Antihaemophilic factor deficiency, capillary defect of von Willebrand type, and idiopathic thrombocytopenia occurring in one family

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SYNOPSIS Thrombocytopenia of the type found in idiopathic thrombocytopenic purpura is described in a family with a deficiency of antihaemophilic factor, and a capillary abnormality. The propositus (father) has thrombocytopenia and abnormal platelet morphology, together with a plasma deficiency of antihaemophilic factor, but normal capillaries. His two daughters each are deficient in antihaemophilic factor with normal platelets but abnormal capillaries.

In 1931, von Willebrand described a familial haemorrhagic disorder which he called hereditary pseudo-haemophilia. The bleeding diathesis, inherited as an autosomal Mendelian dominant, was associated with excessive haemorrhage following minor injury and with spontaneous bleeding from the skin and mucous surfaces. The prolonged bleeding time and increased capillary fragility were accompanied by a normal platelet count and morphology, and a normal blood coagulation time and clot retraction. Dogmatic views of its pathogenesis were not given at that time.

In recent years this disease has been more intensively studied. A number of workers have described cases associated with deficiency in antihaemophilic factor (Larrieu and Soulier, 1953; Alexander and Goldstein, 1953; Quick and Hussey, 1953; Soulier and Larrieu, 1954; Ingram, 1956; Schulman, Smith, Erlandson, Fort, and Lee, 1956; Nilsson, Blombäck, Jorpes, Blombäck, and Johansson, 1957; Nilsson, Blombäck, and Francken, 1958; Biggs and Macfarlane, 1958; Horler and Witts, 1958; Wilkinson, Nour-Eldin, and Israëls, 1958; Blackburn, 1961), while two of Blackburn's (1961) series had a deficiency of Christmas factor in addition to the basic capillary abnormality of von Willebrand's disease. Braunsteiner (1955) and Braunsteiner and Pakesch (1956) showed that cases of von Willebrand's disease and those with abnormal platelet function, as demonstrated by electron microscopical studies and thromboelastography, may occur in the same family. So far as we are aware, however, thrombocytopenia of idiopathic type has not been described before in families of this group. The two daughters in the present family have been included in Blackburn's (1961) series of 158 cases of primary capillary haemorrhage.

LABORATORY METHODS

The three affected members of the present family (father and two daughters) were investigated using the following methods.

For the bleeding time, an Ivy method, as described by Biggs and Macfarlane (1957a), was used and the tourniquet test by the method of Bell, Lazarus, and Munro (1940).

Microscopy of nail-fold capillaries was carried out as described by Macfarlane (1941). The capillaries were examined for increased tortuosity, variation in calibre, and defective contractility of trauma. The platelet count was done by the method of Lempert (1935), and the whole blood clotting time by that of Lee and White (1913). The one-stage prothrombin test was one slightly modified from that described by Biggs and Macfarlane (1957b). Prothrombin consumption was estimated by the method of Merskey (1950). The thromboplastin generation test was carried out by the method of Biggs and Douglas.
(1953), and antihaemophilic factor titration by the method
of Pitney (1956).

Standard methods were used for the determination of
the haemoglobin level, red cell and total white cell
counts and the differential white cell count.

THE PATIENTS

FATHER He is an auditor, aged 34 years, who, when
referred to hospital, gave no history of taking cytotoxic
drugs or of exposure to any toxic industrial hazard.
There was a clear history of excessive bruising for about
14 years, and he had always bled abnormally after
receiving cuts or abrasions. There had never been
spontaneous haemorrhage from mucosal surfaces, but
transient crops of small blue spots had been noticed
under the armpits. Nettlerash had been observed from
time to time on the shoulders. He had never had joint
symptoms. At the age of 5 years he required blood
transfusion after the removal of his tonsils and adenoids.
He had been told that he bled for many days after this
operation and that the bleeding stopped for one and
a half days at one stage during this episode. After dental
extractions he has always bled profusely for 12 hours and
has continued to bleed for up to seven days in spite of
local dental attention. One year previously he had been
transfused with two bottles of plasma after dental
extractions. His past illnesses included chickenpox,
measles, mumps, tonsillitis, sandfly fever, and malaria.
He and his two daughters are the only members of the
family who have been affected by abnormal bleeding.
He has three brothers (one of whom has two sons), and
one childless sister. His father, three paternal uncles
and three paternal aunts and their children, his mother, one
maternal uncle with no children and two maternal aunts,
one of whom has two daughters and one son, are also
unaffected by abnormal bleeding.

Laboratory findings The haemoglobin, red and white
cell counts (including differential), red cell morphology,
one-stage 'prothrombin' time, whole blood clotting time,
bleeding time, tourniquet test, and capillary microscopy
of the nail folds were all within the normal range. The
platelet count was low (70,000 per c.mm.) and hypo-
granularity and many giant and small forms were seen.
The prothrombin consumption index was high, 100%
(normal well below 40%). The thromboplastin generation
test showed a plasma deficiency, and the titre of anti-
haemophilic factor was low, 30% (normal range 50 to
150%). On previous occasions the platelet count had
been as low as 20,000 per c.mm. and the bleeding time
prolonged to 18 minutes. Bone marrow examination
showed an increased number of abnormal megakaryo-
cytes with maturation arrest.

DAUGHTER AGED EIGHT YEARS She has always bled ex-
cessively following cuts and abrasions, and has bruised
with abnormal ease. Recurrent and troublesome epistaxes
began at the age of 5 years. Small crops of purpura on the
trunk and limbs have been noted from time to time.
Dental extractions have always led to abnormal haem-
orrhage. On one occasion the removal of one tooth
necessitated admission to hospital for one week, but
transfusion was not necessary. The extraction of two
teeth on another occasion resulted in admission to
hospital for three weeks, and the need for blood trans-
fusion. She has never had haemarthrosis.

Laboratory findings Haemoglobin, red cells, white
cells, and platelets were normal. The bleeding time was
10 minutes (normal less than five and a half minutes),
the tourniquet test negative, and the whole blood clotting
time seven to nine minutes (normal). The thrombo-
plastin generation test showed a deficiency in a plasma
factor. The one-stage prothrombin time was normal.
The prothrombin consumption index was 39% (probably
abnormal). The antihaemophilic factor titre was low,
namely 30%, 35%. Capillary microscopy of nail folds
showed that tortuosity and calibre variation was con-
siderably increased with defective contractility to trauma
of some forms.

DAUGHTER AGED FOUR YEARS She has always bruised
abnormally easily and has bled excessively following cuts
and abrasions. A plasma transfusion was necessary on
one occasion when three teeth were extracted. Purpura
and haemarthroses had not been noticed by her parents,
but the former was present on examination in small crops
over the shoulders as well as widespread bruising of the
trunk and limbs.

Laboratory findings The haemoglobin, red cells, white
cells, and platelets were normal. The bleeding time was
nine and a half minutes (prolonged), the tourniquet test
was positive, the whole blood clotting time 10 minutes
(normal), the one-stage prothrombin time was normal,
the prothrombin consumption index abnormal (50%),
and there was a deficiency in the patient's plasma
fraction in the thromboplastin generation test. The anti-
haemophilic factor titre was low (25%). Capillary
microscopy of nail folds showed increased tortuosity
and variation in calibre with defective contractility to trauma
of some forms.

DISCUSSION

While a mild to moderate degree of thrombocyto-
penia is well known to occur in some haemorrhagic
phases of von Willebrand's and allied diseases, it
does not persist in between these episodes as it has
done in the father of the two girls.

The precise significance of the vascular abnor-
mality, thrombocytopenia, and plasma deficiency
in antihaemophilic factor in this family is obscure
at present. It would seem that most cases of von
Willebrand's disease are inherited as an autosomal
dominant (Biggs and Macfarlane, 1958; Pitney and
Arnold, 1960; Blackburn, 1961) but this is not
always the case (Blackburn, 1961). While the in-
hheritance of the antihaemophilic factor deficiency
in the father and two daughters in the present family
follows such a pattern, the platelet and vascular
abnormalities clearly do not do so. These three main
abnormalities may show variable penetrance and expressivity as manifestations of a single affected gene. Alternatively, they may be due to the expression of different genes which may be located on the same chromosome.

Recently Raccuglia and Neel (1960) described kindred of 311 individuals in whom Dutch ancestry predominated. The variable manifestations of haemorrhagic disorder included a prolonged bleeding time, a morphological defect in platelets, and antihaemophilic factor deficiency. Genetic analysis suggested that the bleeding tendency was determined by a single dominant gene of variable penetrance and expressivity. A 22-year-old Caucasian man was shown by Perry, Opfell, and Baker (1960) to have plasma deficiencies of antihaemophilic factor and of plasma thromboplastin antecedent factor in association with increased vascular fragility. Different members of his family, however, had isolated abnormalities of each of the three types mentioned and also variable combinations of all three defects.

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REFERENCES