VON WILLEBRAND'S DISEASE IN THE BANTU*

E. GOMPERTS, M.B., B.CH., B.SC. (HONS.), J. GEEFHUYSEN, M.B., B.CH., M.R.C.P. (EDIN.), D.C.H. (LOND.), J. KATZ, M.B., B.CH. AND J. METZ, M.D., M.C. PATH., *Department of Haematology, South African Institute for Medical Research, and Department of Paediatrics, Baragwanath Hospital and University of the Witwatersrand, Johannesburg*

Von Willebrand's disease, an autosomal-dominant inherited bleeding disorder, is characterized by a prolonged bleeding time and a low antihaemophilic factor (factor VIII) level. The disease was first described in 1926 by Von Willebrand when investigating a bleeding diathesis among the Aaland Islanders.[1] Although well described in White populations, the disease appears to be a rarity among the Asiatic and Negro races.[2,3] We have been unable to find documented cases of Von Willebrand's disease in the Bantu.

This paper presents the first report of Von Willebrand's disease in the South African Bantu. The family is of the Tswana ethnic group. Three members presented with severe clinical bleeding and a fourth died of haemorrhage in infancy.

MATERIALS AND METHODS

Platelet count, bleeding time (Ivy), prothrombin time and factor VIII assay were carried out by standard procedures.[4] Kaolin partial thromboplastin time was measured by the method of Langdell *et al.*,[5] plasma fibrinogen by the method of Ellis and Stransky,[6] and euglobulin lysis time by the method of Nilsson and Olow.[7] Platelet adhesiveness *in vivo* was measured by the method of Borchgrewinck,[8] and *in vitro* by the method of Hellem.[9] ADP-induced clumping and platelet factor 3 availability (platelet thromboplastic activity) were assayed by the method of Hardisty and Ingram.[10]

'Fibrinogen concentrate' ('human fibrinogen dried'—South African Blood Transfusion Service) corresponded to Cohn's fraction 1. It was prepared by the ethanol extraction method from time-expired plasma,[11] and the factor VIII content, although variable, was consistently low.

Family Studies (Fig. 1)

Four generations in the family tree show 4 severely affected members (IIIB, IIIC, IIIG, IVA). The propositus IIIB, her son IVA and her half-brother IIIG will be discussed in detail. IIIC, the brother of the propositus, died at the age of 1 year following uncontrollable haemorrhage from a lacerated lip. Coagulation studies were not carried out on this infant, but it is reasonable to conclude that he too was severely affected.

The trait appears to have been transmitted through the mother (IIC) of the propositus (IIIB). The pedigree is complicated by the mother's (IIC) second marriage to the brother (IID) of her first spouse (IIB). Her first spouse (IIB) died of cardiac failure, and her second spouse (IID) was found to be normal, both on clinical examination and coagulation studies. Four siblings of the husbands (IIB, IID) had no history of clinical bleeding. Two maternal cousins (IIIH, IIIJ) of the propositus were affected. The most probable mode of transmission of the Von Willebrand trait is through the family of the mother of the propositus.

Clinical and Laboratory Data of Affected Family Members

IIC, mother of the propositus, is the probable carrier of the Von Willebrand gene. She was clinically unaffected, and the factor VIII level was 80% on 2 separate occasions, but the bleeding time was prolonged to 8½ min.

IIIH and IIIJ, female cousins of the propositus, were both clinically unaffected. Coagulation studies showed normal factor VIII levels (75% and 95% respectively), but the bleeding times of both were prolonged (7¾ and 8 min. respectively).

IIIB, the propositus, a Bantu female aged 21 years, was admitted to hospital 4 days postpartum because of persistent vaginal bleeding. Clinical examination was otherwise normal. Therapy consisted of antibiotics, blood transfusions and curettage, following which the vaginal bleeding diminished. Five days later vaginal bleeding again became severe, and continued despite a further 3 curettages and numerous blood transfusions (Fig. 2). A bleeding diathesis was suspected and coagulation studies showed a factor VIII level of 8% with a bleeding time of 18½ min. (Table I). A provisional diagnosis of Von Willebrand's disease was made. Further therapy consisted of transfusions of whole blood, fresh frozen plasma, vitamin K and calcium. This therapy failed to control the haemorrhage adequately (Fig. 2). Four units of 'fibrinogen concentrate' were then administered daily for 3 consecutive days. Before use, each unit was reconstituted to

*Date received: 9 January 1969.

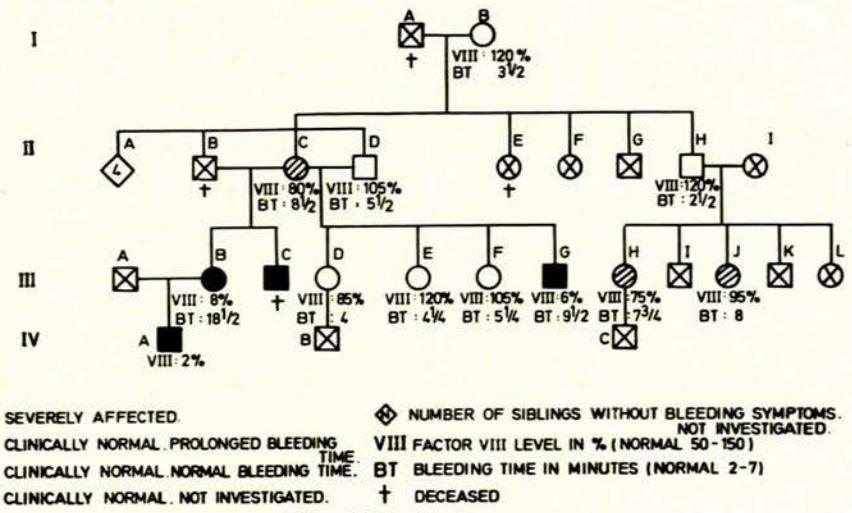

Fig. 1. The family tree.

TABLE I. LABORATORY DATA ON THREE SEVERELY AFFECTED CASES OF VON WILLEBRAND'S DISEASE

Case	*Bleeding time* (*min.*)	*Partial thromboplastin time* (*sec.*)	*Factor VIII level* (%)	*Platelet studies*					*Prothrombin time* (*sec.*)	*Fibrinogen* (*mg./100 ml.*)	*Euglobulin lysis time* (*hours*)
				Platelet count/ cu. mm.	*ADP aggregation*	*Stickiness* in vivo (%)	*Stickiness* in vitro (%)	*Factor 3 availability* (%)			
IIIB	15	65	8	235,000	Normal	84	68	40	11·3	237	3
IIIG	9½	—	6	350,000	Normal	—	—	—	10·1	—	—
IVB	—	73	2	Adequate on film	—	—	—	—	11·0	—	—
Normal range	2-7	35-45	50-150	140,000—400,000	Normal	65	50	25-75	10-12	210	3-5

a concentration of 1 G of resuspended fractionated protein per 100 ml. Factor VIII in the 'fibrinogen concentrate' ranged from under 1% to 12% and the fibrinogen concentration was 1 G/100 ml. Following this therapy the bleeding ceased completely. On the ninth day after cessation of therapy with the 'fibrinogen concentrate', the patient passed a large intra-uterine clot *per vaginam* and heavy vaginal bleeding recurred. This episode of vaginal bleeding was again controlled by the 'fibrinogen concentrate' (Fig. 2).

On careful questioning, the patient admitted to severe menorrhagia for many years. A tooth extraction some years previously had been followed by severe haemorrhage, necessitating blood transfusion.

Further coagulation studies were subsequently carried out (Table I). Platelet number, morphology and function were normal. The factor VIII level was less than 10% and the bleeding time markedly prolonged on numerous occasions. The final confirmation of Von Willebrand's disease was made with infusion studies. The factor VIII level rose rapidly after infusions of both fresh frozen plasma and the 'fibrinogen concentrate' and subsequently fell slowly (Fig. 3). The factor VIII concentration of the fresh frozen plasma was 45% and of the 'fibrinogen concentrate', infused in this study, under 1%.

IVA, the infant son of the propositus, was admitted to hospital at the age of 2 weeks for exchange transfusion for hyperbilirubinaemia, possibly due to absorption of blood from an occipital cephalhaematoma sustained at

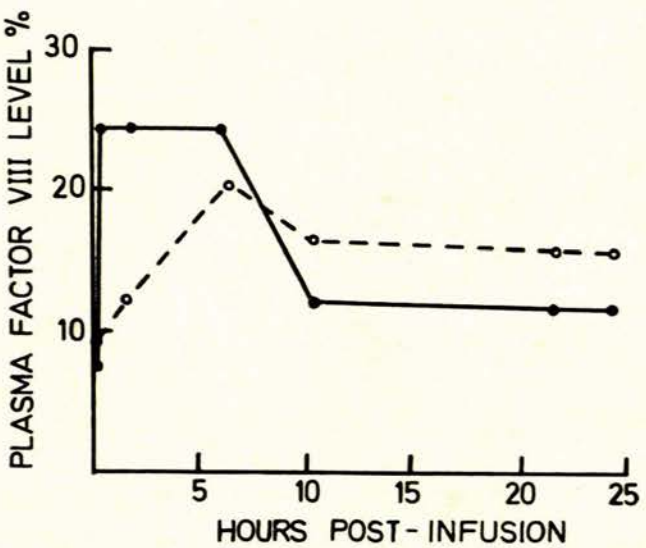

Fig. 3. Factor VIII levels in the propositus (IIIB) following infusion of 1,000 ml. fresh frozen plasma (•———•) and 200 ml. 'fibrinogen concentrate' (o - - - - - o). The factor VIII concentration of the fresh frozen plasma was 45% and of the 'fibrinogen concentrate' less than 1%.

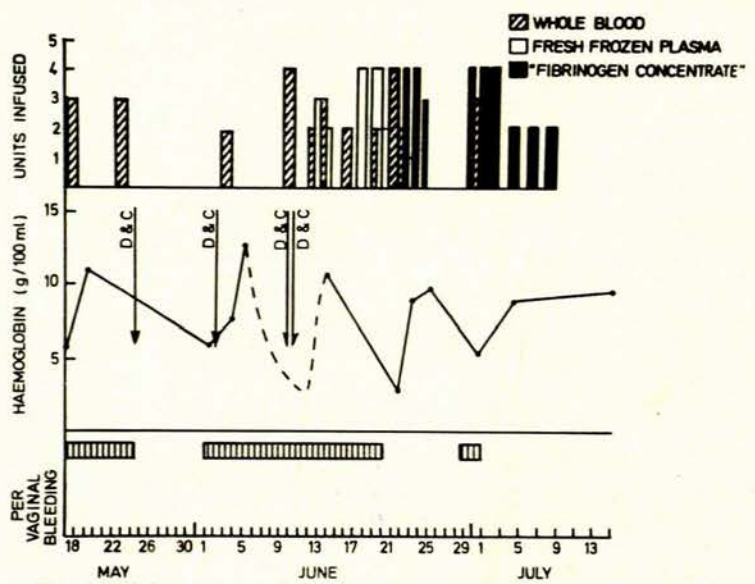

Fig. 2. Clinical course of the propositus (IIIB). D & C = Dilatation and curettage.

birth. Continual oozing from the umbilical stump after the exchange transfusion and excessive bleeding from venepuncture and intramuscular injection sites suggested a haemorrhagic diathesis. Laboratory investigations revealed a factor VIII level of 2% (Table I).

IIIG, a male aged 3 years, had been investigated in 1965, when he presented with numerous subcutaneous haematomata. The bleeding time (Duke) was prolonged and the factor VIII level was 6% (Table I). Platelet function studies were normal. He died early in 1968 of a probable cerebral haemorrhagic episode.

DISCUSSION

Von Willebrand's disease, a bleeding disorder affecting both sexes, is characterized by a prolonged bleeding time and reduced factor VIII level. These abnormalities were demonstrated in the Bantu family presented in this report, 7 members of the family—representing 4 generations—showing prolonged bleeding times and/or low factor VIII levels.

The commonest form of hereditary factor VIII deficiency is classical haemophilia. This disease, with its sex-linked recessive mode of inheritance, affects males but almost never females, and the bleeding time is normal. Differentiation between Von Willebrand's disease and haemophilia can be made by noting the response in factor VIII level following infusion of stored plasma. The infusion of plasma deficient in factor VIII fails to raise the factor VIII level in haemophilia. It is postulated that in classical haemophilia there is deficiency of the end-product of factor VIII synthesis.[12] In Von Willebrand's disease, however, infusion of plasma with low factor VIII concentration will result in a rapid and sustained rise in the factor VIII level, due to '*in vivo* complementation' of factor VIII.[3] This feature is thought to be due to the replacement of a postulated precursor substance, absent in Von Willebrand's disease, with subsequent intrinsic factor VIII synthesis.[3,13] This was demonstrated by the propositus, where infusion of 'fibrinogen concentrate', low in factor VIII, resulted in a rapid rise in factor VIII level, with a subsequent slow fall-off in activity over 24 hours. There can be no doubt that the family here described represents an example of Von Willebrand's disease.

Some of the affected members of the family with prolonged bleeding times had factor VIII levels within the normal range. These subjects are only mildly affected with the disease. Factor VIII levels are variable in affected families, and may even vary from time to time in the same patient.[14] It is possible that these mildly affected subjects may demonstrate lower factor VIII levels if repeatedly tested.[14]

Abnormalities in platelet function have been described in Von Willebrand's disease. Platelet adhesiveness and ADP aggregation were shown to be defective in some patients.[15,16] These features were not demonstrated in the members of the family described, but this is not unexpected, for many other investigators have been unable to show platelet function defects in otherwise typical examples of Von Willebrand's disease.[3,17]

Von Willebrand's disease is transmitted as an autosomal-dominant inherited condition.[3] In the present family, a study of the third and fourth generations shows the typical pattern of autosomal-dominant inheritance. An inadequate number of members of the first 2 generations were available for testing. The variability of expressivity of the coagulation defects necessitates repeated evaluation of the apparently unaffected subject.[14]

The therapy of Von Willebrand's disease differs from that of classical haemophilia. The bleeding diathesis in both diseases is related directly to the factor VIII level. In haemophilia correction of the low factor VIII concentration is achieved passively by transfusing blood products containing high concentrations of factor VIII such as cryoprecipitate, fresh and fresh frozen plasma and 'haemophilic factor concentrates' prepared by pharmaceutical manufacturers. In Von Willebrand's disease the correction may be either active or passive, using fresh or fresh frozen plasma. Cohn's fraction 1 or 'fibrinogen concentrate'.[4,15] These plasma or plasma derivatives with a high factor VIII content will result in an immediate rise in the recipient's factor VIII level, followed in many instances by 'complementation' and a further increment in the factor VIII level, and a slow fall over 24 hours. A 'fibrinogen concentrate' with low factor VIII activity will cause a slow rise in the factor VIII level to a maximum about 4 hours after infusion, corresponding to intrinsic factor VIII synthesis, with a slow fall over the next 24 hours.[3] The propositus aptly demonstrates these features when both fresh frozen plasma and a 'fibrinogen concentrate' were administered. In the control of the vaginal bleeding in the propositus, a response was noted with both fresh frozen plasma and 'fibrinogen concentrate'. It appeared that the response to the 'fibrinogen concentrate' was better, but this may be dose related.

SUMMARY

A bleeding disease in a Bantu family has been investigated. The disease is transmitted in the family in an autosomal-dominant pattern. The affected members of the family show low plasma levels of antihaemophilic globulin (factor VIII) and/or a prolonged bleeding time. The low factor VIII level was shown to rise following infusion of plasma fractions low in factor VIII. These features are diagnostic of Von Willebrand's disease, which has to our knowledge not been previously described in the Bantu.

We wish to thank the Director, South African Institute for Medical Research, for facilities to carry out this study; and Drs W. F. Kenny, Medical Superintendent, and S. Wayburne, principal paediatrician, Baragwanath Hospital, for permission to publish these cases.

REFERENCES

1. Von Willebrand, E. A. (1926): Finska Läk.-Sallsk. Handl., **68**, 87.
2. Prentice, C. R. and Ratnoff, O. D. (1967): Seminars Hemat., **4**, 93.
3. Barow, E. M. and Graham, J. B. (1964): Progr. Hemat., **4**, 203.
4. Biggs, R. and MacFarlane, F. G. (1966): *Treatment of Haemophilia and Other Disorders*, p. 360. Oxford: Blackwell Scientific Publications.
5. Langdell, R. D., Wagner, R. H. and Brinkhous, K. M. (1953): J. Lab. Clin. Med., **41**, 637.
6. Ellis, B. C. and Stransky, A. (1961): *Ibid.*, **58**, 577.
7. Nilsson, I. M. and Olow, B. (1962): Acta chir. scand., **123**, 247.
8. Borchgrewinck, C. R. (1960): Acta med. scand, **168**, 157.
9. Hellem, A. J. (1960): Scand. J. Clin. Invest., **12**, suppl. 57.
10. Hardisty, R. M. and Ingram, G. I. G. (1965): *Bleeding Disorders. Investigation and Management*, pp. 270 and 272. Oxford: Blackwell Scientific Publications.
11. Nitschmann, H., Kistler, P. and Joss, A. (1957): Vox Sang. (Basel), **2**, 100.
12. Lewis, J. H. (1964): Blood, **23**, 233.
13. Blomback, M. and Blomback, B. *in* Brinkhous, K. M., ed. (1964): *The Hemophilias, 3rd International Symposium*. Chapel Hill: University of North Carolina Press.
14. Abildgaard, C. F., Simone, J. V., Honig, G. R., Forman, E. N., Johnson, C. A. and Sceler, R. A. (1968): J. Pediat., **73**, 355.
15. Caen, J. and Cousin, C. (1962): Nouv. Rev. franc. Hemat., **2**, 685.
16. Cornu, P., Larrien, M. J., Caen, J. and Bernard, J. (1963): Brit. J. Haemat., **9**, 189.
17. Cronberg, S., Nilsson, I. M. and Silver, J. (1966): Acta med. scand., **180**, 43.
18. Nilsson, I. M., Blomback, M. and Blomback, B. (1960): Acta haemat. (Basel), **24**, 116.