benign purpura especially of the legs. Involvement of salivary and lachrymal glands causes dry mouth and eyes and there may be enlargement of the spleen, liver, and lymph nodes.

Macroglobulinaemia occurs in elderly men. Bleeding from the mucosae and rarely purpura, with fractures of vertebrae and abnormal lymphocytes and mast cells in the bone marrow are the main features.

Cryoglobulinaemia, in which a gamma globulin crystallizes in the cold in blood and urine and redissolves on heating, may cause purpura, urticaria and Raynaud's phenomenon. It occurs in some cases of leukaemia, myeloma, rheumatoid arthritis, and hepatic cirrhosis.

Amyloidosis may cause purpura by infiltration of the vascular wall with amyloid material.

Conclusion

Although great advances have been made in this field, we are ignorant of the basic causes of haemorrhage in many cases, even after modern techniques have been applied (e.g. Blackburn and Daniel, 1957), and this remains an exciting challenge, while the field of therapeutic endeavour becomes more and more stimulating.

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