(1,140 ml.) of fresh frozen plasma immediately before extraction and on the occurrence of bleeding, provided this was severe enough. Oral antibiotic therapy was used for five days from the time of extraction.

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REFERENCES

Biggs, R., Douglas, A. S., Macfarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., and O'Brien, J. R. (1952). *British Medical Journal*, 2, 1378.
Matheson, W. S. (1949). *Brit. dent. J.*, 87, 312.
Moss, R. L. (1955). *Oral Surg.*, 8, 27.
Qvist, G., Endicott, C. L., and Mitchell, J. H. (1942). *Brit. dent. J.*, 73, 178.
White, P. H., and Mallett, S. P. (1949). *J. oral Surg.*, 7, 237.

CHRISTMAS DISEASE IN A WOMAN

BY

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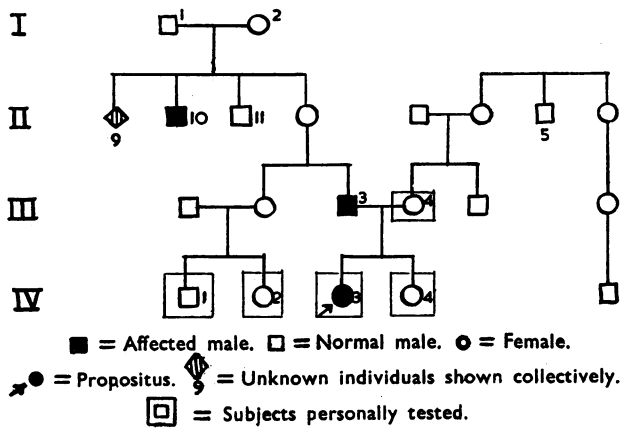
In the majority of affected families the inheritance of Christmas disease is of the same sex-linked recessive pattern as true haemophilia, resulting in the transmission of the disease to males by apparently healthy females. In a small number of instances, however, heterozygous females have been found to be mildly affected, suggesting that the Christmas disease gene may be less completely recessive than that responsible for haemophilia. The case is presented here of a young woman with Christmas disease of the same order of severity as her affected male relatives.

Case History

A single woman aged 22 was investigated because of a history of prolonged bleeding following tooth extractions. She had had teeth extracted on several occasions since the age of 6, and each time had bled from the tooth socket intermittently for 7 to 14 days. It had always proved possible to control the bleeding eventually by plugging, and she had never had a blood transfusion. No abnormal bleeding occurred at the spontaneous shedding of the primary dentitions. Two teeth have been extracted since the diagnosis of Christmas disease was made, and on this occasion bleeding was successfully controlled by packing the tooth sockets with an absorbable dressing soaked in thrombin. With this treatment bleeding stopped within 24 hours, but started again three days after the extraction, necessitating repacking, which resulted in permanent haemostasis.

The patient has had no other haemorrhagic symptoms. She has never had any other operations or serious injuries, and does not bruise excessively from minor traumata. Superficial cuts soon stop bleeding, and menstruation is normal. She has never had haemarthroses, epistaxes, purpura, or haematuria. At the age of 17 she swallowed a small open safety-pin without ill-effect.

Family History.—The patient's family tree is shown in the diagram. Her paternal great-grandparents, I 1 and I 2, are said to have been first cousins. Her father, III 3, suffered from prolonged and excessive bleeding after tooth extraction on several occasions, but had no other haemorrhagic symptoms. He had never had any other operations or serious injuries. He was accepted for military service and was killed at Anzio in 1944. One of his mother's five brothers (II 10), now deceased, is known to have bled excessively after tooth extraction, but another (II 11) has never had any haemorrhagic symptoms. It has unfortunately proved impossible to trace the remaining members of the patient's paternal grandmother's family. There is no history of abnormal bleeding in any other known relatives of either sex on the patient's father's side, nor in any member of her mother's family.



Laboratory Investigations.—The results of tests of the patient's haemostatic mechanism are shown in Table I. It will be seen that these were all within normal limits.

A thromboplastin generation test was performed by the method of Biggs and Douglas (1953), using a suspension of normal platelets with various combinations of serum and $Al(OH)_3$-adsorbed plasma. All sera were obtained from blood shaken with glass beads until coagulation occurred, and then incubated at 37° C. for two hours. The sera were

TABLE I.—*Results of Routine Laboratory Tests on Patient's Blood*

Test	Patient	Normal Control Range
Whole-blood clotting-time (Lee and White) (minutes)	7½–10	5–10
One-stage prothrombin time (Quick) (seconds)	17·3	17·2–18·6
Proconvertin (Owren) (%)	80	70–120
Prothrombin consumption index (Merskey) (%)	18	Less than 40
Bleeding-time (Ivy) (minutes)	3	3–7
Platelet count (per c.mm.)	353,000	200,000–500,000

TABLE II.—*Results of a Thromboplastin Generation Test. The Same Normal Platelet Suspension and M/40 $CaCl_2$ were Used Throughout*

$Al(OH)_3$-adsorbed Plasma (1/5)	Serum (1/10)	Shortest Second Stage Clotting-time (sec.)	Final Thromboplastin Concentration (%)
Normal	Normal	10	100
,,	Patient	13½	65
Patient	Normal	10	100
Normal	50% Patient + 50% Normal	9½	108
Haemophilic	Normal	25	17
10% Normal + 90% Haemophilic	,,	14	52
10% Patient + 90% Haemophilic	,,	11	83
Normal	Christmas disease	23½	19
,,	10% Normal + 90% Christmas disease	12½	65
,,	10% Patient + 90% Christmas disease	21	24

diluted 1 in 10 (vol./vol.) in 0.85% saline, and stored at −20° C. until required. The results in Table II show that the patient has a serum deficiency, and that her serum is incapable of correcting that of a patient with Christmas disease. Her $Al(OH)_3$-adsorbed plasma corrected that of a haemophilic subject better than did that of the normal control, and her own serum was corrected by an equal volume of normal serum, showing that the defect was not due to the presence of an inhibitor of thromboplastin generation. It was concluded that she had a true deficiency of Christmas factor. No PTA-deficient blood (Rosenthal *et al.*, 1953) was available for matching experiments, but the failure of mutual correction of Christmas disease and patient's serum is taken to exclude the diagnosis of PTA deficiency in this case.

On another occasion the Christmas factor content of the patient's serum was determined by measuring its ability to correct the defect of Christmas disease serum in the thromboplastin generation test. Serial dilutions of normal serum in Christmas disease serum were tested, all the other reagents being kept constant, and the concentrations of normal serum were plotted against the corresponding shortest second-stage clotting-times, to obtain a Christmas factor dilution curve. A 10% dilution of the patient's serum in Christmas disease serum was then tested in the same way. By interpolation on the dilution curve, it was found that the patient's serum contained approximately 8% of Christmas factor relative to the control. This method of assay has given results between 0 and 20% of normal in males with Christmas disease investigated in this laboratory. Serum from the most severely affected of these was used as the diluent in the present case.

Christmas factor and proconvertin (factor VII) assays have also been carried out on the serum of the patient's mother, sister, and two first cousins. None of these have any haemorrhagic tendency, and all have had teeth extracted without excessive bleeding. It was found that none had significant deficiency of either factor (Table III), though the amount of each factor in the sister's blood was slightly less than in the other members of the family.

TABLE III.—*Christmas Factor and Proconvertin (Factor VII) in the Patient's Relatives*

Relationship to Patient	Christmas Factor (%)	Proconvertin (%)
Mother (III 4)	80	100
Sister (IV 4)	65	70
Cousin (IV 1)	90	96
,, (IV 2)	90	96

Discussion

The laboratory investigations show that the patient suffers from a Christmas factor deficiency, and her history suggests that it is a congenital one. It is unfortunate that no affected relatives were available for testing, but the family history strongly suggests that her father and great-uncle suffered from the same condition. A unifying though somewhat unusual feature was the limitation of symptoms in each affected member of the family to bleeding after tooth extraction. It may be that this merely indicates the occurrence of a mild degree of the disorder in three people who all escaped serious injury.

There are two genetically possible explanations for the occurrence of Christmas disease in the daughter of an affected male. Unless the patient is homozygous for the Christmas disease gene, it is necessary to postulate that the gene is not completely recessive.

There is no evidence in the present case for the first of these alternatives. Although the silent transmission of the gene to the patient's mother through several generations of carriers cannot be excluded with certainty, the fact that none of her eight known male relatives were affected makes such an explanation extremely unlikely. Still more so is the possibility that the patient has received a second Christmas disease gene as the result of a mutation occurring in the ovum which gave rise to her.

It is therefore reasonable to assume that the occurrence of Christmas disease in this patient represents the effect of an incompletely recessive gene. Some degree of expression of the Christmas disease gene in heterozygotes has already been reported by Biggs *et al.* (1952), Biggs and Macfarlane (1954), Brinkhous *et al.* (1954), Rosenthal and Sanders (1954), and Ramot *et al.* (1955). Graham *et al.* (1953) have observed a similar phenomenon in a large family with a mild form of haemophilia. In most of these cases the heterozygotes have been symptomless, the abnormality being detectable only by laboratory tests; in the remainder the heterozygous females appear to have had milder symptoms than their affected male relatives. The present case differs from these in that the patient's disability is apparently very similar in degree to that experienced by her father and great-uncle. While it must be admitted that such an assessment, based on second-hand evidence, is necessarily inexact, the observation that the patient's serum contains less than 10% of the normal amount of Christmas factor also suggests that the degree of deficiency is of the same order as in her male relatives, whose disability was slight.

It is of interest that the patient's sister, who must also be assumed to be a heterozygote but who has no history of abnormal bleeding, has a slightly reduced amount of Christmas factor in her serum. This finding is consistent with the view that the Christmas disease gene is incompletely recessive in this family; the difference in degree of the defect between the patient and her sister may be taken as evidence of the variable expressivity of the gene, the expression apparently being almost complete in the patient's case.

Summary

The case of a young woman with Christmas disease is reported, in which the presenting symptom was prolonged haemorrhage following tooth extraction.

Her serum was found to contain approximately 8% of the normal amount of Christmas factor.

The family history suggested that the patient's father and his uncle suffered from Christmas disease of a similar degree of severity.

The genetic implication of these observations is that the gene for Christmas disease may be intermediate rather than completely recessive.

I am indebted to the patient and her family for their co-operation, and to Dr. Rosemary Biggs and Dr. C. O. Carter for helpful discussion.

ADDENDUM.—Since this paper was written, the patient has undergone bilateral intranasal antrostomies with diathermy to the inferior turbinates. Following this operation, she bled intermittently from the nose for a fortnight. At the end of this time, when her haemoglobin had fallen to 7.7 g. per 100 ml., she was transfused with three pints (1.7 l.) of fresh blood, which successfully controlled the bleeding. This is of some interest as the only recorded instance of bleeding in this family other than after tooth extraction, and supports the view that the patient's disability is comparable in degree with that of her affected male relatives.

REFERENCES

Biggs, R., and Douglas, A S. (1953). *J. clin. Path.*, **6**, 23.
—— —— Macfarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., and O'Brien, J. R. (1952). *British Medical Journal*, **2**, 1378.
—— and Macfarlane, R. G. (1954). Personal communication to W. R. Pitney and J. V. Dacie, *Brit. med. Bull.*, 1955, **11**, 11.
Brinkhous, K. M., Langdell, R. D., Penick, G. D., Graham, J. B., and Wagner, R. H. (1954). *J. Amer. med. Ass.*, **154**, 481.
Graham, J. B., McLendon, W. W., and Brinkhous, K. M. (1953). *Amer. J. med. Sci.*, **225**, 46.
Ramot, B., Angelopoulos, B., and Singer, K. (1955). *J. Lab. clin. Med.*, **46**, 80.
Rosenthal, M. C., and Sanders, M. (1954). *Amer. J. Med.*, **16**, 153.
Rosenthal, R. L., Dreskin, O. H., and Rosenthal, N. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **82**, 171.