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.

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HEPATITIS DUE TO PHENINDIONE SENSITIVITY

BY

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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

investigations were made: E.S.R., 6 mm./hour, white-cell count 6,600/c.mm. (82% polymorphs), S.G.O.T., 60 units; the urine contained bilirubin but was otherwise normal; blood culture was sterile. A course of penicillin, 500,000 units intramuscularly six-hourly, was begun; five days' treatment had no effect on the pyrexia. On the 23rd day excess urobilinogen was present in the urine; the serum bilirubin was slightly raised (1.08 mg./100 ml.), with a positive direct van den Bergh reaction. Alkaline phosphatase (8 K.A. units), zinc sulphate turbidity (2 units), and serum proteins (total 7.5 g./100 ml., albumin-globulin ratio 2 to 1) were all normal. On October 23 the liver was palpable $\frac{1}{2}$ in. (1.3 cm.) below the costal margin and was slightly tender.

Next day (25th day) the conjunctivae were faintly icteric and the liver was palpable to 1½ in. (3.8 cm.): the E.S.R. had risen to 23 mm./hour, and the white-cell count revealed an eosinophilia of 960/c.mm. (13% of a total count of 7,400); the serum bilirubin was 1.2 mg./100 ml., other liver-function tests remaining unchanged. A further blood culture was negative, agglutination reactions for typhoid, paratyphoid, and brucellosis were normal, and a chest x-ray film was clear apart from a well-defined globular enlargement of the right hilum of similar degree to that in previous films, thought to be the enlarged hilar glands of quiescent sarcoidosis. The Paul-Bunnell test was negative. The liver became progressively enlarged during the next two days, to become palpable 3 in. (7.5 cm.) below the costal margin on October 27 (28th day). The dosage of phenindione was reduced over the next few days, and was finally discontinued on November 1 (33rd day). Further anticoagulant therapy was not felt to be indicated. Reduction in dosage was paralleled by a fall in temperature, which became normal on the 34th day, and by improvement in the size of the liver. Bilirubin was absent from the urine on the 32nd day, and urobilinogen was not present in excess after the 35th day. There was a gradual fall in the serum bilirubin, reaching 0.6 mg./100 ml. on the 41st day, and the E.S.R. was 4 mm./hour and the S.G.O.T. 20 units on that day.

Though improvement in the hepatitis occurred with a reduction in the dosage of phenindione, a slightly pruritic erythematomacular rash appeared on October 29 (30th day); this at first affected the shoulders and arms, spreading to involve the trunk in a few days. It was associated with an enanthem of some petechial haemorrhages of the soft palate, similar to the enanthem of glandular fever. The rash lasted for six days, finally clearing on the 36th day, two days after phenindione had been discontinued. Further progress was uneventful, and he was discharged from hospital on December 10 (72nd day).

Discussion

In all the previously reported cases of severe sensitivity reactions to phenindione, pyrexia has been a prominent feature ; in most instances it has been the first indication of sensitivity, as in the present case. In four previous cases of hepatitis, this has followed about four days after the onset of fever (Kirkeby, 1954 ; Makous and Vander Veer, 1954 ; East and Beamish, 1957 ; Burns and Desmond, 1958). It is of interest that bilirubin was found in the urine of this case within 24 hours of the onset of fever and two days before there was any liver

enlargement. Sherlock (1955) has emphasized the importance of this investigation in infective hepatitis, and points out that it often permits a diagnosis to be made in the pre-icteric phase; its value as a screening test for hepatitis was confirmed in the present case. The disappearance of bilirubin from the urine coincided with improvement in the size of the liver on reducing phenindione, and functional recovery was indicated by the return of urobilinogen excretion to normal four days later.

The present case closely resembles three of the previously recorded cases (Kirkeby, 1954; East and Beamish, 1957; Burns and Desmond, 1958) in the mild elevation of serum bilirubin and in the normality of serum flocculation tests and the serum protein estimation.

Chart showing clinical course.

In the case reported by Makous and Vander Veer (1954) severe hepatitis occurred: the serum bilirubin was 14 mg./100 ml. and thymol turbidity 15 units. Their case was receiving 250 mg. of phenindione daily, and they related the severe reaction to this high dosage: in the present case it was of a similar order, but in the other previous cases lower dosage was recorded (Kirkeby, 112.5 mg.; East and Beamish, 200 mg.; Burns and Desmond, 125 mg.). A positive direct van den Bergh reaction was obtained as in former cases, but the alkaline phosphatase level was normal, in contrast to the raised values, ranging between 19 and 29 units, previously found (Burns and Desmond, Makous and Vander Veer, and East and Beamish). A striking resemblance is seen between the results of these liver-function tests and those found in the hepatitis due to chlorpromazine (Chesney, 1954), methyltestosterone (Werner *et al.*, 1950), and organic arsenicals (Hanger and Gutman, 1940). The jaundice occurring as a result of these drugs is thought to be due to the obstruction of intralobular bile-ducts with the poorly hydrated viscid bile produced by damaged liver cells (Sherlock, 1955). The resemblance is especially close when chlorpromazine is considered, the time of onset of sensitivity (two to four weeks after starting treatment), the frequency of fever and agranulo-

cytosis, and the type of skin rash being similar in the reactions to both drugs.

The white-cell count in this case was not significantly lowered, though a transient eosinophilia was observed; this was not as pronounced as that of Makous and Vander Veer's case (22% of a total count of 22,500/c.mm.). Neutropenia has been a notable feature in reported severe reactions to phenindione, having been recorded in 10 of the 13 cases reviewed by Bingle and Shine (1959). It was present in three cases which terminated fatally (Brown and MacMillan, 1954; Kirkeby, 1954; Burns and Desmond, 1958), and there is general agreement that it constitutes an indication for treatment with steroids and antibiotics.

The skin rash was late in appearing: it may occasionally be the only manifestation of sensitivity, and in view of the possible development of agranulocytosis and hepatitis its occurrence merits withdrawal of the drug, if necessary with replacement by another anticoagulant. The management of patients exhibiting sensitivity to phenindione has been discussed by Bingle and Shine (1959), who have suggested a scheme of treatment.

Summary

A further case of hepatitis occurring as a result of sensitivity to phenindione is reported; the clinical and laboratory findings are described and previously reported cases briefly reviewed.

I thank Brigadier A. P. Trimble, consulting physician to the British Army of the Rhine, and Group Captain J. C. Bowe for their help and advice, and the laboratory staff of the Military Hospitals at Rinteln and Munster for the biochemistry.

Addendum.—Since this paper was completed another case of hepatitis occurring in a patient receiving phenindione has been reported by R. H. Brooks and H. B. Calleja (*Ann. intern. Med.*, 1960, 52, 706); it was associated with fever, a rash, and nephritis. Recovery followed withdrawal of the drug.

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The number of early infectious syphilis cases in America increased from 6,661 in 1958 to 8,178 in 1959, or 22.8%. Gonorrhoea rose from 220,191 in 1958 to 237,318 in 1959, or 7.8%. During 1959 venereal diseases continued to increase in the teenage population: the increase on the 1958 figure was 14.3% in the 10-14-year age group and 11.4% in the 15-19-year-olds. (*Social Health News*, American Social Health Association, February, 1960.)

IDIOSYNCRASY TO PHENINDIONE

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Anticoagulants are being used on an increasing scale in the treatment of cardiac infarction and thrombotic and embolic disorders. The following case reports are presented so that others may be aware of some of the untoward reactions which occur.

Case Reports

Case 1.—A man aged 47 was admitted to hospital on account of sudden right-sided chest pain, dyspnoea, and haemoptysis. Four weeks previously he had had thrombosis of a right calf vein. Pulmonary embolism was diagnosed, and treatment started with phenindione. He was stabilized on a dose of 125 mg. daily, which kept the prothrombin level at about 30% of normal. After 16 days fever developed (Fig. 1) together with nausea, vomiting, and diarrhoea. Culture of urine and stools yielded no pathogens. The white-cell count was 11,400, with a normal differential. The fever and abdominal symptoms subsided when the anti-coagulant was stopped three days later, and he made an uneventful recovery.

FIG. 1.—Case 1. Temperature chart.

Case 2.—A man of 48 was admitted to hospital because of severe central chest pain, vomiting, and sweating. Cardiac infarction was diagnosed and confirmed by E.C.G. Treatment with heparin and phenindione was instituted; on a dose of 75 mg. daily the prothrombin level was about 20%. After 21 days he developed fever, diarrhoea, and an ache in the chest. Chest x-ray examination showed nothing abnormal, W.B.C. 9,800/c.mm. with a normal differential count; culture of blood, sputum, urine, and stools yielded no pathogens. He developed ulcers in the mouth which

FIG. 2.—Case 2. Temperature chart, showing relationship of fever to treatment with phenindione.