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.

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.

We are grateful to Dr. E. Rhys Davies and to the radiology department, Bristol General Hospital, for radiological studies on most of these patients. It is a pleasure to acknowledge the assistance of the patients' general practitioners.

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). *Disch. Z. Chir.*, **245**, 641.
 Kilner, W. J. (1904). *Lancet*, **1**, 221.
 McKusick, V. A. (1966). *Hereditary 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.

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.

Preliminary Communications

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

Brit. med. J., 1967, **4**, 91-92

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

age and eye colour (dark brown), were photographed under standard lighting conditions. The nature of the procedure was fully explained to the parents of these children, and their permission was obtained in every case. A Nikon F single lens reflex camera was used, mounted on a movable stand with bellows attachment. The camera settings were fixed and the whole camera was moved for focusing, resulting in a constant magnification of $\times 2$ when the patient's pupils were in focus. Four photographs of each subject were taken within a 15-second interval every 10 minutes for 30 minutes after the instillation of one drop of the drug under investigation into the conjunctival sac. In the subsequent measurements of pupil size the negatives were projected on to a white screen at a final magnification of $\times 8$. Pupil diameters were measured as the transverse diameter of this image and mydriasis or miosis was expressed as the percentage increase or decrease in pupil diameter from control values determined before drug instillation.

The drugs used were eye-drops containing methacholine 2.5%, physostigmine 0.5%, phenylephrine 10%, or ephedrine 2%. The experiments were carried out over four weeks, a different drug being administered each week.

RESULTS

The results are shown in the Table. Methacholine and physostigmine produced a greater miosis in the patient than in the control subjects. The mydriasis produced by phenyl-

Percentage Miosis and Mydriasis at 30 Minutes After Administration of Drugs into the Conjunctival Sac of One Eye in Four Control Subjects and a Patient with Familial Dysautonomia. The Results are the Means of Four Readings From Each Subject

	% Miosis				% Mydriasis			
	Methacholine 2.5%		Physostigmine 0.5%		Phenylephrine 10%		Ephedrine 2%	
	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Controls	0	0	44	7	25	4	33	5
Patient	39	5	72	7	61	2	0	0

ephrine was also much greater in the patient, but ephedrine, which produced a mydriasis in the controls, did not have a measurable effect in the patient.

DISCUSSION

The mydriatic action of sympathomimetic amines is less in subjects with dark irides than those with light irides (Obianwu and Rand, 1965). It is therefore important to match subjects for eye colour.

Methacholine acts directly on parasympathetic end-organ receptor sites. The exaggerated response to this drug in our patient is characteristic of denervation (Emmelin, 1961) and indicates that usually her pupil has little if any parasympathetic tone. When the anticholinesterase drug physostigmine is given it is apparent that the pupil also reacts to endogenously released

acetylcholine. Physostigmine prevents its breakdown, and the miosis following its administration is good evidence that acetylcholine is being synthesized in parasympathetic nerve endings, though the rate may be reduced or its release impaired. Unfortunately there is no parasympathomimetic drug available analogous to ephedrine on the sympathetic system which releases stored acetylcholine from nerve endings. These findings agree with those of other workers and indicate a partial parasympathetic denervation phenomenon.

The response to phenylephrine, a sympathomimetic drug acting directly on sympathetic end-organ receptor sites, has not previously been documented. Together with the response to ephedrine, which releases noradrenaline from granules in postganglionic sympathetic nerve endings, the responses are similar to those found in surgically induced Horner's syndrome and in chronic treatment with local guanethidine (Sneddon and Turner, 1967).

This is good evidence that the response in familial dysautonomia parallels sympathetic denervation produced artificially. Though this conclusion differs from other reports, it is in agreement with the increased sensitivity to noradrenaline infusion found in this condition (Smith and Dancis, 1964). The absence of ephedrine mydriasis indicates absent or reduced transmitter stores in the sympathetic nerve ending.

We did not use adrenaline eye-drops as absorption is unpredictable, nor cocaine, as it was thought undesirable to anaesthetize the eyes of control subjects of this age. This has been done in older children and a mydriasis reported (Smith *et al.*, 1965), but the degree of dilatation compared with control subjects was not stated.

SUMMARY

Denervation phenomena both in the sympathetic and in the parasympathetic control of pupil diameters are reported in a child with familial dysautonomia.

Exaggerated responses were demonstrated to parasympathetic and direct-acting sympathomimetic agents.

We thank Dr. Dennis Cottom for permission to study patients under his care at the Hospital for Sick Children, Great Ormond Street, London W.C.1.

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REFERENCES

- Emmelin, N. (1961). *Pharmacol. Rev.*, **13**, 17.
- Goodall, J., Shinebourne, E., and Lake, B. D. (1967). In press.
- Obianwu, H. O., and Rand, M. J. (1965). *Brit. J. Ophthalm.*, **49**, 264.
- Riley, C. M. (1957). *Advanc. Pediat.*, **9**, 157.
- and Moore, R. H. (1966). *Pediatrics*, **37**, 435.
- Smith, A. A., and Dancis, J. (1964). *New Engl. J. Med.*, **270**, 704.
- and Breinin, G. (1965). *Invest. Ophthalm.*, **4**, 358.
- Sneddon, J. M., and Turner, P. (1967). *J. Physiol. (Lond.)*, **189**, 20P.