psychology, is described. An argument is developed for using learning theory and behaviour therapy as an alternative approach to psychotherapy in the treatment of certain psychiatric symptoms.

This case was admitted under Dr. E. H. Hare, to whom we are grateful for permission to publish.

REFERENCES

- Eysenck, H. J. (1959). *J. ment. Sci.*, **105**, 61.
 Glover, E. (1955). *The Technique of Psycho-analysis*. Baillière, Tindall and Cox, London.
 Hudson, B. B. (1950). *Genet. Psychol. Monogr.*, **41**, 99.
 Jersild, A. T., and Holmes, F. B. (1935). *J. Psychol.*, **1**, 75.
 Jones, H. G. (1960). In *Handbook of Abnormal Psychology*, edited by H. J. Eysenck, chapter 20, in press. Pitman, London.
 Kendrick, D. C. (1958). *J. exp. Psychol.*, **56**, 313.
 Solomon, R. L., Kamin, L. J., and Wynne, L. C. (1953). *J. abnorm. soc. Psychol.*, **48**, 291.
 Wolpe, J. (1958). *Psychotherapy by Reciprocal Inhibition*. Stanford Univ. Press, Stanford, Calif.
 Yates, A. J. (1958). *J. abnorm. soc. Psychol.*, **56**, 175.

DIFFERENT HAEMOSTATIC DEFECTS IN ONE FAMILY

BY

F. NOUR-ELDIN,* Ph.D., M.B., L.S.A.

Late Research Fellow in Haemophilia, United Manchester Hospitals

Haemostasis is a complex process in which the coagulation of blood as well as the walls of the vessels participate. Haemorrhagic diatheses are therefore apt to occur as a result of defects in the blood-clotting mechanism and/or anomalies of the anatomical construction or the physiological response of the vessel wall. In spite of the multiplicity of the possible causes of defective haemostasis, the various members of a particular family are usually found to have the same anomaly, even when this comprises more than one factor. Few exceptions have been previously recorded: Verstraete and Vandenbroucke (1955) found one member of a known haemophilic family to have combined antihemophilic globulin and Christmas factor deficiency, and Bell and Alton (1955) reported a family in whom both sexes showed deficiency of factor VII, while some of the males were thought to suffer from Christmas disease as well.

The present paper describes a family in whom four different haemostatic defects have been demonstrated in three generations.

The Family

The family tree is shown in Fig. 1. The relevant clinical features are as follows.

II 1. This patient did not recollect any bleeding diathesis in his ancestors, but one of his two brothers complained of swellings in the joints, and died aged 45 as a result of suffocation by a haemorrhage in the pharynx and floor of the mouth. None of his five sisters has been affected. He married twice; both wives were healthy and showed no signs or symptoms of a bleeding tendency. There are two sons and one daughter of the first marriage and three daughters of the second. The patient was first seen in 1956, aged 59, complaining of haemorrhage under the tongue. Since childhood he had suffered from repeated attacks of epistaxis, which remained the only complaint until he was 14. From that age he bruised easily after minor trauma. Spontaneous haemarthrosis of the elbows also became a frequent manifestation. Restriction of their

movement was specially apparent after a knock on the right joint. After an injection in the right arm, the septic haematoma which developed caused contraction of the skin and wastage of muscles. Haematuria for three days occurred only once, at the age of 51. No history of melaena or haematemesis could be elicited. The bleeding which followed the extraction of his remaining 15 teeth, at the age of 36, necessitated his admission to hospital. In spite of his having been transfused with two bottles of blood, slight bleeding continued for a month. A year later he slipped in the bath and developed an extensive haematoma in the muscles of the anterior abdominal wall and retroperitoneal tissues. His condition quickly improved after receiving one bottle (540 ml.) of fresh blood daily for four consecutive days. At the age of 61 he again developed a sudden haemorrhage in the floor of the mouth during his sleep, and died before his doctor was able to see him.

II 2. The second wife of II 1 enjoyed perfect health. Nevertheless, her blood-clotting mechanism was examined; no abnormality was detected.

III 1. Particulars regarding a daughter aged 35 of II 1 by his first marriage were obtained from her father, and some clinical information was supplied by Dr. E. K. Blackburn. She gave a history of excessive bruising and occasional purpuric rash, but did not consider her bleeding from cuts abnormal. Teeth extractions, however, were always followed by a slight oozing of blood for a period of two days. Specks of blood in the sputum were noticeable when she had attacks of bronchitis. A transfusion of six bottles of blood were required after the removal of a fallopian tube nine years previously. One of her daughters (IV 3) is easily bruised and bleeds excessively after cuts or teeth extractions. Both the mother and daughter were found to have a capillary defect, as evidenced by capillary microscopy. The mother, in addition, had a slight deficiency of antihemophilic globulin.

III 2. This patient, the eldest (23 years) daughter of II 1 by his second marriage, complained of easy bruising, occasional epistaxis, and heavy periods lasting seven days. Her only pregnancy at 21 years of age was, however, normal and the childbirth uncomplicated. At the age of 10 she had two teeth extracted; the severe bleeding which ensued was not controlled until the sockets had been plugged five hours later. This bleeding occurred again after the extraction of another two teeth when she was 18. A course of vitamin K for one month prior to the removal of one tooth at the age of 20 did not prevent a similar excessive bleeding.

III 3. The second daughter (aged 13) had an uneventful tonsillectomy five years previously. Nevertheless, her blood-clotting mechanism was investigated. The only finding of interest was a concentration of antihemophilic globulin slightly below the lowest level of the normal range.

III 4. The youngest daughter (aged 8) gave a history of repeated attacks of epistaxis which had ceased for the last

FIG. 1.—Family tree. The following members were found to have: II 1, haemophilia; III 1 and 2, combined A.H.G. deficiency and capillary defect; III 3, slight deficiency of A.H.G.; III 4, factor VII deficiency; IV 1 and 3 capillary defect; and II 2 and IV 2, no abnormality.

*Now at the Blood Transfusion Centre, Crescent Drive, Brentwood, Essex.

two years. Bruising after minor trauma was a marked symptom; no spontaneous lesions were observed. She attended her dentist, who extracted two teeth. The ensuing haemorrhage necessitated her admission to hospital, where the gums were stitched. In spite of this, bleeding continued for nine days. Though the patient's parents were advised not to let her undergo further extractions without supervision of this department, she again attended her dentist, who stitched the gums immediately after one tooth was extracted. As the bleeding did not stop after five days, she was admitted to this hospital, where bleeding was controlled by the local application of thrombin.

IV 1. This grandson of II 1, aged 20, was alleged to have had excessive bleeding after tonsillectomy, but blood transfusion was not required. He also suffered from repeated attacks of epistaxis, for which no local cause could be found.

IV 2. A girl aged 10, she had one tooth extracted a year ago; excessive bleeding was controlled after plugging the sockets. This happened again on two subsequent occasions. Bruises were noticed after only moderate trauma.

Investigations and Results

The blood-clotting tests were carried out essentially as described by Biggs and Macfarlane (1957). Aluminium hydroxide suspension was prepared according to the method of Quick (1957). The estimation of antihaemophilic globulin was carried out as described by Nour-Eldin and Wilkinson (1958b). The nail-bed capillaries were inspected, magnified 20 times, by a Zeiss binocular dissecting microscope after preliminary painting of the skin with "optoil." The results obtained are shown in Tables I and II and the final diagnoses are included in Fig. 1.

From the clinical picture and the laboratory tests presented in Table I, it is apparent that II 1 suffered from haemophilia. His daughter of the first marriage, as well as having herself a combined antihaemophilic globulin deficiency and capillary defect, has a daughter with capillary defect.

One daughter of the second marriage showed a capillary defect and a concentration of antihaemophilic globulin slightly below the lower range of the normal. The latter finding was also made in one of her sisters, while the former defect was found in the grandson (IV 1).

The youngest daughter (III 4) presented a separate problem—namely, a prolonged one-stage prothrombin

TABLE I.—Laboratory Investigations

Investigation	Normal Range	II 1	II 2	III 2	III 3	III 4	IV 1	IV 2
Blood group (ABO, Rh (D))	—	O+	—	O+	O+	O—	AB+	AB+
Blood-clotting time (min.)	4-7	30	5	7	7	5½	5½	7
Prothrombin consumption index (%)	<40 usually <10	150	10	10	24	11	10	10
One-stage prothrombin time (sec.)	11-12	11½	11	11½	12½	17	12	13
Thromboplastin generation (sec.):								
Al(OH) ₃ -plasma 1:5*		36	9	10½	11½	10	10	10
Serum 1:10*		9	9	9	10	10	10	10
Platelets*		9	9	9½	10	9	10	9
A.H.G. concentration (%)	70-140†	4	110	60	60	110	95	120
Bleeding-time (min.)	2-4	4	3	5½	3½	3	6½	3½
Capillary fragility (Hess test)	—	N	N	Ab	N	N	Ab	N
Capillary morphology	—	N	N	Ab	N	N	Ab	N
Platelet count (10 ³ /c.mm.)	150-350	299	283	176	251	221	224	207

* Substrate clotting-time in seconds when the reagent mentioned is incorporated in the incubation mixture. Activity tested 6 minutes after adding CaCl₂.

† Standard 100% was prepared by mixing plasma from five normal individuals.

N = Normal. Ab = Abnormal.

TABLE II.—Correction of One-stage Prothrombin Time (Case III 4)

Reagent (10%) Added to Patient's Plasma	One-stage Prothrombin*
Nil (control)	17 seconds
Normal serum	13 "
Al(OH) ₃ -treated normal plasma	16½ "
Normal plasma	15 "
Factor VII-deficient serum†	18½ "
" plasma†	17½ "

* A normal control gave 11½ seconds. Results are average of two readings.

† Patient receiving phenindione with one-stage prothrombin time of 29 seconds (normal 11½ seconds).

time. Accordingly, further investigations were carried out. Fig. 2 shows that the prothrombin concentration as estimated by the two-stage method is within normal range, but its conversion to thrombin is delayed—that is, the peak of the curve is reached two minutes later than that in a normal control. This denoted a deficiency in an accelerator of blood coagulation—namely, factor V, factor VII, and/or Prower-Stuart factor. Since the one-stage prothrombin time (Table II) was corrected by normal serum and not by Al(OH)₃-treated plasma or serum and plasma obtained from a patient receiving phenindione, it was concluded that the defect was not due to factor V deficiency. This was substantiated by obtaining normal results on using the plasma in the thromboplastin generation test (Table I). Similarly, deficiency of Prower-Stuart factor was excluded by demonstrating that the patient's serum was fully active in this test.

In order to exclude liver disease as a possible cause of this factor VII deficiency, the following tests were carried out; the results indicated normal function:—serum proteins: albumin, 3.7 g. and globulin 2.1 g./100 ml. Paper electrophoresis, using barbitone buffer pH 8.6, also showed normal bands.

A thymol turbidity of 0.4 unit, serum alkaline phosphatase 11.5 units, and bilirubin 0.2 mg./100 ml. were recorded.

Discussion

Two types of antihaemophilic globulin deficiency are at present recognized (Nour-Eldin, 1959). In the first type, true haemophilia, the presence of a blood-clotting inhibitor termed "Bridge anticoagulant" complicates the deficiency (Nour-Eldin and Wilkinson, 1957, 1958a).

FIG. 2.—Two-stage prothrombin estimation. N, normal; P, patient (III 4).

Combined antihæmophilic globulin deficiency and capillary defect, a variety of Von Willebrand's syndrome, constitutes the second type. This is free of the inhibitor (Wilkinson, Nour-Eldin, and Israëls, 1958). Although the former deficiency is usually inherited as a sex-linked recessive character and the latter is transmitted as a dominant gene, new mutations are apt to give rise to either defect as can be indirectly deduced from the absence of a family history in 40% of the cases seen.

The present family, apart from showing four different anomalies of hæmostasis, is of interest because it seems to provide a link between the two diseases mentioned above and the other variety of Von Willebrand's syndrome known as capillary defect. Thus, Patient II 1, though not tested for Bridge anticoagulant (patient died before test was described), appears to be a true hæmophilic as judged from the presence of spontaneous hæmarthrosis and hæmaturia, and the normal capillary functions. Yet two of his daughters (III 1 and III 2) have a slight deficiency of antihæmophilic globulin and capillary defect, while another daughter (III 3) has a slight deficiency of antihæmophilic globulin, and a grandson and a granddaughter have a capillary defect. The plasma of the latter four patients was found to be free of Bridge anticoagulant.

That II 1 was responsible for the capillary and antihæmophilic globulin defects in his descendants may be assumed from their presence in children of both marriages. It is rather difficult, however, to explain the method of transmission to daughters and grandchildren because of, among other obvious reasons, the different nature of the conditions involved. Most probably it occurred by a mutation of chromosome(s) other than the sex chromosome, as evidenced by the absence of the capillary defect in two daughters. Although pure factor VII deficiency in the youngest daughter may appear to complicate the picture, it would support this view—namely, the presence of mutations in the chromosomes derived from the father.

Summary

The family history and clinical pictures are reported of female and male descendants of a hæmophilic patient who presented themselves with bleeding diatheses.

Laboratory investigations demonstrated various hæmostatic defects: factor VII deficiency, low levels of antihæmophilic globulin, and/or capillary defect.

The interrelation between the hæmostatic defects encountered and possible means of their inheritance are discussed.

I thank Dr. J. F. Wilkinson, in whose department this work was carried out, and the department of medical illustration, Manchester Royal Infirmary, for help in the preparation of the illustrations.

REFERENCES

- Bell, W. N., and Alton, H. G. (1955). *Brit. med. J.*, **1**, 330.
 Biggs, R., and Macfarlane, R. G. (1957). *Human Blood Coagulation and Its Disorders*, 2nd ed. Blackwell, Oxford.
 Nour-Eldin, F. (1959). Manchester Medical Society Lecture on April 29.
 — and Wilkinson, J. F. (1957). *Nature (Lond.)*, **180**, 990.
 — (1958a). *Brit. J. Haemat.*, **4**, 38.
 — (1958b). *Ibid.*, **4**, 292.
 Quick, A. J. (1957). *Hæmorrhagic Diseases*. Lea and Febiger, Philadelphia.
 Verstraete, M., and Vandenbroucke, J. (1955). *Brit. med. J.*, **2**, 1533.
 Wilkinson, J. F., Nour-Eldin, F., and Israëls, M. C. G. (1958). *Lancet*, **2**, 115.

HEPATITIS DUE TO PHENINDIONE SENSITIVITY

BY

NORMAN L. JONES, M.B., M.R.C.P.

Major, R.A.M.C.; British Military Hospital, Rinteln, Germany

Sensitivity reactions to phenindione ("dindevan"), at present probably the most widely used anticoagulant, are not common, and even when they do occur are usually of mild degree. In the report of the Working Party on long-term anticoagulant administration (Medical Research Council, 1959) only two cases of sensitivity occurred in the series of 383 patients: both were in the low-dosage (1 mg./day) control group and consisted of skin rashes. Several other large series have been free from severe reactions (Toohey, 1953; Breneman and Priest, 1955). Bingle and Shine (1959), however, emphasize the fact that occasionally sensitivity may be marked; and they point out that these reactions may become more frequent as long-term therapy becomes more commonly used. They review the findings in 11 cases of severe sensitivity to phenindione found in the literature, and present two more cases; in four of these hepatitis was a feature.

The present communication describes a further case of hepatitis due to phenindione.

Case Report

A 49-year-old officer was admitted to hospital on September 30, 1959, having woken that morning with a feeling of retrosternal discomfort associated with sweating. He had had similar symptoms two weeks before admission, but these had settled within a few minutes. There was no other relevant history: unilateral hilar lymphadenopathy had been discovered by routine chest radiography in 1956 and a diagnosis of sarcoidosis was made; serial x-ray films after this had shown little change.

Examination revealed a plethoric, slightly overweight man who was still suffering from severe retrosternal discomfort four hours after its onset. Apart from the presence of a low-pitched atrial sound maximal at the xyphoid, there were no cardiovascular abnormalities, and no other significant findings were present. The electrocardiogram was typical of an acute antero-septal infarct. Other investigations showed: hæmoglobin, 100%; white-cell count 10,200/c.mm. (66% P., 27% L., 4% M., 3% E.); E.S.R., 8 mm./hour (Westergren); serum glutamic-oxaloacetic transaminase (S.G.O.T.) 100 King units.

Anticoagulation was begun at once, using phenindione, together with heparin for the first 36 hours. Progress was very satisfactory, symptoms settling during the first two days; the atrial added sound disappeared during this time. A pyrexia developed on the second day and was later associated with a rise in the E.S.R. to 36 mm./hour (ninth day). Control of the prothrombin time proved somewhat more difficult than usual, and the dosage of phenindione was gradually increased over the first 10 days, a total daily dosage between 200 and 300 mg. being finally necessary (see Chart).

Further progress showed nothing of note until the evening of October 20 (21st day), when he suddenly developed a pyrexia of 101° F. (38.3° C.), with vague malaise and slight headache. There were no other symptoms, and no clinical signs were found on examination. An electrocardiogram did not show any significant changes of deterioration. The pyrexia persisted, and the next morning the following