of hexachlorophane powder in the maternity hospitals (Simpson *et al.*, 1960; Beryl D. Corner, personal communication), there has been a reduction in the incidence of type-80 staphylococcal infections outside hospital.

Sources of Infection in the Family

Other members of the families of 30 patients had recently suffered from boils. Nasal swabs were taken from 22 families, from 14 of which strains similar to those that had afflicted the patients were isolated from one or more relatives. Five cases of recurrent furunculosis were cured only when family carriage was discovered and treated. The following case was instructive.

Swabs from a boil and from the nose, eyelids, and perineum of a man with a 10-year history of furunculosis yielded a phage-type 42E staphylococcus. His carrier sites were twice rendered free from staphylococci, and his furunculosis cleared up, only to recur within two months. It was then discovered that his wife and two sons were nasal carriers of the same strain. All four were treated with neobacrin nasal cream and hexachlorophane baths. No more boils occurred during the treatment or during a subsequent follow-up period of five months.

Discussion

The detection and eradication of sources of reinfection is of primary importance in the treatment of recurrent boils and styes, and should be carried out before resorting to other methods of treatment. A thorough clinical and bacteriological search for carrier sites on the patient's own body should first be undertaken. The nose and superficial lesions such as blepharitis and otitis externa are often important sources of staphylococci, and so is the perineum, especially when boils are affecting the trunk, buttocks, and thighs. The search for sources of reinfection should extend to other members of the family when necessary.

The clinical success of our treatment was remarkable, in view of the fact that complete suppression of nasal carriage was often slowly and sometimes only temporarily achieved. Subsequent experience has shown that a more intensive treatment, with nasal disinfectant cream applied five or six times instead of twice a day, usually suppresses the carrier state within a few days; and that persistence with the treatment for a further two weeks often cures it permanently, provided that other sites are treated simultaneously. Nevertheless, it may be wise to minimize the risk of recolonization by continuing the treatment for longer than this minimum period. A recent study of the treatment of nasal carriage among in-patients suggests that a nasal cream containing neomycin and chlorhexidine ("naseptin") may be the agent of choice. Sensitization to neomycin has been reported, but appears to be very rare (Jawetz, 1956; Calnan and Sarkany, 1958). It did not occur in the present investigation, nor in some thousands of in-patients who used nasal cream containing neomycin (Gillespie *et al.*, 1959).

Since staphylococci may be carried on areas of normal skin other than the perineum, and therefore might not be detected by swabbing, our present practice is to prescribe hexachlorophane baths or powder for all patients.

Successful treatment of the staphylococcal carrier state depends largely on the patient understanding the purpose of the treatment and his diligence in carrying

it out. He should be given a clear and simple explanation of the nature of staphylococcal carriage and infection. Time spent thus is never wasted. The uninformed patient is almost certain to weary of the treatment and to give it up too soon.

Summary

The treatment of chronic furunculosis by disinfecting sites of staphylococcal carriage was investigated in a controlled trial. Most patients were cured by disinfecting their own carrier sites, but it was sometimes also necessary to eradicate staphylococcal carriage in members of their families.

The nasal carrier site was the most important source of reinfection, but staphylococci from the perineum and from superficial lesions of the skin were also important. Perineal carriage was sometimes associated with boils on the trunk, buttocks, and thighs.

We thank Dr. C. D. Evans and Dr. R. P. Warin for their interest in this work, and for allowing us to study their patients.

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HAEMOPERITONEUM IN VON WILLEBRAND'S DISEASE

CASE OF OVARIAN FOLLICULAR RUPTURE

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The term "von Willebrand's disease" is used to describe a somewhat ill-defined haemorrhagic diathesis in which spontaneous bleeding takes place from mucosal surfaces, such as nose, gums, gastro-intestinal tract, urinary tract, and uterus. Only seldom do haemorrhages of deep tissue or joints occur. In most cases there is a definite familial history in which the inheritance is dominant and usually non-sex-linked.

The exact nature of the defect or defects in the haemostatic mechanism in this syndrome is obscure, but laboratory tests show a prolonged bleeding-time in association with normal numbers of circulating platelets. Platelet function is usually normal, while capillary morphology function may be abnormal (Macfarlane, 1941). It is now recognized that in this syndrome low

levels of plasma antihaemophilic globulin (A.H.G.) may be found, and this has led to the use of the term "vascular haemophilia" (Schulman, Smith, Erlandson, and Fort, 1955; Matter, Newcomb, Melly, and Finch, 1956). There is now evidence to suggest that the syndromes named vascular haemophilia and von Willebrand's disease are the same condition (Nilsson, 1959).

Nilsson, Blombäck, Jorpes, Blombäck, and Johansson (1957) have suggested that in this syndrome there is a defect in a plasma factor additional to A.H.G. The Cohn fraction 1-0 of fresh plasma prepared by these workers is capable of shortening the bleeding-time when transfused into patients with von Willebrand's disease, and this effect appears to be independent of the A.H.G. content of the fraction.

The haemorrhagic tendency in this syndrome is usually mild and in most cases only of nuisance value. It is well known that in any given patient there may be a transient increase in the tendency to bleed, and at such times he or she may present as a medical or surgical emergency. Such haemorrhagic episodes rarely require surgical intervention.

Unlike patients with classical haemophilia, those with von Willebrand's disease can sometimes undergo surgical operation without severe secondary bleeding; occasionally and unpredictably, severe secondary haemorrhage does occur post-operatively, particularly from mucosal surfaces, and, once started, is difficult to stop. This latter feature is a serious hazard after removal of tonsils and adenoids and other operations in the nasopharyngeal area in patients with this syndrome.

It is the purpose of this paper to describe an unusual complication of von Willebrand's disease—namely, rupture of ovarian follicular cysts with intraperitoneal haemorrhage on two separate occasions, each requiring surgical intervention.

Case History

A schoolgirl aged 16 was admitted as an emergency case to the Radcliffe Infirmary, Oxford, on April 22, 1957, complaining of six hours' severe lower abdominal pain which radiated to the tips of both shoulders. There had been no nausea or vomiting. Her last period had begun 14 days previously, and she was exactly at the mid-point of her menstrual cycle. She had always bruised easily, and had frequent nose bleeds and heavy menstrual periods, which lasted 10 days in a 27-day cycle. She had bled severely after tonsillectomy at the age of 6. Investigations in 1946 and 1960 had revealed a prolonged bleeding-time but normal platelet counts and whole-blood clotting-time.

Family History.—Both the girl's mother and twin sister had a similar haemorrhagic tendency. The mother bruised excessively and had had repeated epistaxes and menorrhagia; a severe episode of the latter had required an emergency hysterectomy. The twin sister's tendency to bleed presented at the age of 5 months with an epistaxis which had necessitated blood transfusion. Since then she had had repeated episodes of melaena. The patient's father and brother had no bleeding-tendency, but her maternal grandmother and great-uncle had shown a definite haemorrhagic tendency; neither had been investigated. The family tree is shown in the next column.

On examination the patient was pale but in good general condition; temperature 100° F. (37.8° C.), pulse 116, blood-pressure 130/180. The abdomen was tender, with marked guarding, particularly below the umbilicus; rebound tenderness was present and the left flank was dull to percussion. Rectally, a fullness could be felt in the pelvis. She was obviously bleeding into the peritoneal cavity, and the relation between the time of onset of her symptoms and

her menstrual cycle made rupture of an ovarian follicle the most probable diagnosis.

Operation (H. E.)—The abdomen was explored through a right paramedian incision. There was an extensive haemoperitoneum present, due to a bleeding ruptured right follicular cyst, which was oversewn with catgut. Persistent bleeding from the wound edges was controlled with diathermy and close suturing of the incision in layers with catgut. A corrugated drain was placed in the subcutaneous tissues, being removed next day.

A transfusion of 4 pints (2.2 litres) of blood was given during and after the operation. Recovery was smooth apart from considerable bruising of the abdominal wall and slight oozing of blood from the wound, which continued for some 24 hours. A purpuric rash appeared on the chest and arms on the third post-operative day, and faded two days later.

Laboratory Investigations of Family.—The mother had never shown any abnormality in capillary or clotting function; her bleeding-time and platelet count were invariably normal. The twin-sister's bleeding-time was prolonged to 10-35 minutes, but platelet count and clotting-time were always normal. Her prothrombin consumption index (Merskey) had been found to be abnormal in 1951. Unfortunately neither the patient's mother nor sister would submit to re-examination.

Haematological Investigations.—On admission (April 22): Hb, 75% (11.1 g./100 ml.); bleeding-time (Ivy), 12 minutes; platelets, 180,000/c.mm.; blood film—platelets present in normal numbers; 4 pints (2.2 litres) group O blood transfused. April 23 (12 hours post-operatively): Hb, 73% (10.8 g./100 ml.); blood film—only occasional platelets seen; platelet count—capillary blood 17,000/c.mm., venous blood 15,000/c.mm. Platelet count on April 24-27 and 29 was 15,000, 32,000, 37,000, 32,000, and 52,000/c.mm. respectively. May 11: Hb, 88% (13 g./100 ml.); platelets, 102,000/c.mm.; bleeding-time, 15+ minutes; capillary fragility (Hess), normal; clotting-time, 3, 4½, 5 minutes; prothrombin consumption index (Merskey), 46% (abnormal); antihaemophilic globulin level, 34%; clot retraction normal; capillary morphology normal.

Second Admission

In October the patient was readmitted to the Radcliffe Infirmary because of severe anaemia resulting from menorrhagia.

Laboratory Investigations.—On admission (October 21): Hb, 30% (4.5 g./100 ml.); film, iron-deficiency changes; bleeding-time, 15+ minutes; tourniquet test negative; platelets, 42,000/c.mm. October 28: Hb, 46% (6.8 g./100 ml.); platelets, 48,000/c.mm. October 29: Hb, 87% (12.9 g./100 ml.); platelets, 37,000/c.mm. November 2: Hb, 88% (13 g./100 ml.); platelets, 57,000/c.mm. November 12: platelets, 35,000/c.mm. November 13: Hb, 79% (11.7 g./100 ml.); platelets, 49,000/c.mm. A blood transfusion of 4 pints (2.2 litres) of blood was given on October 28.

Third Admission

The persistently low platelet count suggested that thrombocytopenia might be the explanation of this girl's severe haemorrhagic state. With this in mind, she was referred to Professor L. J. Witts in July, 1958. At this time she was still bruising easily, but her menstrual loss had not been excessive for several months. Her general health was good and clinical examination revealed nothing apart from numerous bruises over her body.

Laboratory Investigations, July, 1958.—Blood picture on July 23: Hb, 102% (15 g./100 ml.); reticulocytes, 2.6%; white count, 7,900 (neutrophils: band 237, segmented 4,266, eosinophils 632, basophils 79, lymphocytes 2,212, monocytes 474); platelets, 100,000/c.mm.; E.S.R. 7 mm./hr. Bone marrow: cellular erythropoiesis active and normoblastic. Considerable increase in number of eosinophils. Megakaryocytes present in normal numbers. Prothrombin consumption index (Merskey), 50%. Antihaemophilic globulin level, 18%. Bleeding-time, 11 minutes. Clotting-time, 2 minutes.

Though the platelet count was low it was by no means as low as on the two previous admissions. The prolonged bleeding-time was far greater than could be accounted for by the platelet count. The low level of antihaemophilic globulin was confirmed.

Fourth Admission

The patient remained well until January 9, 1959, when, once again, she had a serious intra-abdominal haemorrhage. She was admitted to Redhill County Hospital, where laparotomy revealed an extensive haemoperitoneum arising from a ruptured follicle in the right ovary. As there had also been haemorrhage into the stroma of the ovary, oophorectomy was performed. Her recovery was uneventful, with no secondary haemorrhage.

Microscopical examination of the ovary showed several recent haemorrhages into the stroma and rupture of a follicle.

Laboratory Investigations.—January 9: Hb, 70%; clotting-time (Dale and Laidlaw), 3 minutes 2 seconds; bleeding-time (Duke), 15½ minutes; prothrombin index, 65% of normal; platelets present in normal numbers. January 21: Hb, 68%; R.B.C., 3,600,000; clotting-time, 1 minute 55 seconds; bleeding-time, in excess of 17 minutes; platelets, 252,000/c.mm. January 22: bleeding-time, 18 minutes; platelets, 209,500/c.mm.

At the time of writing (November, 1959) no further haemorrhagic episodes had occurred.

Discussion

A minor degree of bleeding from the rupture of an ovarian follicle, normally at the mid-point of the menstrual cycle, is common in normal females, and occasionally severe haemorrhage may take place calling for emergency operation and blood transfusion. In 129 consecutive cases of serious haemoperitoneum admitted to the Radcliffe Infirmary, 10 were due to this cause (Ellis, Griffiths, and MacIntyre, 1958). It is therefore surprising, and unexplained, why this complication has not been found more often in von Willebrand's disease, particularly since menorrhagia is a common feature of this syndrome in women.

There is very little doubt that this patient has an inherited haemorrhagic tendency, transmitted from her mother, which can be classified as von Willebrand's disease. On all occasions when she has been examined her bleeding-time has been prolonged and the platelet count has usually been within normal limits. In addition, her level of plasma antihaemophilic globulin has been low. It has not been possible to assess the effect of plasma fraction 1-0 (Nilsson *et al.*, 1957) on the bleeding-time in order to confirm this diagnosis.

An unusual feature in this patient has been the episode of thrombocytopenia which followed the first operation and subsequent blood transfusion. At the time, this was thought to be the result of transfusion of stored bank blood (Krevans and Jackson, 1955). Whether post-transfusion thrombocytopenia is due to a simple dilution effect or to actual destruction of platelets by some coagulant in the stored blood, or by virtue of an incompatibility of the platelet group of the recipient and the donor blood, remains a mystery. The rise in the number of platelets to a reasonable level before discharge from hospital appeared to confirm the theory of the post-transfusion thrombocytopenia, yet on her second admission to hospital with severe menorrhagia she was again thrombocytopenic. This persisted throughout her stay in hospital, but its significance was again obscured by the necessity for blood transfusion.

A subsequent review of her haemorrhagic state did not reveal any persistence of the thrombocytopenia, and confirmed the diagnosis of von Willebrand's syndrome.

No evidence of a circulation immune platelet agglutinin could be found, and it has not been possible to establish whether this girl has, in fact, episodes of cyclical thrombocytopenia due to menstrual endocrine activity. This latter contingency is unlikely, as normal numbers of circulating platelets were present throughout her stay in hospital consequent on the second episode of intraperitoneal haemorrhage. It is evident from previous reports that relatively low platelet counts may be found in patients who have von Willebrand's disease (Estren, Médal, and Dameshek, 1946).

Whatever the explanation of these thrombocytopenic episodes, it is clear that such profound drops in the level of circulating platelets, occurring in association with an already established haemorrhagic state, might have provoked a more severe and prolonged haemorrhage. Therefore in any patient with a congenital or acquired haemorrhagic tendency of whatever cause requiring transfusion with stored bank blood it is essential to establish the presence or absence of thrombocytopenia before and after transfusion. If such does exist, it is advisable to use fresh platelet-rich (less than 24-hour-old) blood rather than stored blood, if further transfusion is required. For this purpose fresh blood collected into plastic or siliconized containers, using disodium ethylenediamine tetra-acetic acid (E.D.T.A., "sequestrene") as anticoagulant, is preferable to blood collected into the conventional glass bottles containing acid citrate dextrose.

Surgery should be avoided in all the haemorrhagic diatheses if at all possible. In von Willebrand's disease, however, surgery can sometimes be performed without any severe immediate or delayed haemorrhage, although, unfortunately, at present it is impossible to predict by any laboratory test when this will be the case.

There appears on record only one fatal case after surgery in von Willebrand's disease; Little and Ayres (1928) reported a lethal haemorrhage a few hours after splenectomy in this condition, and necropsy revealed an extensive haemoperitoneum though the splenic pedicle was well ligated. Buchanan and Leavell (1956) noted that, in 13 patients with pseudohaemophilia (von Willebrand's disease), 14 surgical interventions had been undertaken—haemorrhoidectomy, appendicectomy, perineorrhaphy, caesarean section, hysterectomy, craniotomy, polypectomy, tonsillectomy (two), circumcision (two), and uterine curettage (three). In several of these

operations bleeding was heavy, but all were successful. These authors also quote six reports of splenectomy in von Willebrand's disease. Only the one case mentioned above resulted in a fatality. (It should be noted that splenectomy has no beneficial effect on this syndrome.)

Horler and Witts (1958), in a series of 20 patients, record one example of a successful gastrectomy for haemorrhage and another of an uneventful nasal polypectomy. One patient bled heavily from an antrum operation and mastoidectomy, and later at appendicectomy; subsequently a gastrectomy was attempted but abandoned because of wound-edge bleeding and visceral haematomata. Another patient, after bleeding heavily as a result of tonsillectomy, underwent an uncomplicated appendicectomy. The patient bled heavily after hysterectomy for menorrhagia. Thus in eight operations on five patients only three were uncomplicated by haemorrhage.

This variation in bleeding tendency at operation has also been noted by Estren *et al.* (1946). In one of their patients laparotomy was abandoned because of profuse haemorrhage from all cut surfaces, yet nine months later this patient underwent abdominal hysterectomy without any abnormal loss of blood. This variability in bleeding tendency is a striking feature in von Willebrand's disease, and occasionally the bleeding-time may return to normal. Irvine and Jones (1957) suggest that advantage should be taken of this fact and elective surgery be performed when the bleeding-time is normal or near normal. It is, however, dangerous to assume that the finding of a normal bleeding-time indicates normal haemostatic function in this syndrome.

Summary

The case is described of a patient with von Willebrand's disease in whom rupture of the ovarian follicle twice led to intraperitoneal haemorrhage.

The nature of this syndrome and its management when surgery is called for are described.

We are indebted to Mr. A. Elliot-Smith and Professor L. J. Witts for permission to publish details of this case, and to Dr. R. Earl and Mr. Normal Pitt, of Redhill County Hospital, for so generously providing the clinical and laboratory data of her admission to that hospital.

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In Victoria the State Cabinet has approved in principle a Bill to allow doctors to give life-saving blood transfusions to children if their parents refuse consent. Similar legislation is already in force in some other Australian States. The Government's action follows the death of a baby late last year after its father refused on religious grounds to consent to a blood transfusion being given to the child. (*Radio Australia News*, April 4.)

Medical Memoranda

Photosensitivity Caused by Promethazine

Promethazine hydrochloride ("phenegan") is related to the phenothiazine group of drugs, and is chemically very similar to chlorpromazine, a drug which has been reported as causing both severe photosensitivity (Cahn and Levy, 1957) and contact dermatitis (Seville, 1956). Promethazine is one of the more potent antihistamines, and for that reason is widely prescribed both for its anti-allergic properties and for its sedative effect.

Tzanck *et al.* (1951) published two cases of severe solar dermatitis after the ingestion of phenegan tablets prescribed for contact dermatitis, and Sidi *et al.* (1955) reported on a large number of cases of dermatitis following exposure to summer sunshine after the topical application of phenegan cream. In many of these cases the cream had been given for mild sunburn, and the authors estimated that 50% of all cases of eruptions due to topical medicaments seen by them in 1953 were caused by phenegan cream.

The hot summer of 1959 in the British Isles resulted in many casualties due to heat and sunburn, and three further cases of severe solar dermatitis after the ingestion of promethazine are described.

CASE 1

A housewife aged 28 was 16 weeks pregnant at the time. She had a strong family history of eczema and had herself suffered from atopic eczema of the right wrist and left leg since the age of 14. In August, 1959, she was given phenegan tablets (25 mg. t.i.d.) by her doctor as part of the treatment for this eczema, and a few days later was exposed to hot sunshine. Almost immediately she developed a severe dermatitis of the exposed areas—face, neck, arms, and hands, and both legs below her dress.

The condition was severe enough to warrant admission to hospital, where she was treated with triamcinolone 4 mg. q.i.d., potassium permanganate baths twice daily, and local application of a hydrocortisone alcoholic spray. She was discharged after eight days in hospital, but two weeks later was seen again with a recurrence of the dermatitis after a further prolonged exposure to hot sunshine. Triamcinolone again successfully suppressed the eruption and she was further treated with chloroquine phosphate (250 mg. b.d.) in an attempt to counteract the inflammatory action of sunshine.

When last seen in February, 1960, the eczema was controlled, but sitting by a hot fire tended to cause irritation in the areas previously affected. She had no previous history of photosensitivity and had been able to sunbathe freely. As a child she had suffered from "growing pains" in the legs.

CASE 2

A riding-school mistress aged 40 had no previous history of photosensitivity, but had been investigated three years previously by an allergist for an eczematous rash on the legs, and was found to be sensitive to human hair and horse dander. She had completed a course of specific desensitization to these antigens, but had a slight recurrence of this rash on the legs during a hot period in the early summer of 1958. The rest of that summer had been cold and wet, and she had remained free from further eruptions. In August, 1959, she had a further slight relapse during a spell of hot