severe enough to cause considerable difficulty in blood grouping and saline cross-matching. There are at present few published accounts dealing with this aspect of dextran 110. Ricketts (1966) found rouleaux formation a hindrance to satisfactory saline cross-matching in only two cases, and then with serum concentrations of modified dextran considerably higher than in the present investigation. Though Ricketts found a moderate increase in E.S.R. with modified dextran in experiments in vitro, this could not be compared directly with the marked increase noted here, since Ricketts used the Wintrobe method for estimating the E.S.R.

There is a critical level of molecular weight so far as rouleaux formation by dextrans is concerned (Thorsén and Hint, 1950). Dextrans with an average molecular weight below 60,000 cause no increase in sedimentation rate. As the molecular weight increases above 60,000, red-cell rouleaux formation appears and the sedimentation rate rises progressively.

Macrodex has an average molecular weight of about 70,000. About 10% of the preparation has a mean molecular weight of 108,000 and 9% of 25,800 (Kjellman, 1965 ; Rousell, 1966 ; Nilsson, 1967). Hence on average Macrodex is only slightly above the critical molecular weight. Dextran 110 has an average molecular weight of about 110,000. Ten per cent. of the preparation has a mean molecular weight of 194,000, and 8% of 35,000 (Nilsson, 1967). This is reflected in an increased tendency to cause rouleaux formation and a rise in the erythrocyte sedimentation rate.

Thus from the point of view of effective blood grouping and cross-matching it would seem essential to take blood from a patient for these purposes *before* administration of dextran 110 or dextran 150. If immediate transfusion before withdrawal of blood is required Macrodex will cause little interference, and plasma or plasma-protein solution no interference, with blood grouping and cross-matching.

Summary

Plasma, plasma-protein solution, Macrodex, dextran 110, and dextran 150 were compared for their effect upon red-cell rouleaux formation and erythrocyte sedimentation rate in a series of in vitro experiments.

Plasma and plasma-protein solution do not produce rouleaux formation and have no effect upon the sedimentation rate. Macrodex, in concentrations likely to be found in plasma, does not caused marked rouleaux formation. Therefore administration of these substances before the taking of blood is unlikely to lead to any difficulty in blood grouping and cross-matching.

In contrast, both dextran 110 and dextran 150 produce marked rouleaux formation and a considerable rise in the E.S.R. They are likely to interfere with blood grouping and cross-matching, and should be given to a patient only *after* blood has been withdrawn.

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References

Arndt-Hanser, A. (1956). *Bibl. haemat. (Basel)*, **5**, 181.
Bloom, W. L. (1951). *Arch. Surg.*, **63**, 739.
Bowman, H. W. (1953). *J. Amer. med. Ass.*, **153**, 24.
Brit. med. J., 1967, **1**, 363.
Haynes, B. W. (1960). *Amer J. Surg.*, **99**, 684.
Kjellman, H. (1965). *Farm. Rev. (Stockh.)*, **64**, 86.
Mollison, P. L. (1967). *Blood Transfusion in Clinical Medicine*, 4th ed. Oxford.
Nilsson, K. (1967). Personal communication.
Pettenkofer, H. J. (1959). *Chirurg*, **30**, 25.
Ricketts, C. R. (1966). *Brit. med J.*, **2**, 1423.
Roche, P., jun., Dodelin, R. A., and Bloom, W. L. (1952). *Blood*, **7**, 373.
Rousell, R. H. (1966). *Brit. med. J.*, **2**, 691.
Thorsén, G., and Hint, H. (1950). *Acta chir. scand.*, Suppl. No. 154.
Turner, F. P., Butler, B. C., Smith, M. E., and Scudder, J. (1949). *Surg. Gynec. Obstet.*, **88**, 661.

Paget's Disease: a Family with Six Cases

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Although McKusick (1966) states that 52 families have been reported in which more than one member suffered from Paget's disease, it is a striking fact that there have been only three reports of familial Paget's disease occurring in Great Britain. Kilner (1904) recorded an affected brother and sister, and Smith (1905) an affected father and son. Rast and Weber (1937) described the cases of three affected sisters. The literature on familial Paget's disease has been fully reviewed by Ravault, Lejeune, Robert, and Maitrepierre (1963) and by McKusick (1966). Records have been published of one family with four confirmed and two probable cases (Ravault *et al.*, 1963), two families with six cases (Hanke, 1935 ; Dickson, Camp, and Ghormley, 1945), and one family with five cases (van Bogaert, 1933). The remainder of the reports are of smaller families. McKusick (1966) draws attention to the difficulty of studying the familial incidence of a disease which is often asymptomatic, and suggests that "it may be that a study of families using alkaline phosphatase determinations as a screening procedure would be productive."

The purpose of this paper is to put on record an English family in which six cases of Paget's disease have occurred in three generations, and in which nine unaffected members of the family have been studied. Radiological investigations and alkaline phosphatase estimations have been made in 13 members of the family.

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The Family

Details of the family are set out in the genealogical diagram and in the Table. Thirteen members of the family were visited. All were examined clinically, *x*-ray films of the pelvis and tibiae were taken, and the alkaline phosphatase was estimated. In the case of two members of the family who were dead (I 1 and II 3) it was possible to make a diagnosis of Paget's disease with reasonable certainty from the evidence given by the rest of the family. Four living members of the family had clinical Paget's disease (details are given in the Table), and in all of these the alkaline phosphatase was raised. Nine members, ranging in age from 81 to 17 years, had no clinical evidence of Paget's disease, and their bone radiographs and alkaline phosphatase were normal. The age of onset of Paget's disease in this family seems to be in the decade 40 to 50. Three of the unaffected members are in this age group, and are therefore likely to remain unaffected. Of the remaining six (aged 17 to 29) several are likely to develop the disease in later life. This study suggests that there are no early *x*-ray changes or abnor-

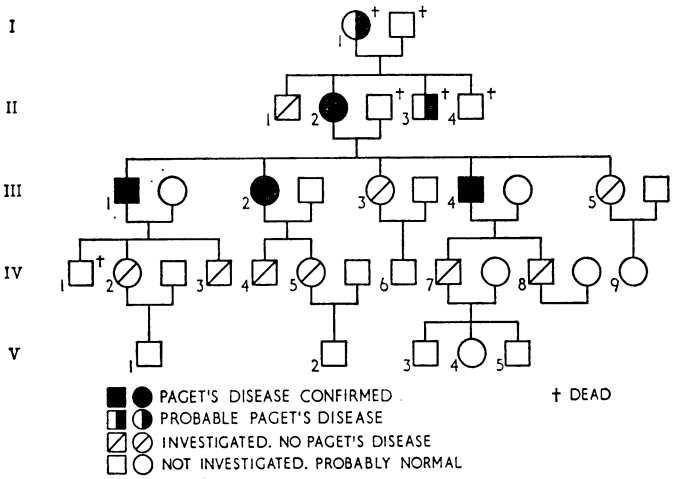
malities of alkaline phosphatase on which it is possible to predict the subsequent development of Paget's disease.

Discussion

Paget (1889), in his original description of osteitis deformans, wrote: "I have tried in vain to trace any hereditary tendency to the disease. I have not found it twice in the same family." Rosenkrantz, Wolf, and Kaicher (1952), in a review of 111 cases, do not mention a familial form of the disease. Most of the previous reports of families with Paget's disease have been from France, Germany, or the U.S.A. The family reported here seems to be the largest family group reported in Great Britain.

All previous reports suggest that the pattern of inheritance is compatible with an autosomal dominant gene with incomplete penetrance, with the exception of Ashley Montagu (1949), who suggested that it was inherited as a sex-linked recessive. Our findings are consistent with an autosomal dominant inheritance.

Clinically the disease in the family studied seems limited to the tibiae, pelvis, and lumbar spine. No case involving the skull has been encountered. The cases are all reasonably benign, with only minor symptoms in most cases and no instance of cardiac failure. This is comparable with the case reports in the literature.



Genealogical diagram. Details of individual members are shown in the Table.

Details of Family

I 1. Very bowed legs; had coffin made specially.
II 1. Aged 81. Normal. Alkaline phosphatase (A.P.) 9.7 K.A. units/100 ml.
2. Aged 80. Paget's disease left tibia and pelvis. A.P. 26.
3. Legs deformed. Died 1937.
4. Aged 66 at death (1960). No evidence of Paget's disease.
III 1. Aged 56. Paget's disease right tibia and pelvis. A.P. 36.
2. Aged 54. Paget's disease pelvis, both femora, both tibia. A.P. 54.
3. Aged 53. Normal. A.P. 7.
4. Aged 52 Paget's disease of lumbar vertebrae and pelvis. A.P. 76.
5. Aged 40. Normal. A.P. 6.
IV 1. Died at age 16 (1957)—accident.
2. Aged 21. Normal. A.P. 14.
3. Aged 17. Normal. A.P. 7.
4. Aged 24. Normal. A.P. 10.
5. Aged 19. Normal. A.P. 6.
6. Aged 20. Not studied.
7. Aged 29. Normal. A.P. 11.
8. Aged 22. Normal. A.P. 7.
9. Aged 10. Not studied.
V The members of this generation are all below the age of 10, and have not been studied.

Summary

An English family is reported in which six cases of Paget's disease have occurred in three generations. Nine unaffected members of the family have also been studied. There is no evidence of radiological abnormality in the clinically unaffected members, and alkaline phosphatase levels are normal. The disease is mild (with onset of symptoms in the fifth decade), and appears to be inherited as an autosomal dominant.

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References

Ashley Montagu, M. F. (1949). *Amer. J. hum. Genet.*, **1**, 94.
van Bogaert, L. (1933). *Z. ges. Neurol. Psychiat.*, **147**, 327.
Dickson, D. D., Camp, J. D., and Ghormley, R. K. (1945). *Radiology*, **44**, 449.
Hanke, H. (1935). *Dtsch. Z. Chir.*, **245**, 641.
Kilner, W. J. (1904). *Lancet*, **1**, 221.
McKusick, V. A. (1966). *Hereditable Disorders of Connective Tissue*, 3rd ed. St. Louis.
Paget, J. (1889). *Illus. med. News*, **2**, 181.
Rast, H., and Weber, F. P. (1937). *Brit. med. J.*, **1**, 918.
Ravault, P. P., Lejeune, E., Robert, J. M., and Maitrepierre, J. (1963). *Rev. Rhum.*, **30**, 824.
Rosenkrantz, J. A., Wolf, J., and Kaicher, J. J. (1952). *Arch. intern. Med.*, **90**, 610.
Smith, S. M. (1905). *Trans. med. Soc. Lond.*, **28**, 324.

Preliminary Communications

Evidence for Autonomic Denervation in Familial Dysautonomia, the Riley-Day Syndrome

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The clinical features and experimental findings in familial dysautonomia have been summarized by Riley (1957), Riley and Moore (1966), and Goodall *et al.* (1967). Vasomotor instability, poor muscular co-ordination, impairment of sweating lacrimation and temperature control, and defective taste all point to a widespread neurological disorder. The absence of a flare in response to intradermal histamine and the exaggerated response to infusions of methacholine or noradrenaline offer further evidence of faulty autonomic control, as does the potentiated miosis following instillation of methacholine drops into the conjunctival sac.

Pupil responses to sympathomimetic amines have recently been used in studies on surgically induced sympathetic denervation and to evaluate the mode of action of adrenergic blocking drugs, such as guanethidine (Sneddon and Turner, 1967). Smith, Dancis, and Breinin (1965) investigated some of the ocular responses to autonomic drugs in familial dysautonomia, and concluded that there was evidence of parasympathetic but not of sympathetic denervation. The pupil responses in a female patient aged 18 months with this condition, reported in detail elsewhere (Goodall *et al.*, 1967), are here described, the results extending and differing from previous accounts.

Method

The experimental procedure is that described by Sneddon and Turner (1967). The eyes of the patient, and of four control children taking no drugs and who were matched for