"ACQUIRED HAEMOPHILIA-LIKE DISEASE"

REPORT OF A CASE WITH STUDIES ON THE MODE OF ACTION OF THE CIRCULATING ANTICOAGULANT

BY

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In recent years an increasing number of cases of haemorrhagic diathesis with long clotting times have been shown to be due to a circulating anticoagulant. Nineteen of these cases have recently been reviewed by Collins and Ferriman (1952) and several other examples have been reported. These cases include a group of haemophiliacs, in whose plasma the development of anticoagulant activity has followed the therapeutic administration of blood or blood products, and a group of other patients in whom the anticoagulant has appeared spontaneously, sometimes in association with some other disease or following a pregnancy. "Acquired haemophilia-like disease" would appear to be the most satisfactory name for this second group of cases in the present state of knowledge of their aetiology.

There is good evidence that the anticoagulant of the haemophilic group is an antibody to antihaemophilic globulin produced in response to its repeated therapeutic administration, usually in the form of blood transfusions (Craddock and Lawrence, 1947; Frommeyer, Epstein, and Taylor, 1950). The exact nature and mode of action of the anticoagulants of the second group, on the other hand, remain obscure. It appears from the more fully investigated cases that they interfere with the formation of plasma thromboplastin, but the manner in which they do so remains in doubt.

A further "non-haemophilic" case is now presented in which the anticoagulant appeared to be an inhibitor of antihaemophilic globulin.

Clinical Report

The patient was a 71-year-old unmarried woman who had had rheumatic heart disease since childhood. In May, 1952, she was admitted to another hospital in severe heart failure with auricular fibrillation, and with large bruises on both arms. She gave a history of repeated spontaneous bruising of the arms and legs for the previous five months. The onset of this bruising tendency was apparently unrelated to injury or illness, and she had never had any blood transfusions. There was no family history of any bleeding disorder, and at no time had she had purpura, haemarthrosis, or haemorrhage from mucosal surfaces, with the exception of one episode of haematuria about three years previously.

Blood examination on May 5, 1952, gave the following results: Hb, 6.8 g. per 100 ml.; R.B.C.s, 2,620,000; W.B.C.s, 14,400 (polymorphs 70%, lymphocytes 28%, monocytes 2%); reticulocytes, 8.8% of R.B.C.s; bleeding time (Duke), 2 minutes; clotting time (Lee and White), 25 minutes; prothrombin time (Quick), 17 seconds (control 15 seconds); platelets, 214,000 per c.mm. A sternal marrow puncture on May 26 revealed a cellular marrow showing normoblastic hyperplasia.

The patient was treated with digoxin, "neptal," and blood transfusions, and was discharged on June 13. Three days after discharge she began to develop fresh bruises and she was readmitted to hospital on August 11 with Hb 7.1 g. per 100 ml. and a clotting time of 70 minutes. She was again treated with blood transfusions, but continued to develop spontaneous haematoma of varying size. On September 20 she began to complain of abdominal pain, and two days later she was transferred to St. Thomas's Hospital under the care of Dr. J. S. Richardson. On admission she was found to have a number of large bruises and deep, subcutaneous haematoma at various stages. All these, she stated, had arisen spontaneously without injury. During the next few days she developed generalized abdominal pain with increasing abdominal distension and tenderness, and began to vomit. On September 26 bowel sounds became practically inaudible, and on the following day she became shocked and cyanosed and died, five days after admission to St. Thomas's Hospital.

Necropsy revealed an area of haemorrhage into the wall of the terminal part of the ileum which appeared to have caused a venous infarction. There was a haemoperitoneum and haemorrhage into both lungs and the posterior mediastinum. The heart was of normal size and showed slight stenosis of the mitral valve. Death was evidently chiefly due to the intestinal haemorrhage.
Laboratory Investigations

General Methods.—All blood used in coagulation studies was collected by clean venepuncture: plasma was obtained by mixing nine parts of venous blood with one part of 3.1% sodium citrate, and centrifuging at 2,500 r.p.m. for 10 minutes. The source of brain thromboplastin was a buffered saline extract of human brain prepared by the method of Owren (1949), stored at −20° until required, and thawed at 37° immediately before use.

Routine Investigations.—The results of the routine laboratory investigations carried out on admission to St. Thomas’s Hospital were as follows:

Hb, 12.7 g. per 100 ml.; platelets, 312,000 per c.mm.; platelet morphology, normal; bleeding time (Duke), 2 minutes; clotting time (Lee and White), 34–35 minutes; prothrombin time (Quick), 14 seconds (control 14 seconds); prothrombin consumption index (Merskey), 104% (normal < 40%).

Demonstration and Mode of Action of a Circulating Anticoagulant.—Table I shows the clotting times of mixtures of various proportions of normal, haemophilic, and the patient’s plasmas.

<table>
<thead>
<tr>
<th>Undiluted Plasma</th>
<th>Diluted Plasma (%)</th>
<th>Clotting Times (Minutes)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>100</td>
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<tr>
<td>Normal</td>
<td>Patient</td>
<td>5.1</td>
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<tr>
<td>Normal</td>
<td>Haemophilic</td>
<td>2.2</td>
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<tr>
<td>Patient</td>
<td>Normal</td>
<td>2.1</td>
</tr>
<tr>
<td>Patient</td>
<td>Haemophilic</td>
<td>1.3</td>
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*0.2 ml. undiluted plasma, 0.2 ml. diluted plasma (or normal saline), 0.2 ml. 25 mM CaCl₂.

These results show that the patient’s plasma contained an anticoagulant, a 50% dilution of which was capable of prolonging the clotting time of normal plasma. Although the patient’s plasma did not correct the haemophilic defect, its effect on normal plasma served to exclude the diagnosis of haemophilia. A further difference from haemophilia is shown by the failure of high dilutions of normal plasma to correct the patient’s defect.

Heparin-like Substances.—An excess of such substances was excluded by titration of the patient’s plasma with toluidine blue.

Antithrombin.—An antithrombin titration, by a modification of the method of Quick (1938), showed a lower titre in the patient’s plasma than in a normal control.

Inhibitors of Human Brain Thromboplastin.—The reaction of the patient’s plasma with serial dilutions of human brain thromboplastin was comparable with that of haemophilic plasma, and provided no evidence of the presence of an inhibitor of the thromboplastin.

Inhibitors of Blood Thromboplastin.—The patient’s plasma clotted in the same time as a normal control plasma on the addition of blood thromboplastin prepared by the method of Biggs, Douglas, and Macfarlane (1953).

Inhibitors of Blood Thromboplastin Generation.—The results so far reported are compatible with the presence in the patient’s plasma of an inhibitor of blood thromboplastin generation. Such a substance might act as an antagonist of either the platelet factor or of one of the plasma factors concerned with this process, or conceivably by preventing the interaction of two or more of these principles. The following two investigations suggest that the anticoagulant in this case was an inhibitor of antihaemophilic globulin.

First, Table II shows the effect of normal plasma and the patient’s plasma, separately and in combination, on the clotting time of haemophilic blood.

| TABLE II NEUTRALIZATION OF ANTIHAEMOPHILIC GLOBULIN BY THE PATIENT’S PLASMA |
|-----------------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Haemophilic whole blood (ml.)                 | 1.0              | 1.0              | 1.0              | 1.0              |
| Normal plasma (ml.)                           | 0.1              | 0.1              | 0.1              | 0.1              |
| Patient’s plasma (ml.)                        | 0.1              | 0.1              | 0.1              | 0.1              |
| Citrate-saline (ml.)                          | 0.1              | 0.1              | 0.1              | 0.1              |
| 25 mM CaCl₂ (ml.)                             | 0.2              | 0.2              | 0.2              | 0.2              |
| Clotting time (minutes)                       | 21               | 31               | 19               | 8               |

It is apparent from Table II that the patient’s plasma not only failed to shorten the clotting time of haemophilic blood, but partially prevented the normal plasma from doing so. It may reasonably be inferred that this effect was due to a direct action on the antihaemophilic globulin of the normal plasma. The small proportion of normal plasma used, relative to the volume of haemophilic blood, virtually excludes the possibility that its correcting effect could have been due to any factor other than antihaemophilic globulin.

Second, it was considered that the anticoagulant in the plasma might take part in a time-consuming reaction with antihaemophilic globulin resulting in the inhibition of the latter substance, and the following experiment was devised to test this hypothesis.

Equal amounts of patient’s and normal plasmas were incubated together and 0.1-ml. samples of this mixture were transferred at intervals to 0.1 ml. of haemophilic plasma, 0.2 ml. CaCl₂ being added simultaneously. The results are expressed in Fig. 1, which shows that the corrected clotting time of the haemophilic plasma increased progressively with the time of incubation of the normal and patient’s plasmas. The initial reading of 120 seconds was obtained by the use of citrate-saline in place of the patient’s plasma, and this figure remained constant, irrespective of the length of the first stage. The uncorrected clotting time of the haemophilic plasma was 600 seconds. These results show that the patient’s plasma causes a rapid and progressive reduction of the ability of normal plasma to correct the haemophilic defect.
and one may infer that this was due to a progressive neutralization of antihaemophilic globulin.

**Precipitin Tests.**—No precipitins could be demonstrated against whole normal plasma or against either of two purified preparations of antihaemophilic globulin.

**Physical Properties of the Anticoagulant.**—The anticoagulant activity of the patient's plasma remained undiminished after storage at −20° for 19 days, but was completely lost on storage at 37° for three days; the serum was found to possess anticoagulant activity after storage at −20° for six months.

Dialysis of the plasma was not performed, as the quantity available was limited by the patient's early death.

The electrophoretic pattern of the patient's plasma was within normal limits.

The results of a crude ammonium sulphate fractionation experiment suggested that the anticoagulant was contained in the fraction of the patient's plasma precipitated by 33% saturation with ammonium sulphate, and that it acted by the inhibition of some factor which was contained in the same fraction of normal plasma.

**Discussion**

The finding of a normal one-stage prothrombin time in a patient with a prolonged whole-blood clotting time serves to rule out deficiencies of prothrombin, factors V and VII, and fibrinogen, and to suggest that the defect is one of thromboplastin generation. Such a defect may be brought about by a simple deficiency of one of the other active principles concerned in this stage of the coagulation process—namely platelets, antihaemophilic globulin, or Christmas factor—or by the presence of an inhibitor of one or other of these.

In the present case, haemophilia and Christmas disease could be excluded on clinical grounds alone, as the bleeding disorder started late in life in a woman with a negative family history. The clinical features, platelet count and morphology, and the bleeding time all combined to exclude platelet disorders. The final diagnosis could thus be arrived at by a process of exclusion based on routine clinical and laboratory observations, and was confirmed by further investigations.

That precipitins to antihaemophilic globulin could not be demonstrated in this case does not, of course, rule out the possibility that the inhibitor was a true antibody. That such investigations have given positive results in only a proportion of the haemophilic group is most probably due to technical causes, and these may also account for the failure in this case. Collins and Ferriman (1952) have pointed out that most of the previously described patients in the non-haemophilic group suffered from conditions which may be associated with disturbances of immunity mechanisms, and the patient presented here is no exception to this rule, suffering as she did from chronic rheumatic heart disease. It may be that this condition represents an instance of auto-immunization, analogous to the acquired haemolytic anaemias and thrombocytopenias. Whether all cases of "acquired haemophilia-like disease" are due to inhibitors of antihaemophilic globulin, or whether similar inhibitors of other clotting factors may be responsible for a proportion of them, is a further point which remains to be investigated.

**Summary**

A case is presented of a haemorrhagic diathesis occurring in a woman of 71 with chronic rheumatic heart disease, and resulting in a fatal intestinal haemorrhage.

Laboratory studies revealed that the condition was due to the presence in the patient's plasma of a circulating anticoagulant.

Evidence is presented that this anticoagulant was an inhibitor of antihaemophilic globulin.

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