without reactions and that this results in a more rapid utilization of the injected iron when treatment is urgently required.

Summary

A radioactive iron-dextran complex was administered intravenously and intramuscularly to normal and iron-deficient patients. Measurements were made of the distribution and movement of the complex.

After intravenous injection the complex was cleared from the plasma by the reticulo-endothelial system, and the iron was then utilized for haemoglobin synthesis. In iron-deficient patients there was substantially 100% utilization of the injected dose.

After intramuscular administration approximately 60% of the injected dose was rapidly absorbed; thereafter clearance occurred only slowly.

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HAEMOPHILIA-LIKE DISEASE DUE TO AN AUTO-ANTIBODY

BY

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Haemophilia is a congenital disease which is determined by the well-known mode of inheritance. Occasionally it arises *de novo* as a fresh mutation. Recently there has been an increasing awareness of the existence of a haemophilia-like state which affects patients hitherto free of bleeding disorders. Such a condition may be brought about by the development of a factor (antithromboplastinogen) which interferes with plasma thromboplastin formation. The interference may take the form of destruction or neutralization of one or more of the components of thromboplastin or, as Hougie and Fearnley (1954) suggest, of inhibition of interaction between these components. The recorded examples comprise in the main those encountered in pregnancy and, relevant to this paper, a more heterogeneous group where a haemophilia-like state appeared after a variety of disorders (Lozner *et al.*, 1940; Conley *et al.*, 1948; Quick and Stefanini, 1948; Dieter *et al.*, 1949; Tzanck *et al.*, 1949; Singer *et al.*, 1950; Collins and Ferriman, 1952; de Vries and Shafir, 1952; Nilsson and Wenckert, 1953; Hardisty, 1954; Bartorelli and Vanacore, 1955; Evans,

1955). In a number of cases no association with another disease was established (Joules and Macfarlane, 1938; Harrington *et al.*, 1950; Pons and Torregrosa, 1952; Hougie, 1953; Spaet and Kinsell, 1954; Evans, 1955).

Other inhibitors of coagulation have been recorded, and one of these is a heparin-like material (Biggs and Macfarlane, 1953). In the case described below there is reason to believe that both an antithromboplastinogen and an excess of a heparin-like material were present.

Case History

A married woman aged 46 was admitted to hospital on January 1, 1956, with a history of tonsillitis three weeks previously. This throat infection subsided after three injections of penicillin, an antibiotic she had never had before. A day or two after the injections a papulo-vesicular eruption appeared on the palms of her hands. This eruption became infected and caused much burning and itching. It gradually became more widespread, involving mainly the limbs. Soreness of the throat recurred after a further few days. On December 25, 1955, she developed a pleuritic pain in her right lower chest, and her right knee became red, swollen, and painful. A day or two later the left big and second toes became similarly affected. The patient was febrile but did not feel particularly ill, and an attempt to treat her with chlortetracycline was given up because she was unable to tolerate it.

On admission she showed discrete papules, some of which were infected, on her hands, arms, abdomen, back and to a less extent on her legs. There were effusions into the right knee and into the joints of the left big and second toes. The chest was clear. Blood cultures were sterile. A swab from a skin pustule grew coagulase-negative staphylococci only. She was treated with systemic penicillin and streptomycin, and locally by chlortetracycline cream. On this treatment the pustules began to clear, but the fever continued and the affected joints remained swollen. The arms were noticed to be oedematous too. Her temperature eventually began to settle, and, although the right knee was still stiff and swollen, her condition was sufficiently improved for her to be allowed up on January 17. Three days later she became pale and was found to have many spontaneous bruises in all limbs. The legs assumed an icteric tinge. Her haemoglobin, which on admission was 11.2 g. per 100 ml., was found to have fallen to 4.6 g.

She was placed on prednisolone, 20 mg. three times a day for two days, and thereafter the dose was reduced to 10 mg. three times a day. A transfusion of 5 pints (2.8 litres) of blood was given without any reaction, although cross-matching was difficult owing to rouleaux formation.

It was observed that a venepuncture performed for the transfusion went on oozing for two days, and a wound in the arm, made to expose another vein to complete the transfusion, continued to bleed for four days. Thereafter the patient began to improve, although on February 3 the cut used for the transfusion began to bleed again, and continued to do so for another four days. The total period during which she bruised and bled intermittently extended over 18 days.

The prednisolone was reduced gradually until by February 22 the dose was only 5 mg. daily, and this was maintained for another three weeks.

When the patient left hospital (February 24) her haemoglobin had risen to 12.6 g. per 100 ml., and her general condition was fairly good. Subsequently she was seen in the out-patient department on several occasions. She gradually regained her strength, and up to the time of writing had not experienced any further bleeding. Two months after leaving hospital she had a recrudescence of the papulo-vesicular eruption on the palms of her hands, and this responded to chlortetracycline cream. On March 5 she was seen with a fresh crop of papules, mainly on her wrists and forearms, and a few on her trunk.

Laboratory Investigations.—On January 1 the W.B.C. was 10,000 per c.mm. (polymorphs 72%). Serum proteins (Table I) were first estimated January 12, when paper electrophoresis

TABLE I.—Serum Proteins (g./100 ml.)

Date:	12/1/56	21/1/56*	9/2/56	13/3/56	16/10/56	7/3/57
Albumin	1.95	22%	3.3	3.65	4.7	4.6
Globulin	8.2	78%	3.9	4.2	4.0	4.25

* By electrophoresis.

showed a considerable increase in gamma-globulin and a slight increase in alpha-globulin. On January 21 the direct Coombs test was positive; Wassermann and Kahn reactions were negative; bleeding-time (Duke) 5 minutes; clotting-time (Lee and White), clotting began at 20 minutes and was complete in 90 minutes; prothrombin time, 19 seconds (control 19 seconds); serum prothrombin time, 18 seconds; platelets, 219,000 per c.mm.

In the thromboplastin generation test the patient's plasma behaved in a grossly abnormal way, while her serum acted normally. Her plasma failed to correct the abnormal thromboplastin generation of haemophilic plasma. When her

plasma and normal plasma were mixed thromboplastin generation proceeded normally (Fig. 1).

Calcium clotting-times of mixtures of normal and of the patient's plasma (Table II) would suggest at first sight the presence of an inhibitor of plasma thromboplastin (Biggs and Macfarlane, 1953), but a similar test (Table III) in which haemophilic plasma was substituted for that of our patient made it clear that more convincing proof of a thromboplastin inhibitor was required.

Fig. 1.—Thromboplastin generation tests. Curve 1=control plasma. Curve 2=haemophilic plasma. Curve 3=equal parts of control and haemophilic plasmas. Curve 4=equal parts of control and patient's plasmas. Curve 5=equal parts of haemophilic and patient's plasmas. Normal serum and platelet suspensions used in all tests. These curves show that the defect in the patient's plasma was corrected by an equal volume of normal plasma, but that the defect was not corrected by haemophilic plasma. Curve 4 also shows that the patient had no immediate inhibitory effect on normal plasma.

Further thromboplastin generation tests based on the procedure described by Hougie and Fearnley (1954) produced this evidence (Dawson, 1957). In these tests defective thromboplastin generation resulted from incubation of the patient's serum with normal plasma and serum, and this defect could be corrected by adding antihemophilic globulin (A.H.G.), but not normal serum, after the period of incubation.

An experiment was then carried out to ascertain whether the patient's serum was capable of inactivating A.H.G. This was done by comparing the influence of two mixtures on

TABLE II.—Inhibition of Plasma Thromboplastin (Biggs and Macfarlane, 1953)

Percentage of Plasma in Mixture		Calcium Clotting-time in Seconds	
Normal	Patient	Immediate	After 2 Hours at 37° C.
100	0	143	186
90	10	134	221
50	50	153	203
10	90	188	238
0	100	285*	345

* The relatively short calcium clotting-time of the patient's plasma in this test, at a time when her clotting-time (Lee and White) was 20 minutes, is attributed to changes in the plasma due to delay in setting up the test.

TABLE III.—Inhibitor of Plasma Thromboplastin

Period of Incubation (mins.):	0	5	10	15	60
	Calcium Clotting-time (secs.)				
Patient + 1/5 normal plasma	208	240	217	282	445
Haemophilic + 1/5 normal plasma	159	210	231	154	280

the thromboplastin generation of severe haemophilic plasma, one being the patient's aluminium-hydroxide-treated serum and A.H.G., and the other being normal alumina serum and A.H.G. In each case the mixture of A.H.G. and serum was first incubated for 10 minutes at 37° C. Serial dilutions of the normal serum and A.H.G. mixture were used to give a relationship between percentage A.H.G. and thromboplastin generation. In this way inactivation of A.H.G. by the patient's serum to a dilution of 1 in 5 was demonstrated (Fig. 2).

No trace of A.H.G. could be detected in the patient's plasma on assay (Douglas and Biggs, 1953), and A.H.G. precipitin tests (Hougie and Fearnley, 1954) were negative. No evidence of destruction of formed blood thromboplastin by the patient's serum was found (Spaet and Garner, 1955). On January 24 the plasma fibrinogen was 280 mg. per 100 ml.; the thrombin-fibrinogen reaction (Biggs and Macfarlane, 1953) was abnormal, and could be corrected by toluidine blue (Table IV).

Fig. 2.—Destruction of antihemophilic globulin by patient's serum. A.H.G. preparation incubated with dilutions of patient's Al(OH)₃-treated serum at 37° C. for 10 minutes in the presence of calcium.

TABLE IV.—Correction of Thrombo-fibrinogen Reaction of Plasma by Toluidine Blue

Thrombin Units Added to Plasma:	20	8	4	2	1
	Clotting-time of Plasma in Seconds				
Control plasma	7.2	10.3	18.8	38.0	85.0
Patient's	8.4	18.6	37.0	368.0	1,500 +
Control plasma + toluidine blue (50 mg./100 ml.)			20.2	54.0	
Patient's plasma + toluidine blue (50 mg./100 ml.)			22.2	73.0	

Evidence of the inhibitor of thromboplastin generation was obtainable until February 2. The clotting-time became normal on February 9, having varied between 11½ and 22 minutes. On the same date the thromboplastin generation test became normal, and for the first time a quantity of A.H.G. (15–20%) was detected. The thrombin-fibrinogen reaction returned to normal on February 8.

Discussion

It is known that after several transfusions or injections of A.H.G. a small number of haemophiliacs become refractory to treatment because they develop an inhibitor of thromboplastin formation (Hougie, 1955). It is assumed that under those circumstances an antibody is formed in response to a foreign protein. In pregnancy cases isoimmunization is thought to explain the production of the antithromboplastinogen. In a high proportion of the reports, other than those associated with haemophilia or pregnancy,

there is a history of some antecedent illness, such as skin disorders (Quick and Stefanini, 1948; Dieter *et al.*, 1949; Tzanck *et al.*, 1949; Bartorelli and Vanacore, 1955) or lymphadenopathy (Lozner *et al.*, 1940; Conley *et al.*, 1948). Spaet and Kinsell (1954) suggest that the factor operative in such cases is an auto-antibody like that found in acquired haemolytic anaemia and idiopathic thrombocytopenic purpura. The positive Coombs test in our patient, although only transitory, the specificity of the anticoagulant which she was found to have, and the great increase in her gamma-globulin fraction all lend support to that theory.

There are a number of instances where a disorder of the serum proteins was found (Lozner *et al.*, 1940; Mueller *et al.*, 1951). Nilsson and Wenckert (1953), who reported a case of essential hyperglobulinaemia with an anticoagulant, express a belief that such dysproteinaemia in itself interferes with the A.H.G. They consider that this explains the haemorrhagic disorder where there is no apparent trigger mechanism for auto-immunization. So far this theory has not been confirmed, and the fact that in our patient the highest level of gamma-globulin was found several days before clinical evidence of bleeding is not consonant with this idea.

It is known that our patient had been subject to dyshidrosis for some time, and it is likely that her throat infection touched off the generalized rash and arthritis with which she first presented. We are inclined to think that these manifestations, the hyperglobulinaemia, and the circulating anticoagulant were all an expression of a reaction to the initial infection. Pregnancy can be ruled out as an operative factor because six years had elapsed since our patient had her last child, and prior to her illness she never had a blood transfusion.

The laboratory findings indicated an abnormality in thromboplastin production. The calcium clotting-times on mixtures of the patient's and normal plasmas (Tables II and III) did not reveal the presence of an anticoagulant. The test recorded in Table III shows lengthening of the recalcification time of the patient's and normal plasma mixture on incubation, but the control-test, using haemophilic plasma in place of the patient's, gave similar results. Thus lengthening of the recalcification times in this test cannot be taken as proof of the presence of a plasma thromboplastin inhibitor. Further, the calcium clotting-time of normal platelet-poor plasma lengthens on incubation (see Table II), and this change makes the interpretation of results obtained with the mixtures difficult. The fact that antithromboplastinogens may take time to exert their full effect (Biggs and Macfarlane, 1953) explains why the ordinary thromboplastin generation test did not show the presence of an inhibitor. Only when the test was modified in such a way as to allow the inhibitor sufficient time to act was proof of the presence of the antithromboplastinogen obtained. Thus the absence of A.H.G. activity in our patient's plasma shown in the routine thromboplastin generation test must have resulted from the action of an inhibitor.

The normal prothrombin time showed that the formation of thrombin from prothrombin was not affected. The test of the final stage, the thrombin-fibrinogen reaction, was performed only when the case was reviewed, and was carried out on plasmas which had been stored up to 14 days at -20°C . The abnormality which was found could be corrected by toluidine blue, and thus was considered to be due to a heparin-like substance. It might be argued that this abnormality was caused by denaturation of fibrinogen during storage, but experiments with plasma stored for periods of up to four months at -20°C . showed that any deterioration could not be corrected by toluidine blue. On the other hand, the fact that a heparin-like substance was present clearly did not account for the disturbance in the thromboplastin generation test because the addition of toluidine blue did not improve the performance of the patient's plasma in that test. Also, on adding heparin to normal blood it was found that the prothrombin time was lengthened before

the thromboplastin generation test became abnormal, whereas in our case the prothrombin time was normal. We can offer no explanation for the hyperheparinaemia in our patient, and would refer to a paper by Waldenström (1948), in which he describes this condition in macroglobulinaemia.

The prognosis in cases such as ours is generally regarded as poor (Stefanini and Dameshek, 1955). The satisfactory outcome of our patient's illness may have been due to prednisolone, blood transfusions, or both, or else the disorder may have terminated spontaneously. If we accept that this patient's acute illness was in some way analogous to the disorders in which auto-antibodies form, then it is likely that prednisolone played an important part in her recovery. A review of the literature does not encourage this belief, though van Creveld *et al.* (1953), whose technique was criticized by Hougie (1955), thought corticotrophin was effective; and in the second patient described by Evans (1955) cortisone appears to have contributed to recovery. Stefanini and Dameshek (1955) found large doses of corticotrophin of temporary benefit in one of their patients with pemphigus. Their conclusion about corticotrophin and cortisone is that "these drugs have proved of little value in the management of those diseases, but their use is suggested by lack of other satisfactory therapeutic agents."

Our patient has not shown any further tendency to abnormal bleeding, but it is important to note that her plasma protein pattern remains abnormal and that she still suffers from time to time from a papular skin eruption.

Summary

The case of a woman aged 46 who developed a transient haemophilia-like state is described.

It is shown that this was due to the development of an antithromboplastinogen active against antihaemophilic globulin.

An increase in circulating heparin in this case is also recorded.

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On October 23 the DUCHESS OF GLOUCESTER laid the foundation-stone of the new Ulster Hospital for Children and Women at Dundonald, on the outskirts of Belfast. It will provide 500 beds and cost about £2.5m. The new hospital is planned as four distinct buildings—for adults, children, maternity cases, and out-patients—and the end of each building will be left so that the hospital can be expanded easily if necessary. The first stage of the building will include a maternity unit of 44 beds, a children's section with 128 beds, radiology, laboratory, and physiotherapy units, and out-patient and administrative units.