evacuated, but no true calculi were found. She was well when last seen as an out-patient on November 22, 1951.

During her first admission to hospital she was given 2 codeine compound tablets (*N.F.*) crushed, with a little water, on three successive days after admission, without knowing that she was being given aspirin. In the past all aspirin preparations, including codeine compound tablets and also the "soluble" brands of the drug, had made her sick within a few hours, even when taken crushed and with a cupful of water. She vomited several times in the first few days in hospital, but not after the haematemesis.

In view of the equivocal findings of the opaque meal, it is suggested that there is strong presumptive evidence that the bleeding in this case was caused by the administration of aspirin.

Discussion

These observations were made in the course of a survey of the underlying lesions of gastric and duodenal haemorrhage. This was not primarily concerned with the role of aspirin in causing exacerbations of symptoms, or haemorrhage, in patients with peptic ulcer. Muir and Cossar (1955) show that patients with peptic ulcer have a much higher incidence of intolerance to aspirin than the rest of the population, and this is confirmed. Some of the undiagnosed cases in the "acute lesion group" had taken aspirin in the 24 hours before admission, but only those cases are reported in which the connexion appears to be unequivocal.

Aspirin is so valuable a drug, and so ubiquitously used, that any toxic effects are likely to have an economic significance, as well as causing distress to patients individually. Gastric haemorrhage is undoubtedly one of the most serious of its toxic effects, and an inquiry should always be made about it in any case of gastro-intestinal bleeding, because it is so frequently self-administered and so easily obtained. The doses taken may be massive—for example, Neale (1936) has recorded a case in which the patient took 200 gr. (13 g.) in 36 hours, for the pain of a tuberculous hip-joint.

However, only a small number of people have an intolerance to the drug serious enough to warrant complete abstention from it in any form. Various preparations have been tried, many of which are far less apt to cause trouble than the simple compound. These include calcium aspirin (Thompson and Dragstedt, 1933), buffered aspirin (Tebrock, 1951), and enteric-coated aspirin (Talkov *et al.*, 1950). Finally, there are a few people who are liable to develop really serious allergic reactions with aspirin, and they should be careful, especially when under medical care, to avoid it —no easy task when so many tablets and mixtures contain it. Such people are rare, and it would be a pity if the advantages of so valuable an analgesic were to be denied unnecessarily to those who would benefit from it.

Summary

Of 165 patients admitted to hospital with haematemesis and melaena 151 were studied with regard to the taking of aspirin; 34 never took aspirin; of the other 117, 28 complained of some undesirable side-effects, of which 24 were epigastric pain, nausea, vomiting, or heartburn. There was no correlation between the method of taking it and the occurrence of these symptoms. Among 170 episodes of haematemesis or melaena there were three which gave reasonably good evidence for supposing that the aspirin had caused the bleeding, in the absence of any other gastric lesion.

These three cases, together with a fourth case not in the series of 170, and others from the literature, are analysed. The analysis shows that this bleeding occurs in one of three circumstances: (1) aspirin taken for some painful disorder independent of the gastro-intestinal tract; (2) self-medication for abdominal pain; or (3) the unwitting treatment of a sensitive patient in hospital.

As serious intolerance occurs in only a small number of patients, and as aspirin is so valuable an analgesic, patients should not be forbidden it unless this is really necessary, but, if they are, they should be warned to be suspicious of any analgesic offered to them, for many of these contain aspirin. Those who have minor gastro-intestinal symptoms from the drug should take a preparation such as calcium aspirin or enteric-coated tablets if these are available.

I am indebted to the consultant staff of Addenbrooke's Hospital for allowing access to their patients, and particularly to Dr. Laurence Martin for his interest in the subject. I am grateful to Mr. S. J. Hopkins, pharmacist to the United Cambridge Hospitals, for various criticisms.

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COMBINED ANTIHAEMOPHILIC GLOBULIN AND CHRISTMAS FACTOR DEFICIENCY IN HAEMOPHILIA

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In the last year haemophilia has been separated into different types—namely, the well-defined classical haemophilia A (antihaemophilic globulin deficiency) and Christmas disease or haemophilia B (Christmas factor deficiency, factor IX deficiency, plasma thromboplastin component deficiency). Another haemorrhagic diathesis resembling haemophilia but apparently dominant in character has been described as plasma thromboplastin antecedent deficiency (P.T.A. deficiency or haemophilia C).

Since the different types of haemophilia have been discovered only one case of mixed haemophilia has been described (Soulier and Larrieu, 1953). This condition is extremely rare.

The patient described in this paper is one of 43 patients clinically thought to have haemophilia, of which 4 had haemophilia B and 39 had haemophilia A. Our purpose is to study the haemorrhagic diathesis occurring in one family in which five males of the last generation were affected. Two of them bled to death in childhood. The remaining three were fully investigated. The point of particular interest in this family is that the type of haemophilia is not the same in all the affected members.

Methods

Platelets were counted by the method of Van Goidsenhoven (1926). The clotting-time was determined by the Lee and White (1913) method, the bleeding-time

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by Duke's (1910) technique, the one-stage prothrombin time as described by Biggs and Macfarlane (1953), and the heparin-tolerance test and prothrombin consumption test by minor modifications of Soulier's techniques (Soulier, 1948; Soulier and Le Bolloch, 1950; Verstraete *et al.*, 1954). The thromboplastin generation test has been performed according to the technique of Biggs and Douglas (1953). The activity of Christmas factor in serum was studied in controlling the correcting power of this serum on the serum of a patient with Christmas disease.

Case 1

A man aged 22 had suffered from a haemorrhagic diathesis since childhood. This was characterized by recurrent haemarthrosis without important ankylosis, large haemorrhages into muscles, subcutaneous ecchymoses after minimal trauma, and recurrent epistaxis. The latter became less frequent after the age of 18. In 1946 an operation for acute appendicitis necessitated repeated blood transfusions. These did not stop the bleeding; it did not cease until the operation wound was completely healed. In 1948 a large cephalohaematoma resulted from a blow on the head.

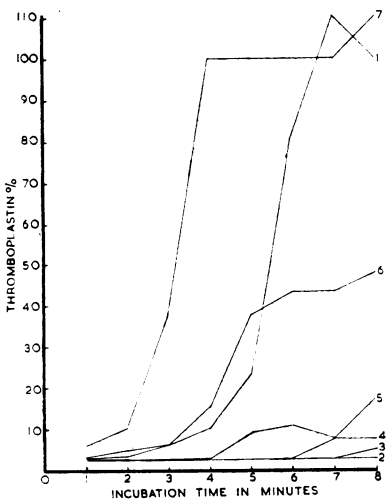


FIG. 1.—Thromboplastin generation test. Curve 1: with normal reagents—that is, normal platelet suspension, a antihaemophilic globulin, factor V, and serum. Curve 2: with same reagents from Case 1. With same reagents from Case 1 *except* normal platelets (curve 3), normal factor V preparation (curve 4), normal antihaemophilic globulin preparation (curve 5), normal serum (curve 6). Curve 7 represents the thromboplastin formed with patient's platelets and factor V and normal antihaemophilic globulin and serum.

In 1954 he suddenly had a severe haematuria lasting between five and seven days. This had never occurred before. Two male first cousins, children of two different maternal aunts, suffered from a haemorrhagic diathesis. Two other first cousins bled to death in the first years of their life.

The platelet count (268,000 per c.mm.), capillary fragility, bleeding-time, clot retraction and prothrombin one-stage test were normal. The clotting-time was determined on several occasions, and was always at the upper limit of normal (8 to 12 minutes), as was the clotting-time of recalcified plasma (190 seconds). The heparin-tolerance test was diminished, and corresponded with the slightly prolonged clotting-time (25 minutes, compared with a normal of 13 minutes). The serum consumption time after six hours was 34 seconds (normal, more than 40 seconds). These last two results, occurring with a normal one-stage prothrombin time, suggested that the coagulation defect occurred during the first phase of coagulation—that is, the formation of plasma thromboplastin.

The separate factors concerned in the first phase of blood coagulation were tested by the thromboplastin generation test of Biggs and Douglas (1953). The reagents required for this test (platelets, factor V, antihaemophilic globulin, and serum) were prepared from both normal and the patient's blood. The results of this test are shown in Fig. 1. Platelets, alumina plasma, and serum prepared from the patient's blood showed deficient formation of active thromboplastin. The platelets and factor V had normal activity when tested in a normal system. Antihaemophilic globulin and serum both showed deficient thromboplastin formation in a similar system. Antihaemophilic globulin from the patient's plasma was prepared by precipitation by 33% $(NH_4)_2SO_4$ saturation at 0° C. This protein fraction from the patient's plasma reacted in the same way as similar preparations from haemophilic plasma.

Normal serum contains several factors necessary for blood coagulation—namely, factor VII, Christmas factor (factor IX), and possibly the plasma thromboplastin antecedent (Rosenthal *et al.*, 1953). According to Rosenthal *et al.* (1953) the factor lacking in plasma antecedent deficiency is present in normal serum and is not absorbed by $BaSO_4$. The addition of $BaSO_4$-treated normal serum did not improve the formation of thromboplastin by the patient's platelets, alumina plasma, and serum. His serum did not correct the abnormal thromboplastin formation of serum from a patient treated with dicoumarin anticoagulants. In the latter, the abnormal thromboplastin formation is caused in the first place more by the Christmas factor deficiency than by factor VII deficiency (Verstraete, 1955; Verstraete and Vandenbroucke, 1955a). The last two experiments therefore indicate a deficiency of Christmas factor in the patient's serum. The presence of an inhibitor was excluded by determining the clotting-time of mixtures of recalcified patient's and normal plasma. The presence of 1/10 normal plasma corrected the abnormal clotting-time of recalcified plasma (see Table). The addition of Cohn's fraction 1 partly corrected the defect. This latter fraction contains potent antihaemophilic globulin, but no Christmas factor activity. The patient's plasma did not correct the defect in haemophilia A or haemophilia B plasma.

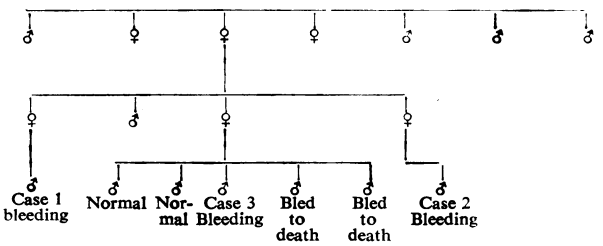
Recalcification Times (in minutes and seconds) of Mixtures of Platelet-free Plasma of Case 1 and (A) Normal Platelet-free Plasma, (B) Fraction 1 Cohn, (C) Plasma of Haemophilia A, (D) Plasma of a Patient with Christmas Disease

Mixture		Recalcification Time			
Plasma of Case 1	+$CaCl_2$ M/40 at 37° C.	A Normal Plasma	B Fraction 1 Cohn	C Plasma Haemoph. A	D Plasma Haemoph. B
0·1 ml.	0	5′ 19	5′ 30	5′ 44	5′ 30
0·09 ,,	0·01 ml.	2′ 34	2′ 53	5′ 41	—
0·075 ,,	0·025 ,,	1′ 52	3′ 26	5′ 12	—
0·050 ,,	0·050 ,,	1′ 40	3′ 24	8′ 13	6′ 12
0·025 ,,	0·075 ,,	2′ 23	1′ 51	7′ 57	—
0·01 ,,	0·09 ,,	1′ 28	2′ 05	10′ 02	—
0	0·1 ,,	1′ 50	—	12′	13′

All these results point to a combined deficiency of both antihaemophilic globulin and Christmas factor.

Investigation on the Haemostatic Defect of Two Other Bleeders in the Same Family

The mother of the patient had two sisters who each had an affected son still alive. As detailed in the family tree, two first cousins of Case 1 bled to death.



All the members of the last generation were examined. Two of the five still alive were normal. No members of the two previous generations were known to be bleeders.

Case 2.—A garage proprietor aged 45 had suffered from the age of 3 from recurrent haemarthrosis and haemorrhages into muscles. In the last 20 years the only manifestations of this tendency to bleed had followed tooth extractions. The clotting-time was at the upper limit of normal (10 minutes); the clotting-time of recalcified plasma (3 minutes, 36 seconds) and the heparin-tolerance test (16 minutes—normal 10 minutes) were prolonged. All other tests were

within normal limits (platelet count, bleeding-time, Rumpel–Leede test). The thromboplastin generation test, using platelets, alumina plasma, and serum prepared from the patient's blood, was abnormal (Fig. 2). Normal serum did not produce normal generation. Normal antihaemophilic globulin and haemophilic B antihaemophilic globulin produced normal generation when substituted for the patient's antihaemophilic globulin. Therefore antihaemophilic globulin was the only abnormal factor.

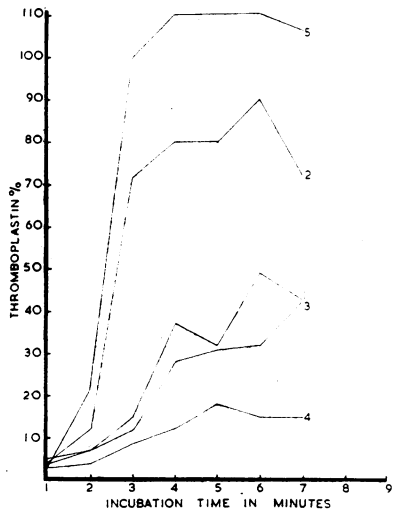


FIG. 2.—Thromboplastin generation performed with the reagents of Case 2 (platelets, factor V, antihaemophilic globulin, and serum) (curve 1); with the same reagents except antihaemophilic globulin prepared from the plasma of a case of Christmas disease (curve 2); with the same reagents except normal serum (curve 3). Curve 4 represents the thromboplastin generation with platelets, factor V, antihaemophilic globulin, and serum of Case 3; and curve 5 with normal reagents (platelets, factor V, antihaemophilic globulin) and serum of Case 3.

Case 3.—A male clerk aged 32. This man's bleeding diathesis was first noticed at the age of 2, when he required blood transfusions for excessive haemorrhage. Further severe bleeding followed repair of an inguinal hernia, and transfusion was necessary. Repeated haemarthroses occurred into the elbow-joints. The clotting-time was 16 minutes (venous blood). Recalcified plasma clotted in 6 minutes 48 seconds; the heparin-tolerance test was also pathological (24 minutes, against a normal of 10 minutes). The serum consumption time four hours after clotting was 34 seconds; it was 51 seconds 24 hours after clotting. Thromboplastin formation was deficient when reagents made from the patient's blood were used. As in Case 2 the defect lay in the antihaemophilic globulin fraction and not in the serum (Fig. 2).

Therefore these relatives of Case 1 had a deficiency of antihaemophilic globulin (haemophilia A) as the only abnormality.

Discussion

If the frequency of haemophilia A is 1 in 10,000 and haemophilia B (Christmas disease) 1 in 100,000, then a combined defect must be extremely rare. However, it must be taken into consideration that if one chromosome anomaly exists a second anomaly may not be so uncommon. For instance, the incidence of colour blindness in haemophiliacs is statistically greater than normal. Both defects are linked to the X-chromosome.

A case of combined antihaemophilic globulin and proaccelerin (factor V) has been described (Koller, 1954). The combination of antihaemophilic globulin deficiency and a prolonged bleeding-time has been reported in the son and two daughters of one family (Verstraete and Vandenbroucke, 1955b). Larrieu and Soulier (1953), Alexander and Goldstein (1953), Quick and Hussey (1953), and van Creveld and Jordan (1954) have published single cases showing a similar combination.

Another interesting feature of Case 1 was the finding of typical haemophilia A in two male first cousins. So far no family has been found in which both types of haemophilia have occurred as separate or combined defects.

Koller (1954) has, however, described the finding of haemophilia A in one patient and haemophilia B in another patient whose relationship was eventually traced in sixteenth-century records.

In the present family there are two cases of haemophilia A. The bleeding tendency is milder and the antihaemophilic globulin level higher in Case 2 than in Case 3. This statement can be made in regard to the clinical history of both patients. Case 3 is still bleeding frequently and has been transfused several times. Case 2 had had haemarthrosis in childhood, but has not bled seriously in the last 25 years. He has never been transfused. The results of the thromboplastin generation test and other investigations also suggest a marked difference in antihaemophilic globulin level.

Quick and Hussey (1952) have stated that the type and severity of haemophilia should be identical in the one family. The above findings do not agree with this concept. The possibility that a similar A+B deficiency might occur as a transient event in some families cannot be excluded.

It is clear that the blood of a haemophilia A and that of a haemophilia B case would partially correct the coagulation defect where both clotting factors (antihaemophilic globulin and Christmas factor) are deficient. If these latter deficiencies were mild, either blood might render the less sensitive clotting-time normal, and so a combined defect might be missed.

The presence of a circulating anticoagulant must be carefully excluded. If inhibitors are present in the serum they must be present in a higher concentration in the plasma or whole blood, as the anticoagulant is partially neutralized by the process of coagulation. No such inhibitor was demonstrable in the plasma or whole blood of Case 1.

The finding of a combined defect of haemophilia A+B is of considerable interest in relation to the discovery of plasma thromboplastin antecedent by Rosenthal *et al.* (1953). Theoretically, it is possible that they are identical defects, but unfortunately we have so far been unable to compare a case of plasma thromboplastin antecedent deficiency with Case 1.

Summary

A routine investigation of a man who had had classical haemophilia since childhood revealed a defect in both antihaemophilic globulin and Christmas factor (haemophilia A+B).

The defect in the patients' serum was proved not to be a circulating anticoagulant.

Two male first cousins were found to have a pure deficiency of antihaemophilic globulin: in one the defect was mild, in the other severe.

The theoretical possibility of a combined A+B deficiency is discussed.

The possibility of plasma thromboplastin antecedent deficiency and haemophilia A+B being identical defects is considered.

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