A CONGENITAL BLOOD-CLOTTING ANOMALY RESEMBLING COUMARIN-INDUCED DEFECT

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In spite of the various investigations carried out on the blood-clotting defect caused by the administration of coumarin drugs, their precise mode of action is still undetermined. It is, however, generally agreed that they produce a diminution in the concentration of prothrombin in plasma (Roderick, 1931; Quick, 1937), delay the conversion of prothrombin to thrombin by brain extract (Owen and Bollman, 1948), and reduce the formation of plasma thromboplastin (Biggs, Douglas, and Macfarlane, 1953). Recent studies revealed that the latter defect is most probably due to a deficiency of Christmas factor (Sise, Kimball, and Adamis, 1955; Douglas, 1955; Naeye, 1956; Douglas and Mair, 1958), and Prower factor (Denson, 1958).

The purpose of this paper is to present a case with a congenital blood-clotting defect simulating that produced by coumarin drugs.

Case Report

The patient was first seen at the age of 6 years, one week after eight teeth had been extracted. Bleeding from the sockets had continued for six days despite plugging. One month prior to this he had a mild attack of epistaxis. At the age of 5 years a small cut of the skin over the right eye did not cause much trouble. No history of haematuria, melaena, haematemesia, haemarthrosis, or spontaneous bruising could be elicited. He was of normal appearance and intelligence. No abnormality was detected on physical examination. Examination of the nasal passages showed no vascular abnormalities. Both the capillary fragility (Hess test) and the bleeding-time were normal. Laboratory tests carried out at that time showed that the one-stage prothrombin time was prolonged. Accordingly he was given a course of vitamin K, 30 mg. daily for nearly eight months. Unfortunately, he was not seen for the next five years. During this period he continued to suffer from mild attacks of epistaxis mostly from the right side and occurring more often in the summer. Skin cuts, however, seemed to heal satisfactorily.

On the patient's recent attendance for the extraction of five teeth a more detailed study of the clotting defect was carried out; the results are presented below. Removal of the teeth was followed by a slight oozing of blood for 48 hours, but no transfusion was required.

The patient's paternal aunt and grandfather had a history of bleeding after teeth extractions. These subjects, however, were not available for investigation.

Investigations

The blood-clotting tests were carried out essentially as described by Biggs and Macfarlane (1957). The results (Table I) show that the blood and plasma clotting-times and the prothrombin consumption index are within normal range, while the one-stage prothrombin time is prolonged. The latter is corrected by the addition of 10% normal serum or normal plasma, but not by $\text{Al}(\text{OH})_3$ -treated plasma or plasma from a patient receiving coumarin drugs. Since the

latter two reagents contain factor V, but little prothrombin and factor VII, its lack of effect on the one-stage prothrombin time demonstrates the absence of factor V deficiency. On the other hand, serum contains factor VII and normal untreated plasma contains both factor VII and prothrombin. The shortening of the prothrombin time by these two reagents indicates that the patient's plasma is deficient in factor VII and possibly prothrombin.

The estimation of prothrombin by the two-stage method demonstrated that both factors were deficient. The results obtained using this test are illustrated in the Chart. Analysis of the two curves in this figure shows that the peak of the concentration of thrombin formed in the patient's plasma is delayed. This delay can be encountered in either factor V or factor VII deficiency. Since the former anomaly has

TABLE I.—Blood-clotting Tests

Test	Normal	Patient
Whole-blood clotting-time (min.)	4-7	5½
Plasma clotting-time (min.)	2-4	3½
Prothrombin consumption index (%)	<40, usually <10	6
One-stage prothrombin time (sec.)	11-12	20
Normal $\text{Al}(\text{OH})_3$ -treated plasma adding 10%	—	20
serum	—	15
plasma	—	16
Factor-VII-deficient serum*	—	19½
Plasma with coumarin-induced defect†	—	20½

* Obtained from a patient with this congenital defect, one-stage prothrombin time being 17 seconds.

† Patient receiving phenindione; one-stage prothrombin time 27 seconds.

already been excluded by studying the effect of different reagents (Table I) on the one-stage prothrombin time, this would appear to incriminate factor VII. The Chart also shows that the area covered by the patient's curve is equal to 68% of that covered by the normal, indicating a prothrombin concentration of this magnitude in the patient's plasma.

The thromboplastin generation test demonstrated that the $\text{Al}(\text{OH})_3$ -treated plasma of the patient did not lack either antihæmophilic globulin or factor V and did not contain an anticoagulant. On the other hand, it indicated that his serum was deficient in a factor necessary for the formation of plasma thromboplastin. This defect was corrected by normal or Christmas disease serum (Table II), but was unaffected by serum obtained from patients receiving ethyl biscoumacetate or phenindione.

Effect of Factor-VII-deficient Serum.—Although it is now believed that factor VII is not essential in the formation of plasma thromboplastin (Ackroyd, 1956), it was thought advisable to study the effect of serum procured from a patient with this congenital anomaly. This did not influence the one-stage prothrombin time (Table I), but it shortened the substrate clotting-time in the thromboplastin generation test from 25 to 16½ seconds, thus denoting and confirming that factor VII is not the only factor lacking in the patient's blood. On the other hand, sera from patients treated with

Estimation of prothrombin by the two-stage method. A= Normal plasma. B=Patient's plasma.

TABLE II.—*Effect on Thromboplastin Generation Test of Adding Various Sera to the Patient's Serum*

Serum Incubated with Al(OH) ₃ -plasma, Platelets, and 0.025 M CaCl ₂	Substrate Clotting-Time, (sec.)
Normal serum	10
Patient's	25
Serum of patient receiving ethyl biscoumacetate	43
phenindione	29½
Christmas disease serum	38
Patient's serum mixed with 10% of:	
Normal serum	16
Serum of patient receiving ethyl biscoumacetate*	27
phenindione†	25
Christmas disease serum	18
Congenital factor-VII-deficient serum‡	16½

* One-stage prothrombin time 42 seconds (normal 12 seconds).

† One-stage prothrombin time 29 seconds (normal 11 seconds).

‡ The activity of thromboplastin produced in each mixture was tested after six minutes by taking 0.1 ml. thereof together with 0.1 ml. of 0.025 M CaCl₂ and adding them simultaneously to 0.1 ml. of normal citrated plasma (substrate) at 37° C., recording the clotting-time.

§ This gave normal results (10 seconds) when tested by the thromboplastin generation method.

ethyl biscoumacetate or phenindione were ineffective in correcting the clotting defect (Tables I and II). Similarly, the coumarin-induced defect was not corrected by the patient's plasma or serum.

Liver-function Tests.—Paper electrophoresis of serum, using barbitone buffer pH 8.6, showed normal bands. Serum thymol turbidity was 0.2 unit and serum alkaline phosphatase 22 units.

Effects of Vitamin K.—The blood-clotting tests were repeated before and during a course of vitamin K, 40 mg. daily for four weeks. The blood-clotting defect was not affected by this treatment. Furthermore, the clinical picture was not improved, the patient having an episode of epistaxis while receiving the drug.

Examination of Father's Blood.—This was found to be normal.

Discussion

The condition described in this paper seems to be a congenital anomaly; the haemorrhagic tendency appeared before the age of 6 in the patient, who received no coumarin drugs. The results of the blood-clotting tests are similar to those found in patients receiving these drugs. Thus the patient has normal blood and plasma clotting-times but a prolonged one-stage prothrombin time, and his serum is lacking in factor(s) necessary for the generation of normal levels of plasma thromboplastin (Biggs *et al.*, 1953). Furthermore, the two-stage method shows that the concentration of prothrombin is below normal levels and demonstrates a retardation in the conversion of this factor to thrombin. Unlike the coumarin defect, however, the patient's deficiency was not influenced by vitamin K therapy.

Walker and Hunter (1954) provided evidence which suggested that the action of coumarin drugs on the blood-clotting mechanism is not restricted to prothrombin and factor VII only; another factor, termed factor X, was, in addition, thought to be involved. This view has been followed by various reports which seem to indicate that these drugs produce multiple defects (Koller, 1955; Biggs, 1956; Greig and Tattersall, 1956), the exact nature of which is still far from being solved. Whatever the final outcome of further investigations in this respect, however, it is apparent that the blood-clotting factors affected by these drugs are also lacking in the blood of our patient, as can be deduced from the failure of mutual correction.

Several workers have described cases in which plasma gave an abnormal one-stage prothrombin time. Some of these were presumed to be due to a deficiency of factor VII and have been reviewed by Ackroyd (1956). Patients diagnosed as having hypoprothrombinaemia

have been mentioned by Biggs and Macfarlane (1957). Of the recorded cases, only those described by Newcomb *et al.* (1956) and Biggs (1956) seem to bear some resemblance to our patient.

Summary

The clinical features of a patient with a mild haemorrhagic diathesis are reported. Laboratory investigations demonstrated that, although the congenital blood-clotting defect is basically similar to that produced by coumarin drugs, no improvement was achieved by vitamin K therapy.

We thank the Department of Medical Illustration, Manchester Royal Infirmary, for help in preparing the Chart.

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EFFECT OF CASTOR OIL, SOAP ENEMA, AND HOT BATH ON THE PREGNANT HUMAN UTERUS NEAR TERM A TOCOGRAPHIC STUDY

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The administration of castor oil, followed by a soap enema and a hot bath, is probably one of the oldest and most frequently attempted methods of inducing labour. This regime is also used as a complement to other induction procedures, such as an oxytocin ("pitocin") drip or surgical rupture of the membranes.

Recently, however, some obstetricians have tended to regard castor oil as an ineffective oxytocic drug and have abandoned its use altogether in the induction of labour. Nabors (1958) carried out a clinical trial of the effectiveness of "rupture of membranes and pitocin" either alone or combined with castor oil or enema, or castor oil and enema together. On the basis of his findings he concluded that castor oil is of no value in the induction of labour. However, a study of his figures shows that there were fewer "failed inductions" in the group which was given castor oil.

Castor oil has so many unpleasant features, such as its taste and its tendency to produce nausea, vomiting,