Endocrine causes are rare. Electrocardiographic changes are found commonly even among the milder cases.

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REFERENCES

- Bechgaard, P. (1946). *Acta med. scand.*, Suppl. 172.
 Becker, B. J. P. (1943). Cardiovascular Disease in the Bantu and Coloured Races of South Africa. M.D. Thesis, University of the Witwatersrand.
 Comstock, G. W. (1957). *Amer. J. Hyg.*, 65, 271.
 Donnison, C. P. (1929). *Lancet*, 1, 6.
 Gelfand, M. (1957). *The Sick African*, 3rd ed. Juta, Johannesburg.
 Gillanders, A. D. (1951). *Brit. Heart J.*, 13, 177.
 Lennard, H. L., and Glock, C. Y. (1957). *J. chron. Dis.*, 5, 186.
 Levin, N. W. (1957). *Leech (Johannesburg)*, 27, 29.
 Ordman, B. (1948). *Clin. Proc.*, 7, 183.
 Pickering, G. W. (1955). *High Blood Pressure*. Churchill, London.
 Sjøbye, P. (1948). *Heredity in Essential Hypertension and Nephrosclerosis*. Munksgaard, Copenhagen.
 Uys, C. J. (1953). Renal Disease in the Bantu. M.D. Thesis, University of the Witwatersrand.
 Williams, A. W. (1944). *E. Afr. med. J.*, 21, 328.

TREATMENT WITH CORTISONE OF HAEMORRHAGIC DISEASE DUE TO A CIRCULATING ANTICOAGULANT

BY

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Reports of haemophilia-like disease due to circulating anticoagulants are still comparatively rare, though they have become more frequent since the introduction of the thromboplastin generation and other sensitive tests which help to distinguish these cases from true haemophilia or Christmas disease. Two cases have, however, been seen in this hospital within a period of three years. The first, in an old lady with rheumatoid arthritis, has already been reported by Hardisty (1954).

Reviewing the literature since Lozner *et al.* (1940) first reported a case, Verstraete and Vandenbroucke (1956) were able to find 61 cases. Of these, 20 were in patients with haemophilia or Christmas disease who had developed the anticoagulant following blood transfusions; 16 were in women within one year of a pregnancy; one was in a newborn infant; eight were in females unrelated to pregnancy; and 16 in non-haemophiliac males. Most of the latter cases were associated with one or other of a variety of constitutional diseases, a list of which is given by Hougie (1955), but in a few no associated disease could be found (Joules and MacFarlane, 1938; Pons and de Torregrosa, 1952; Hougie, 1953; and others). The case reported here comes into the latter group.

Case History

A gardener aged 56 was sent into hospital by his doctor with a history of having spontaneously started passing blood-stained urine five weeks previously. At times it had been profuse, and small clots had been present. There was no frequency or dysuria. In the last two weeks he had also noticed the appearance of spontaneous bruising of his skin and had bled more readily after shaving. He also had palpitations on exercise and cramp-like substernal pain.

In the past he had had "black measles" during the 1914-1918 war and also nephritis, for which he was in hospital three months. He had never had any bleeding episodes or bruising previously. There was no family history of any bleeding disease.

On admission on April 8, 1955, he was very pale and slightly jaundiced. There were large bruises on both his arms. Petechiae were not seen in the skin. His pulse was 100 and blood pressure 120/70. A systolic murmur was present at the apex and there was slight oedema of the right ankle. Neither the liver nor the spleen was palpable, but the right kidney could be felt though it was not tender.

The urine on admission contained fresh blood, and microscopy showed red cells + + + + and occasional leucocytes. Culture grew *Escherichia coli*.

Cystoscopy revealed spurts of blood coming from the right ureteric orifice. Retrograde pyelography showed an irregular caliceal pattern on the right, with the ureter dilated and tortuous; it was supposed that this was due either to a new growth or to the presence of blood clots. Preliminary laboratory investigation showed: Hb 56% (8.3 g./100 ml.); red blood cells 2,990,000/c.mm.; C.I. 0.94; white cells 10,400 (neutrophils 79%, monocytes 10%, lymphocytes 1%); platelets 425,000/c.mm.; serum bilirubin 1.15 mg./100 ml.; blood urea 70 mg./100 ml. The blood group was A rhesus positive. It was noticed that the blood sent to the laboratory for grouping and cross-matching had not clotted after four hours, so further investigations were carried out.

Laboratory Investigations.—E.S.R. (Westergren) 62 mm. at first hour, 100 mm. at second hour. W.R. and Kahn tests were negative. Examination for cold agglutinins was negative. Agglutination against *Salmonella* and *Brucella* organisms was negative. Serum proteins 6.08 g./100 ml. (albumin 3.44 g., globulin 2.64 g.). A/G ratio 1.3:1. Electrophoresis of plasma showed a slight increase in the α_2 globulin, but was otherwise normal. Fibrinogen 650 mg./100 ml. Thymol turbidity and alkaline phosphatase were normal. Blood culture grew *E. coli* from the bile salt broth. The direct Coombs test was negative.

Investigation of Coagulation.—Clotting-time (Lee and White), 70 minutes. Prothrombin time, 15 seconds (control 15 seconds). Bleeding-time (Duke) normal. Clotting-time of recalcified plasma 430 seconds (control 160 seconds). Mixing-tests with patient's plasma and normal plasma showed that the patient's plasma, when mixed with normal plasma, had the power of prolonging the clotting-time of the latter (Table I). A modified prothrombin consumption test was abnormal.

TABLE I.—Clotting-times of Mixture of a Normal and Patient's Plasma on Admission

Source of Plasma	Quantities of Plasma (ml.) Used				
	0.1	0.1	0.1	0.05	0.01
Patient	—	—	—	—	—
Normal	0.1	0.1	0.1	0.1	0.1
Saline	0.1	0.1	—	0.05	0.09
M/40 CaCl ₂	0.2	0.2	0.2	0.2	0.2
Clotting-time in seconds ..	430	160	255	170	155

The results suggested the presence of a circulating anticoagulant in his blood, and on April 15 samples of plasma and serum were sent to Dr. W. R. Pitney, of the department of haematology, Postgraduate Medical School, Hammer-smith, who kindly performed a thromboplastin generation

TABLE II.—Results of Thromboplastin Generation Tests on Mixture of Patient's and a Normal Blood

	Plasma	Serum	Platelets	1	2	3	4	5	6
A	Normal 0.2	Normal 0.2	Normal 0.2	60	19	10	10	10½	
B	Patient 0.2	" 0.2	" 0.2	70	60	60	60	45	45
C	Normal 0.1 Saline 0.1	" 0.2	" 0.2	28	13	13	12½	11	10½
D	Normal 0.1 Patient 0.1	" 0.2	" 0.2	60	40	26	23	22	22
E	Normal 0.2	Normal 0.1 Saline 0.1	" 0.2	60	28	16	14	14	13½
F	" 0.2	Normal 0.1 Patient 0.1	" 0.2	37	15	11½	11	12	11½
G	" 0.2	" 0.2	" 0.2	37	16	12	12	12	12½

test, the results of which are given in Table II, and on which Dr. Pitney commented as follows:

"These results showed a gross impairment of thromboplastin formation when the patient's $Al(OH)_3$ absorbed plasma mixture (B) is substituted for normal plasma mixture (A). An equal mixture of normal and patient's plasma showed defective generation, although normal plasma and saline mixture (C) was satisfactory. Probably there is some defect also in the patient's serum (12-second thromboplastin compared with normal of 10 seconds), but this was not evident on mixing-tests.

"Plasma thromboplastin was generated from normal plasma, serum, and platelets, and then the patient's plasma was added. This was unable to affect the potency of the thromboplastin formed, as judged by the speed of clotting of the normal high-spun plasma. The patient's plasma was clotted by normal plasma thromboplastin in the same time as normal plasma.

"These findings agree with the diagnosis of a circulating anticoagulant. The anticoagulant appears to be used up during coagulation. It is probable that the Christmas factor activity of the serum is normal. The anticoagulant is not effective against formed plasma thromboplastin and therefore is probably acting either against anti-haemophilic globulin (A.H.G.) or an intermediate product of thromboplastin formation."

A further sample of blood was kindly examined by Dr. Biggs, at Oxford, who confirmed the presence of an anticoagulant in the serum which inhibited the production of thromboplastin up to a dilution of 1:64.

Treatment and Progress

A transfusion of 3 pints (1½ litres) of group A rhesus-positive blood was given soon after admission, and this raised his Hb to 72%. Two weeks later a hard painful haematoma arose below the right buttock, and his Hb fell to 54%, so a further 2 pints (1 litre) of blood was given to which three ampoules of fibrinogen were added, after which he remained well and his Hb rose to 58%. On April 27 he was started on cortisone, 200 mg. a day, and this dose was gradually reduced to 25 mg. a day, as his general condition was good and no more haemorrhagic episodes had occurred. His haematuria had ceased on May 5 and never recurred again, but on May 22 a large painful haematoma arose in the deep tissues of the left calf and it was thought advisable to raise his cortisone to 200 mg. daily again. He remained well for the next three weeks and his cortisone was again gradually reduced to 50 mg. daily, but on June 16 another haemorrhage occurred into his left thigh and he was put back on to 200 mg. of cortisone daily. The next day he had extensive bruising of the chest wall, was pyrexial, felt ill, and his Hb had fallen to 42%.

Two pints (1 litre) of blood was transfused, and it was noticed that his ear bled all day from the prick done to estimate his Hb, and bruising had occurred where the drip was put up. These bruises and the haematoma gradually settled, and on July 4 he was reduced to 150 mg. of cortisone daily. Later in the month he had a haemarthrosis of his right knee and a large bruise developed on his back,

but after this he was free for several weeks. He was discharged from hospital on August 31, still taking cortisone 100 mg. daily.

At no time during his stay in hospital did his Lee and White clotting-time fall below 40 minutes. The plasma clotting-times and mixing-tests were repeated but there was no improvement (Table III).

After discharge the patient was seen regularly at the outpatient department, and the cortisone was changed to prednisolone, the dose varying between 20 and 45 mg. daily, being adjusted to obtain a balance between his increase in weight if given too much and haemorrhagic episodes which seemed to occur if the dose was reduced too much. In spite of this he had repeated minor haemorrhagic episodes not severe enough to require hospitalization, and he was, of course, not allowed to resume his work as a gardener.

TABLE III.—Clotting-time of Mixtures of a Normal and the Patient's Plasma 17 Months After First Admission

	Quantity of Plasma in ml.					
Normal plasma ..	0.1	0.1	0.1	0.1	0.1	—
Patient's plasma ..						0.1
Patient's plasma diluted 1:2 ..					0.1	
Patient's plasma diluted 1:5 ..				0.1		
Patient's plasma diluted 1:10 ..			0.1			
Patient's plasma diluted 1:100 ..		0.1				
Normal saline ..	0.1					0.1
M/40 $CaCl_2$..	0.2	0.2	0.2	0.2	0.2	0.2
Clotting-time in seconds ..	126	160	182	215	235	330

This caused considerable social upset, as he had to give up his job and the cottage that went with it, and his wife had to go out to work.

He was readmitted for the first time in January, 1956, because of a large haematoma following venepuncture, and after this was comparatively well until his second admission in June, 1956, because of a large painful discharging swelling of his left elbow following a blister three days previously. He was found to have an abscess and cellulitis of his left arm, for which he was given oral oxytetracycline and his prednisolone was stopped. The abscess (which on culture grew *Staph. pyogenes*) had to be incised and drained surgically, and following this there was severe bleeding and he had to be given 3 pints (1½ litres) of blood.

He gradually improved and was discharged in the middle of July, 1956; he remained well without taking any prednisolone at all until November, when a large bruise developed on his left hand. Prednisolone, 15 mg. daily, was restarted, and, as further bruising appeared later in November, the dose was raised to 30 mg. daily.

The thromboplastin generation test was repeated and gave essentially similar results to the original test 18 months previously, both revealing the presence of a circulating anticoagulant in the plasma active at a dilution of 1 in 80.

A large haematoma of the right thigh sent him into hospital again in December, 1956, and his haemoglobin was then down to 56%, whereas it had been maintained at 90% during the previous months. In February, 1957, he developed a large haematoma of the left buttock, and in March a further haemorrhage into the left thigh for which he was admitted for the fourth and last time.

Whilst in hospital on March 22 he suddenly developed a large haemorrhage on the right side of the neck which spread under the tongue and into his throat, causing respiratory embarrassment, from which he finally died just two weeks short of two years since his first admission.

Post-mortem Findings

External Appearances.—The body was that of a middle-aged man of average nourishment. A large swelling due to a haematoma was present in the upper part of the chest and neck. There was swelling of the right side of the face

due to a haematoma in the subcutaneous tissues. Large bruises were seen on the left arm, left side of chest, and back, and smaller bruises on both hands.

Internal Examination.—This revealed extensive haemorrhage into and oedema of the soft tissues of the larynx, soft palate, uvula, and beneath the tongue, spreading into the muscles of the neck around the larynx and upper part of the trachea. The airway through the larynx was obstructed by this oedema and haemorrhage. The lungs appeared normal. The heart was normal. Gastro-intestinal tract:

there were small haemorrhages on the peritoneal surfaces of the stomach but no bleeding into stomach or any other part of intestines. Liver and gall-bladder appeared normal. The kidneys were normal macroscopically, and the prostate was enlarged. The cortex of the adrenals was thin and of a bright yellow colour.

Histological examination of prostate, liver, and spleen disclosed no significant abnormality. The kidneys showed fibrosis of several glomeruli and focal lymphocytic infiltration only. The adrenals showed atrophy of the cortex, presumed to be due to prolonged cortisone therapy. No underlying organic disease could be found.

Discussion

An interesting feature of this case was the apparent reduction in frequency and severity of the haemorrhagic episodes during treatment with cortisone or prednisolone (see Chart) without any comparable improvement in the whole-blood clotting-time or the titre of the circulating anticoagulant.

Evans (1955) reported similar findings in one of his cases, and in the other case the clotting-time was reduced and the anticoagulant disappeared from the blood during treatment with cortisone; but these results may have been due to natural remission, as the titre of these anticoagulants has been shown to fluctuate spontaneously from time to time and even to disappear altogether (Soulier and Larrieu, 1953).

Most observers have failed to find any clinical or laboratory improvement when using cortisone (Frick, 1953, 1955; Hougie, 1953, 1955; Hougie and Fearnley, 1954; Verstraete and Vandenbroucke, 1956). Van Crefeld *et al.* (1953), however, reported a fall in activity of the anticoagulant following cortisone therapy, but the technique he employed to demonstrate this may give unreliable results (Hougie, 1955). They also found that, following corticotrophin or cortisone, the clotting-time could be reduced by plasma transfusions to a greater

degree than before. As reported by previous authors, the anticoagulant in this case was shown to inhibit the formation of thromboplastin by interfering with the activity of A.H.G., but had no effect on thromboplastin once it had been formed. Richards and Spaet (1956) produced an antibody in rabbits by giving them doses of A.H.G., the properties of which were identical with the circulating anticoagulants found in humans. Craddock and Lawrence (1947) have also produced evidence that the anticoagulant appearing in haemophilic cases was an immune antibody and probably present in the gamma-globulin fraction of the serum or plasma.

Craddock and Lawrence were also able to demonstrate precipitins to A.H.G. in the serum of two cases, and several other workers have also obtained positive precipitin tests (Frommeyer *et al.*, 1950; Hougie and Fearnley, 1954; Verstraete and Vandenbroucke, 1956; and others). Collins and Ferriman (1952) suggested that the anticoagulant arising in non-haemophilic cases is an auto-antibody similar to that appearing in cases of acquired haemolytic anaemia, and Evans (1955) suggested that a response to cortisone in some of these cases could therefore be anticipated, considering the favourable response obtained sometimes in haemolytic anaemias. On the other

hand, the apparent clinical improvement may be due to direct action on the capillaries similar to the symptomatic improvement seen in cases of thrombocytopenic purpura treated with cortisone, even when the platelet count remains low.

It is possible that the prednisolone precipitated the development of the cellulitis and abscess of the arm in this case, and the drug was withheld as soon as these developed.

However, until some more specific treatment becomes available it would seem well worth while giving prednisolone, as symptomatic improvement, at least, may result.

Summary

A case of haemorrhagic disease in a man aged 56, due to the presence of a circulating anticoagulant in his blood, is described.

The impression was gained that cortisone or prednisolone improved his clinical condition and reduced the frequency of his haemorrhagic episodes, although there was at no time any improvement in his whole-blood clotting-time or the titres of the anticoagulant. He survived for two years, eventually dying from asphyxia following haemorrhage into the larynx and base of the tongue.

No underlying organic disease could be found at necropsy.

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REFERENCES

- Collins, I. S., and Ferriman, D. G. (1952). *Lancet*, 2, 712.
- Craddock, C. G., jun., and Lawrence, J. S. (1947). *Blood*, 2, 505.
- Evans, D. M. D. (1955). *J. clin. Path.*, 8, 168.
- Frick, P. G. (1953). *Blood*, 8, 598.
- (1955). *Ibid.*, 10, 691.

- Frommeyer, W. B., jun., Epstein, R. D., and Taylor, F. H. L. (1950). *Blood*, **5**, 401.
 Hardisty, R. M. (1954). *J. clin. Path.*, **7**, 26.
 Hougie, C. (1953). *Ibid.*, **6**, 30.
 — (1955). *Brit. med. Bull.*, **11**, 16.
 — and Fearnley, M. E. (1954). *Acta haemat. (Basel)*, **12**, 1.
 Joules, H., and MacFarlane, R. G. (1938). *Lancet*, **1**, 715.
 Lozner, E. L., Jolliffe, L. S., and Taylor, F. H. L. (1940). *Amer. J. med. Sci.*, **199**, 318.
 Pons, E. R., jun., and de Torregrosa, M. V. (1952). *Blood*, **7**, 20.
 Richards, M. D., and Spaet, T. H. (1956). *Ibid.*, **11**, 473.
 Soulier, J. P., and Larrieu, M. J. (1953). *J. Lab. clin. Med.*, **41**, 849.
 Van Crefeld, S., Hoorweg, P. G., and Paulssen, M. M. P. (1953). *Blood*, **8**, 125.
 Verstraete, M., and Vandenbroucke, J. (1956). *J. Lab. clin. Med.*, **48**, 673.

CLINICAL METHOD OF ASSESSING TONUS AND VOLUNTARY MOVEMENT IN HEMIPLEGIA*

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During the trial of a new method of spasmolysis in a series of hemiplegic patients difficulty was experienced in finding a method of clinical examination capable of providing an accurate record of the response to treatment. It was desirable to assess its effect upon both tonic spasm and voluntary movement, improvement in the latter being the ultimate aim. Some treatises, such as that by Kendall and Kendall (1949), give excellent guidance on examining individual muscles showing flaccid paresis, but no complete system of examining muscle groups presenting motor deficit and hypertonus has been found, though several workers have made valuable contributions (Teitelbaum and Vyner, 1949; Rinzler *et al.*, 1951; Twitchell, 1951; Hinckley, 1954).

Many difficulties and pitfalls are encountered in elaborating a satisfactory method. Foremost is the influence exerted by certain intrinsic and extrinsic factors upon the tonus and activity of spastic muscle. Among these are temperature, emotion, attitudinal reflexes, and synergy movement. A method of examination which aims to detect spontaneous change, or change in response to treatment, must have a rigid standardization of all such factors during each examination, otherwise the clinical findings may be quite misleading. When this has been done, some means of measuring change in the degree of tonus and in the range and power of voluntary movement is required. Electromyography or mechanical apparatus has usually been used (Berger and Schwartz, 1948; La Joie and Gersten, 1952; Basmajian and Szatmari, 1955), but it appears unsatisfactory that trials of new therapeutic agents of such increasing importance as the spasmolysants should be restricted to the few institutions where such instruments are available. Furthermore, neither apparatus is adequate for examining both of the above modalities.

The following clinical method was devised to study the hypertonic musculature of patients with residual hemiplegia, but it was also found applicable to most other upper motor neurone diseases. It is best described

in two sections: the avoidance of errors which may arise through inadequate control of influencing factors and the method of examination. It is reported in the hope that it may provide a basis for further work.

Control of Factors Influencing Tonus and Activity in Skeletal Muscle

Temperature.—It is thought that external heat facilitates and that cold depresses voluntary muscle action (Schneider and Karpovich, 1948). Again, warming hypertonic muscle reduces the intensity of tonus and cooling increases it. Therefore, to avoid the influence of wide variations in temperature at different examinations all were conducted in a room which was comfortably warm—that is, between 70 and 80° F. (21 and 26.5° C.). More careful control of temperature does not appear to be required, since La Joie and Gersten (1952), studying the effect of heat on hypertonus, found that it was lessened only when the limb was thoroughly warmed by close-range heating.

Emotion.—Bucy (1949) noted that tonic muscle spasm was intensified by emotional stress. In my study it was found that excitement or worry could influence the examination findings to an appreciable extent. Certain steps were therefore taken to avoid strain. These were: exclusion from the examining room of all persons other than the patient and doctor; the patient was settled comfortably; examination was conducted quietly and methodically.

Attitudinal Reflexes.—Several workers have shown that these reflexes exert significant effects upon tone and movement in human hemiplegic patients (Yamshon, Machek, and Covalt, 1949; Twitchell, 1951; La Joie and Gersten, 1952). Their influence cannot be eliminated, but it can be standardized so that the findings are affected to equal degree at successive examinations. The following method was used: the upper limb was examined with the patient sitting upright and looking straight ahead at eye level; the lower limb was examined with the patient lying on the unaffected side, his head supported on a pillow so that it lay in line with the body. These positions were also convenient for conducting the examination.

Flexion and Extension Synergies.—If voluntary movement is not confined to the joint controlled by the muscle groups being tested the influence of synergy movements (Twitchell, 1951) may falsify the findings. The part of the limb (or body) proximal to the joint whose movement was being examined was therefore held immobile.

Volition.—It was observed that voluntary contraction of a hypertonic muscle group often led to a temporary increase in the tone of that group. Tonus was therefore assessed after active movement.

Rate of Passive Movement.—One of the methods used in estimating the intensity of tone was measuring the degree of resistance offered to passive movement. It has been noted (Twitchell, 1951) that the amount of resistance varies directly with the speed at which a hypertonic muscle group is stretched. An attempt was made to standardize this factor by moving the joint through its full range in the space of one second. It was not always possible to do so where hypertonus was pronounced, but only by attempting always to carry the movement through in that time could change in resistance be fairly assessed at different examinations.

*The work presented is part of the material submitted for the M.D. examination of Glasgow University.