FAMILIAL HYPERPARATHYROIDISM

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DESPITE the increasing frequency with which primary hyperparathyroidism has been recognized in recent years (Dent, 1962), reports of its familial occurrence are few: search of the literature reveals only 13 examples. This paper records another affected family and draws attention to the need for more systematic study of the relatives of patients with this disorder.

The Family

The pedigree is shown in Fig. 1. The affected members, II 1, II 3 and II 5, were all female and all suffered from primary chief cell hyperplasia of the parathyroids. Brief clinical details are recorded in the appendix; the cases are reported at greater length elsewhere (Adams, Chalmers, Peters, Rack and Truscott, 1965). Serum calcium* and in some cases serum phosphate and alkaline phosphatase estimations were carried out on eight other members of the family (Table 1). All were within normal limits with the exception of the infant III 6 whose calcium values ranged between 10.6 and 11.9 mg. per 100 ml. Normal values in this age-group are uncertain. At present (age 18 months) the level appears to be falling and the child is in good health.

*All serum calcium values were corrected for serum specific gravity as suggested by Dent (1962).

Genetic Studies

Blood groups of the ABO, MNS, P, Rhesus, Lutheran, Kell, Lewis, Duffy, and Xg^a systems were determined in the hope of establishing a gene linkage. Xg^a is the only blood-group system which is inherited in a sex-linked manner, the linkage shown by the other groups being autosomal. Autosomal linkage is exemplified in the association of the nail-patella syndrome with the ABO blood group (Renwick & Lawler, 1955). The blood-groups (Table 2) show no evidence of linkage with the gene responsible for the production of hyperparathyroidism in this family. Although the affected members are all female, the blood-group studies provide no additional evidence of sex-linkage.

The secretor state and the ability to taste phenylthiourea were also investigated. The results show all the family to be non-secretors and to be unable to taste phenylthiourea in the concentrations recommended. 23% of the population are non-secretors (Clarke, Edwards, Haddock, Howel-Evans, McConnel and Shepard, 1956) and about 25% of the population are non-tasters (Falconer, 1947). Chromosomes derived from blood-cell culture were examined and found to be normal.

Discussion

Review of the Literature

Familial hyperparathyroidism was first reported by Goldman and Smyth (1936) who described a 17-year-old girl and her 23-year-old brother. The girl presented with a pathological fracture and renal colic while her brother had a giant-cell tumour of the mandible. Each had a single parathyroid adenoma removed from the

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FIG. 1.—Pedigree. Affected members of the family shown in black.

TABLE 1.
BIOCHEMICAL DATA

	Serum Calcium mg. per 100 ml. corrected	Serum Inorganic Phosphate mg. per 100 ml.	Serum Alkaline Phosphatase King-Armstrong units
I 1	10.4		
I 3	10.05		
I 4	10.65	3.2	7
I 6	10.75		
II 1	11.7	2	10.8
II 2	10.0	3.7	4.3
II 3	12.9	2.5	5.5
II 4	10.7	3.2	7
II 5	12.1	2.5	
III 6	10.6 to 11.9	3.5 to 6.8	28
III 9	9.95		

region of the left lower pole of the thyroid. Eleven years later Schneider, Kyger and McCullagh (1947) reported two female cousins, one of whom presented with tumours of the jaw at the age of 20 years. At operation a parathyroid adenoma was removed from the region of the left lower pole of the thyroid. Her cousin had already undergone an operation five years earlier for the removal of a parathyroid adenoma diagnosed because of polycystic bone

disease. Shallow and Fry (1948) noted the occurrence of parathyroid adenomas in a father and daughter, the former being 35 years old and the latter 14 years old at the time of diagnosis. Each presented with bone disease and had an adenoma of the left lower parathyroid. The father later developed renal and recurrent bony lesions and another adenoma was discovered in the mediastinum 15 years after the first operation.

TABLE 2.
BLOOD GROUPS OF FAMILY

	ABO	MNS	P	Rh	Lu	K	Le		Fy	Xg ^a
							a	b		
I 4	A 1	MNS	+	R2 r	—	—	+	—	+	+
I 5	A									
II 1	A 1	NsNs	+	R1R2	—	—	+	—	+	+
II 3	A 1	NsNs	+	R1R2	—	—	+	—	+	+
III 4	A 1	MM	+	R1R2	—	—	+	—	+	+
III 5	A 1	MMS	+	R1R2	—	—	+	—	+	+

Frohner and Wolgamot (1954) described four sisters and a brother with primary hyperparathyroidism; moreover the father died from what was probably the same disease. Another brother and sister were apparently normal. Of those affected, some had pathological fractures or other manifestations of bone disease, whereas others presented with renal calculi or nephrocalcinosis. At operation double adenomas were found in two of the patients; the other three had single adenomas removed but one of these required re-exploration and the removal of a second adenoma eight months later. Four of these patients were in their twenties and one was aged 30 at the time of diagnosis. Nielsen (1955) reported hyperparathyroidism in two sisters. The younger, aged 47, had renal calculi and bone pain in addition to the symptoms of hypercalcaemia. Remission followed the removal of a "typical adenoma" of the left lower parathyroid. Her sister had been found to have hypercalcaemia some years previously when she was 33 years old. At operation no parathyroid abnormality had been found. She died of uraemia seven years later.

Snapper, Yarvis, Freund and Goldberg (1958) described identical male twins with the disease. One presented with sarcoidosis (confirmed histologically), the features of which recurred on a number of occasions. Six years later the patient developed generalised weakness, joint pains and polydipsia, and was found to be hypercalcaemic. Cortisone administration did not produce the expected fall in the level of the serum calcium although the signs and symptoms associated with the sarcoidosis improved. The serum calcium returned to normal levels after the removal of an adenoma of the left upper parathyroid. The older twin had earlier presented with vomiting and left loin pain and had been shown to have hypercalcaemia. This was corrected by the removal of an adenoma of the left lower parathyroid.

Jackson (1958) reported five proved and two probable cases of hyperparathyroidism in two generations of a family. Two brothers had tumours of the mandible; in each a parathyroid adenoma was found. One of their sisters also had a tumour of the jaw and at operation two parathyroid adenomas were removed. Another sister had a tumour of the maxilla excised. At necropsy three years later nephrocalcinosis was discovered but the state of the parathyroids was not recorded. A third sister had recurrent abdominal pain thought to be due to pancreatitis and was found to have an elevated serum calcium. Two of her sons also had recurrent abdominal pain and hypercalcaemia; in both cases the abnormalities disappeared following the removal of an adenoma of the right lower parathyroid. The same author has briefly described three other families with hyperparathyroidism (Jackson, 1959; Jackson, Talbert and Caylor, 1960; Jackson, Yoder and Caylor, 1961).

Cassidy and Anderson (1960) reported a mother and two sons with primary hyperparathyroidism. The mother had renal stones and a chronic duodenal ulcer. At the age of 62 years she underwent two operations at which several enlarged parathyroids and the thyroid gland were removed. Her elder son, aged 39 years, had bilateral renal calculi; both lower parathyroids were found to be enlarged and were removed. Her younger son, aged 31 years, also had renal calculi; a subtotal parathyroidectomy was performed, four enlarged parathyroids having been found. All the enlarged parathyroids in these three patients were thought to show adenomatous change but the account is not sufficiently detailed to rule out chief cell hyperplasia.

Cutler, Reiss and Ackerman (1964) described a family in which seven proven and four probable cases of primary hyperparathyroidism occurred among the descendants of two brothers

who married sisters from a distant branch of their family. The seven proven cases comprised three adult women with renal calculi, three men with hypercalcaemia, and a 17-year-old girl with hypercalcaemia. Three of them also had peptic ulcers. Most if not all of the patients had chief cell hyperplasia; the authors comment on the difficulty of distinguishing this condition from adenoma.

Hillman, Scriver, Pedvis and Shragovitch (1964) have recently reported the occurrence of primary hyperparathyroidism in the two infant sons of first-cousin parents. The first child died with severe hypercalcaemia and was found at necropsy to have parathyroid hyperplasia. The younger child had a serum calcium of 24.8 mg/100 ml. Subtotal parathyroidectomy was performed at the age of 20 days. The glands were enlarged and showed the histological features of chief cell hyperplasia.

Clinical Features

No sex preponderance is evident in the previous literature. The three members of the present family with proved hyperparathyroidism are female. The male infant III 6 may however be affected. The ages at which the diagnosis was made in our family were 26, 20 and 36 years, although one was known to have renal stones five years earlier and another had what was probably renal colic eight years before.

A relatively early onset of the disease appears to be characteristic of familial hyperparathyroidism (Fig. 2). This was also pointed out by Snapper and others (1958) and by Laubinger and Mellinger (1959). By contrast the sporadic form of the disease is usually found in older patients: Riddick and Reiss (1962) reported the age range of 30 cases as 26-78 years with a peak at 45-55 years.

All three patients in the present family had renal calculi without clinically evident bone disease. Previous reports show that the clinical presentation tends towards consistency within families, particularly in that described by Jackson (1958). The frequency of renal manifestations relative to bone disease appears to be somewhat less than in sporadic hyperparathyroidism (Cope, 1960; Keating, 1961) but the number of familial cases is too small to permit a firm conclusion. None of our patients had evidence of other endocrine abnormalities; nor was there clinical evidence of peptic ulceration. There is therefore no reason at present to suspect that they are suffering from the syndrome

FIG. 2.—Familial Hyperparathyroidism; age at onset in 38 cases.

of multiple endocrine adenomas and peptic ulceration (Ballard, Frame and Hartsock, 1964), although patients with that syndrome can occasionally present with hyperparathyroidism alone, other manifestations being delayed for many years or appearing only in relatives (Wermer, 1954).

Pathology

The affected members of our family all had chief cell hyperplasia of the parathyroids; the histological appearances showed a striking similarity from case to case. Previous reports do not always include histological details, and until chief cell hyperplasia was described by Cope, Keynes, Roth and Castleman (1958) it may often have been misinterpreted as adenomatous change. However more than one gland was affected in about half the reported cases and we have concluded that at least a third had primary chief cell hyperplasia. In sporadic primary hyperparathyroidism the incidence of this condition is only 3-6 per cent (Cope, 1960; Hellström and Ivermark, 1962; Riddick and Reiss, 1962). On the other hand chief cell hyperplasia is the characteristic lesion affecting the parathyroid glands in the syndrome of multiple endocrine adenomas and peptic ulceration (Ballard and others, 1964).

Genetic Aspects

From a study of the pedigree (Fig. 1) it appears that the disorder is transmitted by a dominant gene. There is insufficient evidence to deduce whether the gene is sex-linked but it is noteworthy that the three proved cases were female. Previous reports, however, indicate

an autosomal inheritance. Screening tests on the father indicate that he is not suffering from the disorder. The mother died from carcinoma before this study was undertaken.

Practical Implications

Primary hyperparathyroidism is not infrequently familial. More systematic investigation of relatives would undoubtedly uncover further affected families. Family studies are particularly indicated in cases of primary chief cell hyperplasia. Conversely, when primary hyperparathyroidism occurs in more than one member of a family chief cell hyperplasia should be suspected. When the neck is explored all the parathyroid glands must be examined with more than usual care and may need to be removed (Adams and others, 1965). Additional indications for careful family studies are the occurrence of primary hyperparathyroidism in young persons and its association with the syndrome of multiple endocrine adenomas and peptic ulceration.

Summary

Three sisters with hyperparathyroidism were found to have primary chief cell hyperplasia. It is likely that more thorough investigation would show that familial hyperparathyroidism is by no means as rare as the paucity of previous reports would suggest. The disease appears to be inherited as an autosomal dominant. Familial hyperparathyroidism occurs in younger patients than the sporadic form and is more likely to be due to primary chief cell hyperplasia.

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APPENDIX

Case Reports

Case No. 1. (II 3)

Mrs. E. M., born 25.2.34. In 1959 she was found to have bilateral renal calculi and a serum calcium of 13.2 mg/100 ml. Hypercalcaemia persisted despite three explorations of the neck at which abnormal parathyroid tissue was removed. In December 1963, she gave birth to a normal male child (which did not develop tetany). At a fourth operation in January 1964, all remaining parathyroid tissue was removed. The serum calcium fell to 7 mg/100 ml. and calcium supplements and calciferol 5 mg daily have been

required to maintain it within normal limits. Microscopic examination of the parathyroids showed chief cell hyperplasia.

Case No. 2. (II 5)

Mrs. R. B., born 8.9.43. At 20 weeks in her first pregnancy she developed renal colic and passed a calcium phosphate stone. Serum calcium was 12.1 mg/100 ml. Shortly afterwards, in October 1963, an exploration of the neck showed an enlarged left upper parathyroid which was removed. The other glands were identified and were of normal size and appearance. Histological examination of the enlarged gland showed the features of chief cell hyperplasia; similar features were found in the small pieces taken from the normal-sized glands.

There has been no recurrence of hypercalcaemia (up to July 1965) and she has not required calcium supplements.

Case No. 3. (II 1)

Mrs. J. T., born 2.10.27. On survey of the family in October 1963, she was found to have a serum calcium of 12.4 mg/100 ml. and an intravenous pyelogram later showed bilateral renal calculi. In September 1964, an exploration of the neck showed that the two upper parathyroids were enlarged and the left lower gland of normal size. These three glands were removed together with the right lower pole of the thyroid, which was later found to contain a fourth normal-sized parathyroid. The histological features of all four parathyroid glands were those of chief cell hyperplasia, closely resembling those found in cases 1 and 2. The serum calcium fell to 7.9 mg/100 ml. She has since received oral calcium and vitamin D.

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