may have been encouraged by a hot intrauterine douche. Adequate blood coagulation was again demonstrated by the douche nozzle becoming blocked by clots. During the fifth hour after delivery only 1 pint (570 ml.) of blood was lost, and after this the loss gradually ceased. The patient had by this time received a total of 17 pints (9.7 litres) of blood and 1½ pints (850 ml.) of plasma, together with 5 mg. of ergometrine, 30 units of oxytocin, and 30 ml. of 10% calcium gluconate solution.

The haemoglobin level, which had been 10.3 g./100 ml. prior to delivery, was only 8.4 g./100 ml. on the day after. All coagulation tests done after delivery were entirely normal. The patient was discharged well 14 days after delivery.

Discussion

Blood-coagulation failure is now accepted as an uncommon but by no means rare hazard of pregnancy, and the circumstances in which it may occur have been detailed (Reid *et al.*, 1956; Hodgkinson, 1956; Jeffcoate and Scott, 1956; and Sharp *et al.*, 1958). Usually it is associated with foetal death, either in severe placental abruption or after prolonged retention of a dead foetus *in utero*. Amniotic fluid embolism, however, is a rare cause of coagulation failure which occurs when labour is tumultuous and the clotting defect may then present after the birth of a live child.

It is not surprising that coagulation failure sometimes affects the same patient in different pregnancies. Fyfe and Grant (1960) recorded such a case and we have experience of a similar happening. In the case recorded here, however, coagulation failure not only recurred 24 days later in the same pregnancy but a live foetus was eventually delivered. The cause is not certain, but inspection of the placenta suggested that a minor degree of abruption had occurred some weeks before delivery.

This case also illustrates how rapidly fibrinogen can be replenished from the natural sources (see Chart). This is important, as fibrinogen administration carries risks. If given during a period of thromboplastin release it may act as "fuel to the flames of the fibrination process" and lead to a deterioration in the patient's condition (Jeffcoate and Scott, 1959), while it also may cause homologous serum hepatitis. Pritchard (1958) quotes a minimum figure of 5% based on the finding that 37 out of 727 patients treated with fibrinogen were known by the obstetrician concerned to have developed jaundice. It is likely that the true incidence was higher. Longo *et al.* (1959) record 2 cases in 38 patients (5.3%), while Skinner (1957) found that 6 out of 17 patients developed hepatitis. It is known that the homologous serum hepatitis virus is transferred in the fibrinogen fraction of plasma and the relatively large pools of plasma needed for fibrinogen preparation must increase the hazard.*

Hodgkinson (1956) recommended that patients treated with fibrinogen should receive gamma-globulin to prevent hepatitis. There seems, however, much to be said for Pritchard's (1958) advice to withhold fibrinogen in obstetric defibrinogenation except if (a) an operation becomes necessary, (b) genital-tract lacerations are present, or (c) there is post-partum failure of uterine retraction.

We are indebted to Professor T. N. A. Jeffcoate for advice and to Mr. D. Pryor Jones for providing us with details of the patient's history when she was under his care.

*The fibrinogen available in this country is prepared from a 300-donor pool (Maycock, 1961, personal communication). Plasma is normally prepared from a 10-donor pool.

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CHRISTMAS DISEASE ASSOCIATED WITH PRIMARY CAPILLARY ABNORMALITIES

BY

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A number of patients with capillary defects of the von Willebrand type have been shown to have antihæmophilic globulin (factor VIII) deficiency. Biggs and Macfarlane (1958), Horler and Witts (1958), and Blackburn (1961) are some of the authors who have described such cases and who have reviewed the literature on the subject. The object of the present paper is to record a demonstrable deficiency of Christmas factor (factor IX) associated with a primary capillary defect in two unrelated females. Care was taken to exclude in both patients the existence of hypertension, renal disease, diabetes mellitus, thrombo-embolic diseases, scurvy, and ovarian deficiency, all known causes of capillary abnormalities.

Case Reports

Case 1.—A confectioner's assistant aged 16 had always bruised more readily than her blood relatives and had always bled excessively after cuts and abrasions. On the single occasion when a permanent premolar tooth had been extracted, abnormal hæmorrhage had continued for three days. Incision of a small abscess in the region of the right ankle had been followed by persistent oozing of blood for 48 hours. Recurrent crops of purpura had been noticed on the feet, legs, and arms for many years. Treatment for a tuberculous right knee-joint had been completed at the age of 12; hæmarthrosis of this joint having been mistaken for

a tuberculous lesion. On review the radiological appearances were consistent with a haemarthrosis, and a Mantoux test (dilutions 1/1,000 and 1/10,000) performed two years later was negative. On examination scanty purpuric lesions on the arms, legs, and dorsal aspects of the feet were noted. Some muscle-wasting persisted above and below the right knee-joint, from which crepitus was elicited on movement. All her other joints were normal. The family history was negative. Three brothers, three sisters, her parents, grandparents, and three maternal uncles, two maternal aunts, one paternal uncle, two paternal aunts, and their children were unaffected by abnormal bleeding.

Case 2.—A schoolgirl aged 10 had suffered from readily bruising, excessive haemorrhage from cuts and abrasions, and epistaxis since infancy. Blood transfusions had been necessary from time to time, including one occasion when she had had a haematemesis. Purpura of the limbs and trunk had been noticed since babyhood. There had never been haemarthrosis. On examination widespread purpura of the limbs and trunk, especially where the straps of her vest passed over her shoulders, was seen. Bruising was limited to small areas of the right thigh and knee. Again the family history was negative. Two sisters, father, mother, grandparents, and two maternal great-aunts, one maternal great-uncle, paternal great-aunts and uncles, and their children were unaffected by abnormal bleeding.

Laboratory Methods

The bleeding-time was measured by an Ivy method (Biggs and Macfarlane, 1957a), and the tourniquet test was that described by Bell, Lazarus, and Munro (1940). Microscopy of the nail-fold capillaries was performed, using reflected light and the 2/3 objective (Macfarlane, 1941). The method of Lee and White (1913) was used to measure the whole-blood clotting-time, and that described by Biggs and Macfarlane (1957b) for the one-stage prothrombin test. Platelets were counted, using Lempert's (1935) method, and platelet morphology was assessed on a well-stained peripheral Leishman film. Thromboplastin generation was estimated by the method of Biggs and Douglas (1953). In addition correction tests against known haemophilic alumina-treated plasma and known Christmas disease serum were made, using the mixtures shown in Table II. Christmas factor assays were measured by a technique based on Pitney's (1956) method of antihemophilic globulin assay.

Results

The results of preliminary tests are shown in Table I and those of further investigations in Table II. Abnormal nail-fold capillaries were demonstrated in both patients on capillary microscopy. A prolonged bleeding-time and a strongly positive tourniquet test were also found in Case 2. The bleeding-time in Case 1

TABLE I.—Results of Preliminary Tests

Tests	Case 1	Case 2	Comments
Bleeding-time	5½ min.	>30 min.	Normal average 2½–5 min.
Tourniquet test	Negative	Positive ++	
Capillary microscopy	+	+	
Tortuosity	+	+	
Calibre variation	+	+	
Defective contractility to trauma*	+	+	
Whole-blood clotting-time	12½ min.	7 min.	Normal 3–12 min.
One-stage pro-thrombin time	15 sec.	18 sec.	Normal
Patient	15	17	
Control	15	17	
Platelet Count (per c.mm.)	200,000	160,000	
Platelet Morphology	Normal	Normal	

* This was not observed in all capillaries.

TABLE II.—Results of Thromboplastin Generation Tests

Source of Plasma and Serum Reagents		Case	Clotting-time in Seconds after Incubation for			
Alumina-treated Plasma	Serum		1 min.	2 min.	3 min.	4 min.
Normal	Normal	1	45	12	9	9
		2	25	15	13	11
Patient's	"	1	38	19	11	11
		2	26	12	11	10
Normal	Patient's	1	36	31	23	22
		2	28	15	14	11
Patients'	"	1	61	38	28	26
		2	21	17	15	12
Haemophilic	Normal	1	60	31	22	20
		2	50	45	43	38
1 part normal, 9 parts haemophilic	"	1	37	17	13	14
		2	41	35	33	28
1 part patient's, 9 parts haemophilic	"	1	35	32	19	15
		2	43	37	30	25
Normal	Christmas	1	60	50	45	40
		2	55	31	25	23
"	1 part normal, 19 parts Christmas	1	38	25	16	16
		2	43	20	19	18
"	1 part patient's, 19 parts Christmas	1	60	47	45	40
		2	62	51	43	35

Similar results have been found on repeated occasions in each patient. A level of Christmas factor (factor IX) of 12% of normal was found in Case 1 and of 25% of normal in Case 2.

It will be noted that a serum deficiency was not obvious in Case 2, using the "ordinary" thromboplastin generation test.

Normal platelets were used throughout.

has always been at the upper limit of normal to slightly abnormal range, and the tourniquet test negative; the whole-blood clotting-time was slightly prolonged. Both patients showed a definite deficiency of Christmas factor and normal one-stage prothrombin test and platelet count and morphology.

Comments

The laboratory findings show that these two patients have a deficiency of Christmas factor and an associated capillary defect, the latter being supported by the clinical histories of recurrent purpura. It is known that Christmas disease is inherited as a sex-linked recessive character like haemophilia (Biggs, Douglas, Macfarlane, Dacie, Pitney, Merskey, and O'Brien, 1952), although the deficiency may not be completely recessive, and that primary capillary defects, including that of von Willebrand, are usually but not always inherited as non-sex-linked dominant characters (Blackburn, 1961). The two abnormalities of deficiency of Christmas factor and of primary capillary defect, whose exact significance in the present patients is obscure, may show presumably variable penetrance and expressivity as manifestations of one affected gene. They may be due, alternatively, to the expression of different genes which may be located on the same chromosome. As there is no family history of a haemorrhagic disorder in either patient, the abnormalities may be due to gene mutation, or the relevant genes may have been suppressed in the patients' forebears.

Finally, it is interesting to note the association of a further blood-coagulation defect—namely, plasma thromboplastin antecedent factor deficiency—with increased vascular fragility and deficiency of plasma antihemophilic factor in the same family as reported by Perry, Opfell, and Baker (1960).

Summary

The association of a primary capillary defect with deficiency of Christmas factor in two girls is described. The families of both patients are unaffected by abnormal bleeding.

We thank Dr. Rosemary Biggs for confirming the diagnosis in Case 2.

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Preliminary Communications

Double-blind Trial of Betamethasone

Topical applications of steroids have been recognized as effective in the control of numerous dermatoses since the introduction of local hydrocortisone by Sulzberger and Witten (1952). There have been many attempts to find more potent local steroids (Vickers and Tighe, 1960) or to reduce the cost of such treatment (Inman, 1959). This paper reports experience with a new topical steroid, betamethasone (16- β -methyl-9- α -fluoro-prednisolone), and presents the results of double-blind paired comparison trials of the new steroid and hydrocortisone. The betamethasone was supplied in two forms—the relatively insoluble free alcohol and the readily water-soluble phosphate ester. In the double-blind comparison trials betamethasone phosphate was compared with hydrocortisone and, in addition, the two forms of betamethasone were compared directly. The new steroid is approximately 20% cheaper than hydrocortisone.

INVESTIGATION

Double-blind Trials.—(1) Betamethasone phosphate and hydrocortisone: Only patients with eruptions which might be expected to respond to local steroid therapy were admitted to the trial and all had symmetrical lesions on the limbs. The two steroids were supplied in a water-miscible base and in identical tubes labelled B (blue label) and Y (yellow label). The concentration of hydrocortisone was 1% and that of betamethasone phosphate 0.1%. Only the manufacturer was aware of the identity of the tubes until the trial was completed. The patients were supplied with a tube of each steroid and instructed to apply Y to one limb and B to the other. The side treated with B was selected at random. If all four limbs were involved then B was applied to one upper limb and the contralateral lower limb, thus giving two paired results on one patient. Subjective and objective observations were made from five to ten days after entering the trial. Whenever possible two observers reviewed each patient, and care was taken that the reviewer was not aware of the side of application of B and Y till the assessment had been made. (2) Betamethasone phosphate and betamethasone alcohol: This trial was conducted under identical conditions to the first trial, except that the steroids were supplied in a greasy base and the tubes were labelled

A and B. Both the betamethasone phosphate and the betamethasone alcohol were used in a concentration of 0.1%.

Clinical Use of Topical Betamethasone.—In addition to the double-blind trial, betamethasone was used topically as a lotion, a non-greasy cream, or a greasy ointment in the treatment of 52 other patients without symmetrical lesions but who were thought likely to respond to local steroid treatment.

RESULTS

Double-blind Trials.—(1) Betamethasone phosphate and hydrocortisone: Thirty-eight patients were admitted to the trial. The results are shown in Table I. When a difference was noted between the effect of betamethasone phosphate 0.1% and hydrocortisone 1% it was very slight. (2) Betamethasone phosphate and betamethasone alcohol: Fifty-two patients were admitted to this trial; the results are shown in Table II. Once again the differences noted were slight.

TABLE I

Dermatosis	No. of Cases	Pairs	Betamethasone Phosphate (B) Better than Hydrocortisone (Y)	Hydrocortisone (Y) Better than Betamethasone Phosphate (B)	No Difference
Atopic eczema ..	23	34	13	10	11
Discoid ..	4	5	1	2	2
Seborrhoeic ..	4	4	2	2	0
"Autosensitization eruptions" ..	7	7	1	0	6
Total ..	38	50	17	14	19

TABLE II

Dermatosis	No. of Cases	Pairs	Betamethasone Phosphate Better than Betamethasone Alcohol	Betamethasone Alcohol Better than Betamethasone Phosphate	No Difference
Atopic eczema ..	36	42	14	10	18
Discoid ..	5	5	1	1	3
Seborrhoeic ..	1	1	0	0	1
Lichen simplex ..	1	1	0	1	0
Contact dermatitis (fabric) ..	2	3	0	3	0
"Autosensitization eruptions" and eczema (unspecified) ..	7	7	0	2	5
Total ..	52	59	15	17	27

Clinical Use of Topical Betamethasone.—The 52 patients in whom the new steroid topical preparations were used as routine treatment were mainly suffering from atopic eczema (23), contact dermatitis (16), or ano-genital pruritus (9). The results of treatment were little different from those seen with local hydrocortisone in similar cases, though, contrary to the results of the double-blind trials, certain patients with very chronic dermatoses found local betamethasone more effective than local hydrocortisone or even triamcinolone.

DISCUSSION

The results of the double-blind trials show that betamethasone—as either the phosphate or the free alcohol, both at concentrations of 0.1%—is an effective local steroid with a potency equal to that of 1% hydrocortisone. Day-to-day use of the betamethasone local applications in another group of patients has confirmed this impression. It seems possible that those