TABLE III.—Changes in Total Serum Lipids on a High-protein Diet

	On Admission	$\frac{1}{2}$ Week	1 Week	2 Weeks	3 Weeks
No. of cases	35	28	28	22	11
Mean (mg./100 ml.)	271	456	560	531	403
Range	46–1,200	149–960	194–915	296–894	225–625

TABLE IV.—Changes in Thymol Turbidity on a High-protein Diet

	On Admission	$\frac{1}{2}$ Week	1 Week	1½ Weeks	2 Weeks	2½ Weeks	3 Weeks
No. of cases	107	97	90	83	81	53	40
Mean MacLagan units	5.1	6.1	6.2	6.2	6.3	6.9	6.4
Range	0–18	0–25	0–29	0–18	0–27	0–19	0–18
Standard deviation	4.15	4.12	4.63	3.77	4.67	4.54	3.70

TABLE V.—Influence of High-protein Diet on Bromsulphthalein Retention

	On Admission	$\frac{1}{2}$ Week	1 Week	2 Weeks	3 Weeks
No. of cases	51	35	40	31	21
Mean (%)	15.0	5.4	3.9	2.7	1.9
Range (%)	2.4–40.0	1.1–24.3	0.2–27.3	0.1–16.0	0.8–4
Standard deviation	9.25	7.29	4.98	3.68	1.91

affect bromsulphthalein abstraction, but the mechanism of abstraction is not simple, and, in fact, contradictory (Culbertson *et al.*, 1951; Bradley *et al.*, 1952; Heineman *et al.*, 1952). It appears, however, that the liver is capable of removing a definite proportion of the bromsulphthalein injected (Myers, 1949; Casselman and Rappaport, 1954), with the hepatic artery and the distribution of blood in the arterial bed holding key positions in the abstraction of bromsulphthalein from the blood (Andrews, 1955).

It has been suggested that the fat-laden liver cells of kwashiorkor compress the sinusoids, with resultant low abstraction of bromsulphthalein (Gillman and Gillman, 1951). Bromsulphthalein retention was normal within three days in 84% of cases, and coupled with this was the finding of elevated blood fats also at three days. It is tempting to postulate a liver source for the elevated blood fat. With the relief on tension in the liver cells and consequent decompression of sinusoids a better blood supply would give more efficient abstraction of bromsulphthalein from the blood. Evidence from liver biopsies tends to make the clearing of fat from the liver cells a slow process (Trowell *et al.*, 1954); however, there is often no correlation between structural changes in the liver and functional efficiency as judged by current liver-function tests.

Elucidation of the bromsulphthalein test is under investigation in this laboratory, using bromsulphthalein clearance as index (Kinnear and Pretorius, 1957).

Summary

Groups of kwashiorkor patients were treated with high-protein diets of different composition. The effect of these different diets on serial liver-function tests was assessed.

No difference in efficacy in returning liver-function tests to normal could be found between the various diets tested.

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ANTIHAEMOPHILIC GLOBULIN DEFICIENCY ASSOCIATED WITH A CAPILLARY DEFECT

BY

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A report by Ingram (1956) of a case of multiple haemostatic defects in a female prompted us to record the following examples in a brother and two sisters. Our cases, although less prolific in abnormalities than Ingram's, are of interest in that they conform to a pattern described by others (see Table) of an increased bleeding-time and defective thromboplastin generation due to antihaemophilic globulin deficiency. We feel that these cases constitute a distinct entity which until now has been included in the omnibus terms "von Willebrand's disease" and "pseudohaemophilia." The low antihaemophilic globulin level emphasizes the need for differentiation.

Case 1

A youth aged 17 had a tendency to bleed excessively. This was discovered following circumcision when he was 3 months old. He has always bruised easily and has had spontaneous purpuric rashes. He bleeds readily from nose and gums. There is a history of joint haemorrhage in the knees and shoulders. Following swelling of the left knee aspiration of the joint produced blood only. Persistent haemorrhage following this necessitated transfusion. He had had two teeth extracted at 7 years of age and bled for seven weeks. Again he had to be transfused.

Laboratory Findings.—Red blood cells, 5,270,000 per c.mm.; haemoglobin, 96% (14.3 g. per 100 ml.); colour index, 0.91; white blood cells, 8,800 per c.mm. (polymorph neutrophils 72%, polymorph eosinophils 2%, lymphocytes 20%, monocytes 6%); platelets, 342,000 per c.mm.; serum proteins, 7.23 g. per 100 ml. (albumin 3.72 g.; globulin 3.51 g.); plasma fibrinogen, 0.2 g. per 100 ml. Blood group O, Rh positive, phenotype CCDee, which in all probability corresponds to the genotype CDe/CDe. Tourniquet test positive. Bleeding-time—Ivy's (Ivy *et al.*, 1941) method—22 minutes. No capillary abnormality was demonstrated. Clotting-time—Lee and White's (1913) method—at 37° C., 11 minutes. Prothrombin time (Quick's method, using human brain extract), 12 seconds (control, 12 seconds).

Prothrombin consumption index (Dacie, 1956), 88% (normal, 0-40%). Thromboplastin generation test (Biggs, Douglas, and Macfarlane, 1953): The patient's plasma with control platelets and serum showed defective thromboplastin generation. The patient's platelets with control plasma and serum showed normal thromboplastin generation, thus excluding a functional platelet defect such as Glanzmann's disease. Assay of antihæmophilic globulin (Pitney, 1956), 20% of normal. There was no evidence of a circulating anticoagulant. The test for plasma antithromboplastin (Biggs and Macfarlane, 1953) was negative.

Family History.—There was no history of abnormal hæmorrhage in other members of the family apart from Cases 2 and 3, described below. Father and mother: all tests, including thromboplastin generation, were normal. A sister of Case 1, aged 14, is alive and well: all investigations were normal. A sister aged 2 is Case 2. A sister (Case 3) died at 11 months.

Case 2

This girl, aged 2, has bled profusely after minor injury since birth. She bruises easily and has frequent nose-bleeds. She recently fell and cut her cheek. Following admission to hospital her hæmoglobin was found to be 30% and she had to be transfused.

Laboratory Findings.—Red blood cells, 5,560,000; hæmoglobin, 86% (12.8 g. per 100 ml.); colour index, 0.77; white blood cells, 14,500 per c.mm. (polymorph neutrophils 28%, polymorph eosinophils 1%, lymphocytes 61%, monocytes 10%); platelets, 342,000 per c.mm. Films show anisocytosis, poikilocytosis, hypochromia, and slight polychromasia. Tourniquet test positive. Bleeding-time (Ivy's method), 20 minutes. Tests to demonstrate capillary abnormality were not attempted because of the patient's age and lack of co-operation. Clotting-time

Case	Sex and Age	Author	Personal History	Family History	Bleeding-time	Clotting-time	Prothrombin	Capillary Fragility	Abnormal Capillaries	Prothrombin Consumption	Antihæmophilic Globulin	Other Investigations
I	F 5	Alexander and Goldstein (1953)	Bleeding from birth	Brother died from hæmorrhagic disorder. Mother, non-bleeder, had abnormal capillaries	Prolonged	Slight to moderate increase, rectified by normal plasma	Subnormal	Increased	Present	Defective	10-20% of normal	Factors V and VII and platelets normal. No anticoagulant. No antithrombin
II	M 30	" "	Bleeding for 8 years	Normal	"	Borderline	Normal	Normal	"	Occasionally retarded	" "	Factors V and VII normal
III	F 6	Larrieu and Soulier (1953)	Epistaxis from age of 2 weeks and hæmorrhages	3 sisters and 1 brother normal	Over 15 mins.	8-10 mins. (Lee and White)	Quick, one-stage prothrombin time normal	—	—	—	Deficient as shown by thromboplastin generation test	Clot retraction and platelets normal. No anticoagulant present
IV	F 6	Quick and Hussey (1953)	Severe bleeding condition, including frequent epistaxes	Brother (24) has identical condition. Father, mother and older brother normal	Over 30 mins.	8 mins.	Normal	—	—	—	Deficient	Platelets normal. Does not correct hæmophilic blood
V	F 15	Bigelow (1954)	Epistaxes, bleeding gums. Joint hæmorrhages. Easy bruising and menorrhagia	Normal	Prolonged	Moderately increased	Not given	Increased	—	Defective	"	Factor VII deficiency at times. Platelets normal. No circulating anticoagulant
VI	F Not given	"	Easy bruising and menorrhagia	—	"	Prolonged	—	—	—	—	"	—
VII	F 24	Van Creveld <i>et al.</i> (1955)	Bleeding from infancy from ear, mouth, and nose. No spontaneous hæmorrhages into skin but bruises easily. Menorrhagia. No hæmorrhages	Elder sister died at 3 years with cerebral hæmorrhage. Others normal	Over 25 mins. (Duke's method)	Slightly prolonged	Quick, one-stage prothrombin time normal	—	Absent	—	Deficient as shown by thromboplastin generation test	Bone marrow and clot retraction normal. Plasma fibrinogen 2.5 g./litre. No anticoagulant. No fibrinolysin. Clinically spleen not palpable
VIII	M 9	Darte (1955)	Bruised and bled easily for 7 years. Spontaneous hæmorrhage	Mother has prolonged bleeding time and defective thromboplastin generation. Sister died at 5, had a prolonged bleeding-time	15 mins. Prolonged	Normal	Normal	Increased	—	Upper limit of normal	Defective thromboplastin generation. Moderate	Clot retraction normal
IX	M 17	Present Case I	Bleeding from 3 months, from nose and gums. Easy bruising, spontaneous purpura rashes. Hæmorrhages	Case X and XI	22 mins. (Ivy)	11½ mins. (Lee and White)	Quick, one-stage prothrombin time normal	"	—	Defective	Deficient as shown by thromboplastin generation test. A.H.G. = 20% of normal	No circulating anticoagulant. No plasma antithromboplastin. Plasma fibrinogen 2 g./litre. Platelets normal
X	F 2	" 2	Bleeding since birth after minor injury. Very easy bruising and epistaxes	(Above)	20 mins. (Ivy)	10 mins. (Lee and White)	"	"	—	—	"	Platelets normal
XI	F 11 mths.	" 3	Always bruised easily and bled excessively after minor injury	(Above)	Prolonged	Prolonged	—	—	—	—	—	Died at 11/12 from bleeding from throat followed by gastro-enteritis
XII*	F 13	Singer and Ramot (1956)	Bled since age of 2½. Nose bleeds; bruising	Elder brother died. Known to bleed excessively	30 mins. +	Normal	Normal	Normal	—	—	A.H.G. deficient by thromboplastin generation test 19-22% of normal	Clot retraction normal. Blood failed to correct defect in known hæmophilias. No anticoagulant demonstrated

* Report published after this paper was submitted. Other less well documented cases have been described by: Koch and Schultz (1952); Verstraete and Vandenbroucke (1955); three cases, one son and two daughters of same family; Soulier, Larrieu, and Warrelle (1955); 2 females and 1 male, all unrelated; Schulman, Smith, Eriandson, and Fort (1955); 3 males and 3 females.

(Lee and White's method at 37° C., 10 minutes. Prothrombin time, 12 seconds (control, 12 seconds). The thromboplastin generation test showed defective generation with the patient's plasma. With patient's platelets and control plasma and serum, generation was normal—that is, no functional platelet defect. No circulating anticoagulant was present. Blood group B, Rh positive, phenotype CcDe, which in all probability corresponds to the genotype CDe/cDE.

Case 3

This child, a girl who died in 1949 at the age of 11 months, was not investigated by us. The following is a summary of the notes kindly supplied by Dr. J. M. Garvie. The patient was admitted to the Manor Hospital, Walsall, on October 9, 1949, with a history of bleeding from the throat for several hours. She had always bruised easily and had had a similar haemorrhage at the age of 3 months. On admission there were bruises over the limbs and head, and fresh blood was exuding from the base of the tongue. Eleven days later she developed offensive stools and went steadily downhill, dying on November 7.

Laboratory Investigations.—October 10: red blood cells, 3,250,000 per c.mm.; haemoglobin, 65% (9.7 g. per 100 ml.); white blood cells, 17,600 per c.mm. Platelets plentiful. Bleeding-time, 12 minutes. Clotting-time, 15 minutes. October 20: red blood cells, 3,500,000 per c.mm.; haemoglobin, 70% (10.4 g. per 100 ml.); white blood cells, 11,000 per c.mm. Bleeding-time, 10 minutes. Clotting-time, 10 minutes.

Post-mortem Findings.—Enlarged cerebral ventricles with thrombosis of the surface vessels of the brain. Congested lungs. Large pale liver. Patchy ulceration in the small intestine. Cause of death, toxæmia following gastro-enteritis.

Discussion

About 25 years ago von Willebrand described a haemorrhagic diathesis in 16 females and 7 males of one family in the Åland Islands, off the coast of Finland. Since that time a fairly extensive literature has arisen. The disease occurs in either sex and has one constant laboratory abnormality—namely, a prolonged bleeding-time. About 50% give a positive tourniquet test. The disease, which consists of a capillary defect with failure of normal contractility, should be differentiated from hereditary thrombasthenia or Glanzmann's disease. The latter is due to a functional platelet defect which gives rise to a characteristic pattern of abnormalities: (1) increased bleeding-time; (2) positive tourniquet test; (3) defective clot retraction; (4) defective prothrombin consumption; and (5) defective thromboplastin generation, using the patient's platelets.

The abnormalities found in the condition we describe are:—Capillary defect: increased bleeding-time, positive tourniquet test, and purpura. Antihæmophilic globulin deficiency: may or may not have increased clotting-time, easy bruising, hæmarthrosis, defective prothrombin consumption, and defective thromboplastin generation.

It is obvious that differentiation of this group is of great importance to the patient, since management is influenced by the antihæmophilic globulin deficiency. Fresh plasma or blood should be used when surgery is contemplated and bleeding excessive. Generally speaking, the antihæmophilic globulin deficiency must be fairly mild, since most of the cases described have either a normal or slightly prolonged clotting-time.

We wish to thank Dr. Garvie for referring both patients to us for investigation and allowing us to use his notes on Case 3.

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CONGENITAL HAEMOLYTIC ANAEMIA COMPLICATED BY MEGALOBlastic ANAEMIA OF PREGNANCY

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Megaloblastic anaemia of pregnancy in association with a haemolytic anaemia is rarely found. A search of the available literature suggests that only Davidson (1952) has described it. In his report of a case in which a megaloblastic anaemia of pregnancy was superimposed on a pre-existing microspherocytic anaemia he comments on the surprising rarity of this finding in view of the greatly increased requirement of hæmatin agents such as folic acid which must necessarily follow the sustained overactivity of hæmatopoietic tissue in chronic hæmolytic anaemias.

We have observed a similar case over a period of three years; a report of the case is given below.

Case History

A 2-para aged 32 attended the antenatal clinic at the National Maternity Hospital on February 3, 1953. Although her family doctor had given her iron in large doses she was very anaemic and was admitted to hospital. She gave a history of diarrhoea and complained of sore tongue. The spleen was enlarged.

On admission her blood count was as follows: haemoglobin, 2.5 g. per 100 ml.; erythrocytes, 1,040,000 per c.mm.; leucocytes, 5,120 per c.mm. Sternal marrow showed a well-defined megaloblastic hyperplasia. Treatment was by transfusion (packed cells) and folic acid, 20 mg. intramuscularly daily. There was a reticulocyte response with a peak at 11% on the seventh day, following the institution of folic acid therapy. Re-examination of the sternal marrow on the 10th day after admission showed conversion to normoblastic erythropoiesis. A test meal (histamine) on March 4 showed achlorhydria. While the peripheral blood picture demonstrated a sustained improvement for 25 days after admission to hospital (Hb, 10 g.; R.B.C., 4,000,000), a transient deterioration followed. At the time the reason for this setback was not apparent. It now seems certain that a mild exacerbation of the hæmolytic anaemia occurred at this period.

Between the 25th and 50th days of observation the erythrocyte count did not rise above 3,700,000, but on the 76th day it was 4,200,000 and the haemoglobin was 11.6 g. per 100 ml. On the 84th day (May 2) the patient was delivered of a living male infant weighing 7 lb. 9 oz. (3.4 kg.). She did not present herself for examination until seven months