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Primary Hyperparathyroidism—A Review of Cases in the Sheffield Area

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The association of a tumour in the neck with the classical bone changes of von Recklinghausen was first reported in 1904 but it was not until 1925 that the first parathyroidectomy was performed in Vienna (Mandl, 1926). In the same year parathyroid hormone was extracted from bovine parathyroid glands by Collip (1925) and its hypocalcaemic properties demonstrated in dogs. The association of hyperparathyroidism with renal stones was recognised in 1932 (Cope, 1966) and since that time the association between peptic ulceration (Rogers *et al.*, 1947) pancreatitis

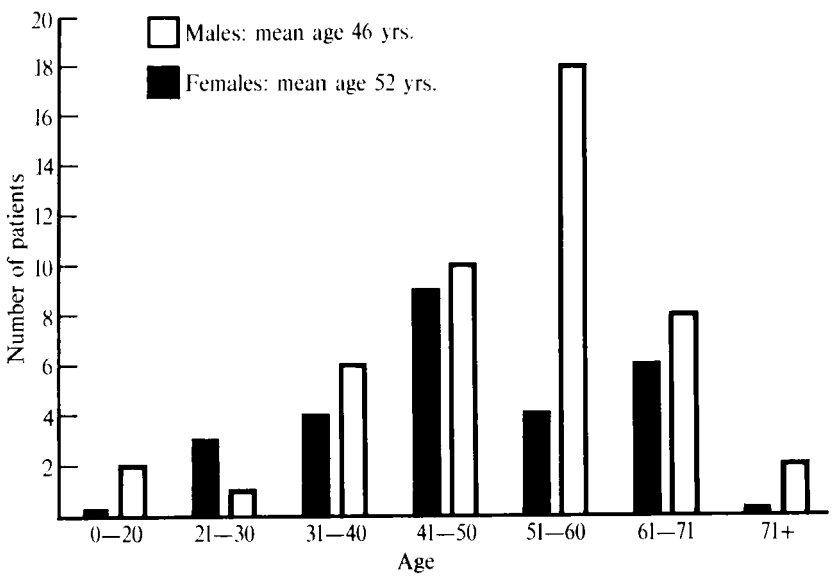

Fig. 1. Age distribution of patients with hyperparathyroidism.

(Cope *et al.*, 1957) and hypertension (Hellstrom, Birke and Edvall, 1958) has been reported in patients with hyperparathyroidism.

Until recently, hyperparathyroidism has been considered to be a rare disease, large series of cases being collected by a few centres with a special interest in the problem (Cope, 1966; Purnell *et al.*, 1974; Watson, 1974).

After re-examining histological material submitted to the pathology department from 1955 to 1976, 97 patients were found to have abnormal parathyroid tissue. Patients with secondary

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Table I

Presentation in 73 Patients

	%
Renal stones	46 (63)
Skeletal changes	9 (12)
Abdominal pain	4 (6)
Hypercalcaemia	6 (8)
Hypertension	2 (3)
Chance finding	6 (8)

Table II

Associated Symptoms

	Total cases (%)
Nocturia	41
Hypertension	25
Abdominal pain	24
Constipation	23
Depression	17
Headache	10
Polyuria	10
Muscular weakness	8

Table III

Distribution of Stones

Renal	
Unilateral	20
Bilateral	11
Nephrocalcinosis	1
Renal + ureteric	14
Ureteric	10
Bladder	1

and tertiary hyperparathyroidism have been excluded as they were too few to be submitted to meaningful analysis. The records of 73 patients with primary hyperparathyroidism have been traced and the information is presented here.

Patients

There were 26 males and 47 females (Fig. 1). The mean age was 46 years for men and 52 years for women.

The majority of patients presented with symptoms due to urinary calculi (Table I). 9 presented with skeletal changes. 6 of these had generalised bone pains; 2 pathological fractures of the femur and 1 an expanding giant-cell lesion in the jaw. Of the 4 patients who presented with abdominal pain, only 1 had a peptic ulcer and none had pancreatitis. 6 patients presented with hypercalcaemic symptoms of polyuria, thirst and vague abdominal discomfort. 1 patient required urgent correction of hypercalcaemia before surgery. 2 patients were found to have hypercalcaemia during investigation for their hypertension and 6 others while being investigated for unrelated problems.

Associated symptoms are summarised in Table II. 41% had significant nocturia, voiding at least twice in the night although diurnal frequency was unusual.

57 patients (78%) had urinary calculi but only 51 of these had symptoms referrable to them. 77% of these patients had multiple stones or nephrocalcinosis compared with only 45% of a series of 100 consecutive stone formers in Sheffield.

The anatomical distribution of stones is shown in Table III, the majority being renal.

22 patients had a history of stones for 2 to 20 years before the diagnosis was made. During this time recurrent stones had formed in 16 (73%). Following correction of the hyperparathyroidism new stones formed in only 5 (9%) of the 57 patients.

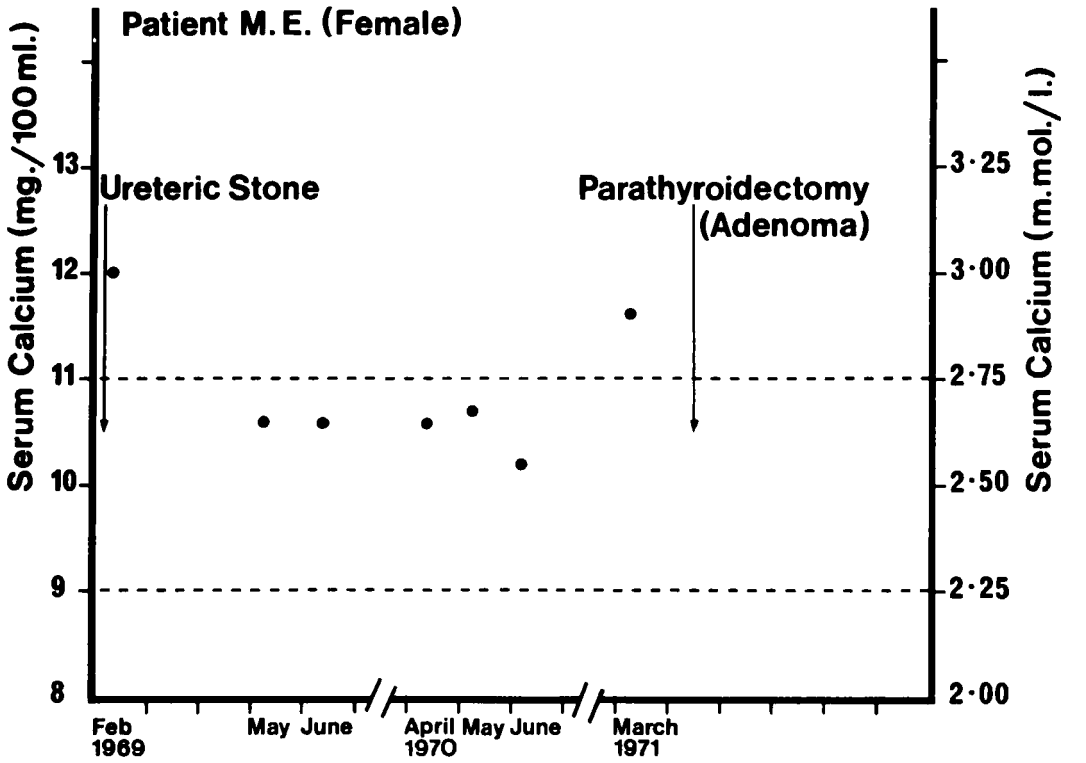


Fig. 2. Serial serum calcium levels in a patient with hyperparathyroidism.

Diagnosis

In each case the most important diagnostic index was the serum calcium which is corrected for serum protein levels. Within the normal range quoted by our laboratories, 51 patients had persistent hypercalcaemia until parathyroidectomy was performed. However 22 patients had intermittent hypercalcaemia, the clinical course of 1 such patient being represented in Figure 2. In Figure 3 the highest serum calcium level recorded in all patients with primary hyperparathyroidism is compared with the highest serum calcium level in a group of non-hyperparathyroid stone formers. Figure 4 shows the lowest recorded serum calcium for each patient. Patients with radiological evidence of bone changes have somewhat higher calcium levels than patients without such changes.

Hypercalciuria was a common finding although there was a large overlap with a series of non-hyperparathyroid stone formers and approximately 1 in 5 patients had normal calcium excretions (Fig. 5).

The serum phosphate was an unreliable diagnostic index in this series (Fig. 6) and was probably higher than expected (Watson, 1974). Serum should be rapidly separated from erythrocytes to prevent leakage of intracellular phosphate if true values are to be obtained.

Plasma chloride was measured in only a small number of cases but in no instance was the level less than 101 mEq/l.

Elevated levels of serum alkaline phosphatase were found in patients with and without radiological evidence of bone disease, although the proportion of those with an elevated level was greater in patients with bone changes (Table IV).

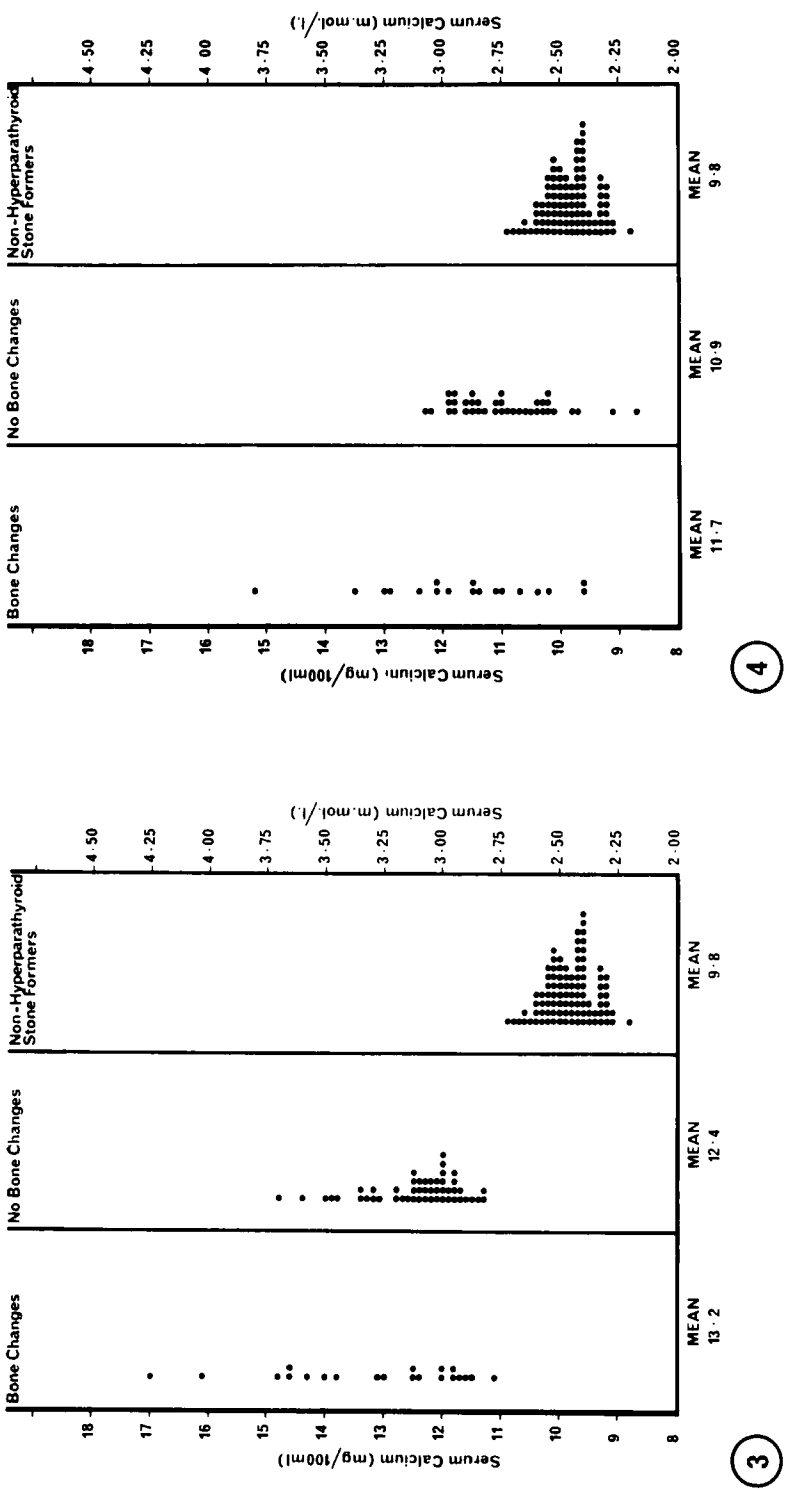


Fig. 3 Highest recorded serum calcium in hyperparathyroid patients and a series of non-hyperparathyroid stone formers.

Fig. 4. Lowest recorded serum calcium in hyperparathyroid patients and a series of non-hyperparathyroid stone formers.

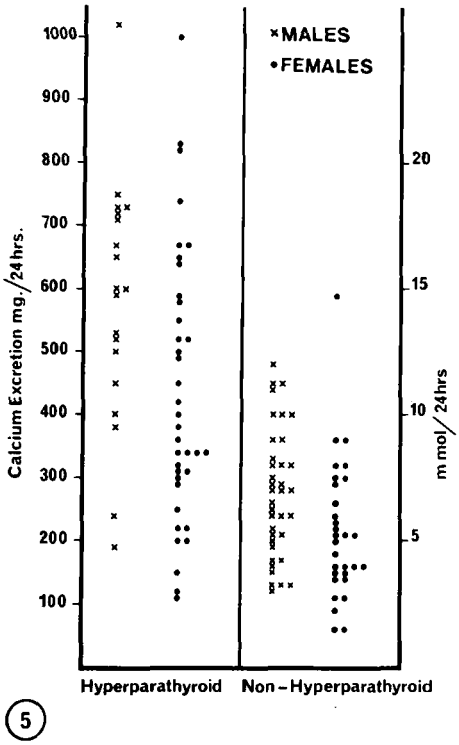


Fig. 5. Urinary calcium excretion in hyperparathyroid patients and a series of non-hyperparathyroid stone formers.

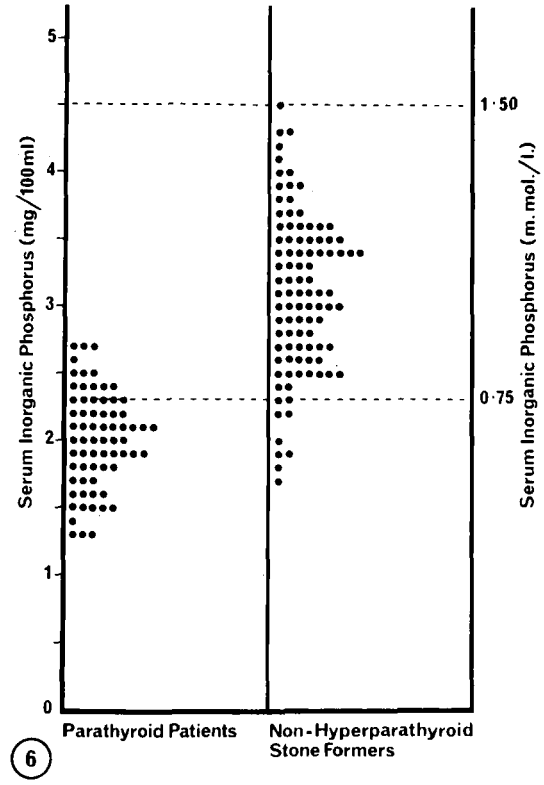


Fig. 6. The distribution of serum inorganic phosphorus in hyperparathyroid patients and a series of non-hyperparathyroid stone formers.

Parathyroid hormone was estimated by radioimmunoassay, in the peripheral venous blood of 22 patients. An elevated level was observed in 15 and in 7 (32%) the level was misleadingly low or undetectable. Assay by multiple sampling from the large neck veins was performed in 7 patients, the tumour being accurately located in 5.

49 patients were examined for radiological evidence of bone disease, definite bone changes being seen in only 43%.

Surgery

The neck was explored in all cases. Recently we have used intravenous methylene blue as a means of identifying abnormal parathyroid tissue (Dudley, 1971). This technique was felt to have been helpful in the rapid identification of parathyroid tumours in 12 out of 14 patients.

True mediastinal tumours were not encountered in this series although in several instances the tumour was partially situated in the upper mediastinum but could easily be delivered through the cervical incision. The distribution of adenomas in the neck is shown in Table V. The lower parathyroids were involved most frequently and there appears to be a difference in lateralisation between males and females.

Table IV

Serum Alkaline Phosphatase

	Bone changes	No bone changes
Normal level	5	22
Elevated level	16	14

Table V

Distribution of Adenomas in the Neck

	Males		Females	
	Right	Left	Right	Left
Upper	5	3	2	5
Lower	12	6	12	26

Table VI

Histology

Adenoma	
Chief cell	28
Clear cell	22
Oxyphil cell	6
Unclassified	12
Hyperplasia	
Chief cell	3
Clear cell	1
Carcinoma	1

Table VII

Postoperative Serum Calcium

Total patients		73
Normocalcaemic	66	
Hypocalcaemic	5	
Hypercalcaemic	2	

There was no mortality associated with surgery. 4 patients developed a wound infection or haematoma. Immediate short-lived hypocalcaemia was common but tetany occurred in only 1 patient.

Pathology

Most of the patients had adenomas (Table VI). Histologically the majority were chief or clear cell, but there were 6 oxyphil tumours. Hyperplasia involved all 4 glands in 3 patients but only 2 glands in 1. 1 patient had a carcinoma of the parathyroid.

The weight of tissue removed varied from 150 mg to 8 g. There was no difference between the sexes or between patients with or without bone changes. A loose relationship exists between tumour size and serum calcium level (Fig. 7).

Results

69 patients were cured by a single operation. 1 patient had an initial negative exploration but an adenoma was found 6 months later. A further patient had recurrence of hypercalcaemia after a right lower parathyroid adenoma had been removed. Re-exploration 6 years later revealed hyperplasia of the upper parathyroids. 2 patients had persistent hypercalcaemia. 1 of these had a parathyroid carcinoma with local recurrence and the other was lost to follow-up.

The postoperative calcium status is shown in Table VII. 5 patients who developed prolonged hypocalcaemia required out-patient calcium therapy. In each case at least 2 normal parathyroids were seen and preserved when the neck was explored.

Following correction of the hyperparathyroidism, the calcium excretion of 15 patients who were previously hypercalciuric, fell towards normal levels (Fig. 8). In 5 patients who formed recurrent stones after parathyroidectomy, the postoperative calcium excretion was normal.

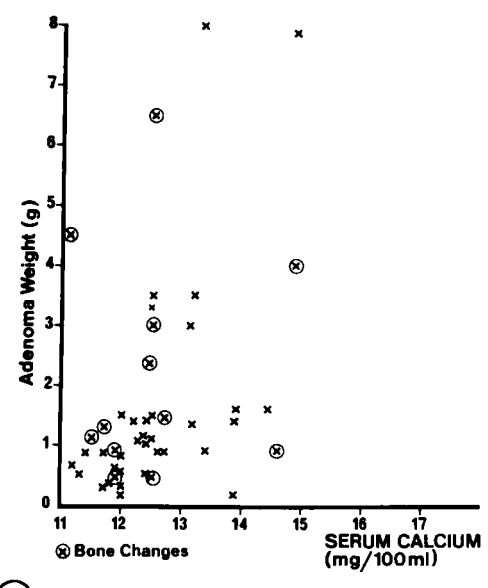
Discussion

Primary hyperparathyroidism is a disease with a peak incidence in the fifth decade affecting women approximately twice as often as men (Cope, 1966; Pyrah, Hodgkinson and Anderson, 1966; Watson, 1974). The age range is, however, wide and cases have been reported in children (Nolan, Hayles and Woolmer, 1960).

Bone disease was the predominant presenting feature earlier in the century and has now given way to calculous disease of the urinary tract which accounted for 63% of the presenting symptoms in this series. Stones associated with hyperparathyroidism are more likely to be multiple (Pyrah *et al.*, 1966) and recurrent (McGeown, 1961). 45% of stones in non-hyperparathyroid patients in Sheffield are multiple contrasting with 77% in this series. The reduction of recurrent stone formation from 73% to 9% after parathyroidectomy lends support to the findings of McGeown (1961) who showed by statistical analysis, a reduction in the rate of recurrent stone formation after correction of hyperparathyroidism.

Few of our patients had peptic ulcers although an association between hyperparathyroidism and peptic ulceration was noted by Rogers *et al.* (1947). It is possible that the association is valid only in the more uncommon condition of multiple endocrine adenomas (Reiss and Canterbury, 1974). Abdominal pain of undefined aetiology is more common (Watson, 1974) and in half our patients with this symptom there was an immediate dramatic relief following parathyroidectomy. We have not observed pancreatitis in association with hyperparathyroidism although it was diagnosed in 7% of a series of 155 cases from the Massachusetts General Hospital (Mixter, Keynes and Cope, 1962).

25% of our patients were hypertensive. Hellstrom *et al.* (1958) found hypertension in 70%



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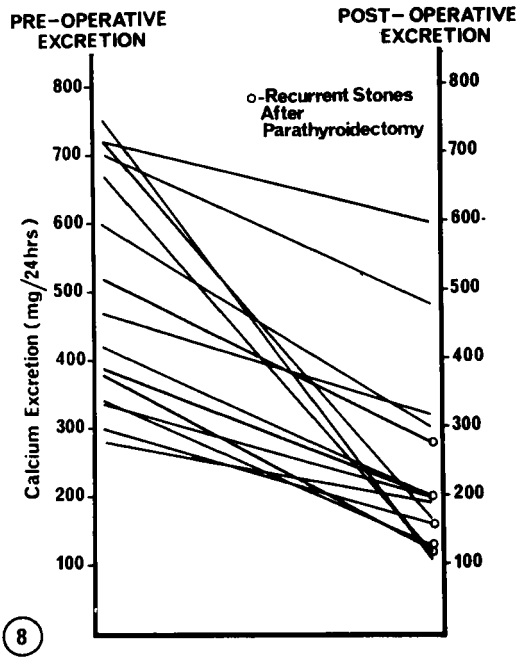

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Fig. 7. The correlation between adenoma weight and serum calcium in hyperparathyroid patients. Patients with radiological evidence of bone change are indicated by a ringed cross.

Fig. 8. Urinary calcium excretion in hyperparathyroid patients before and after parathyroidectomy.

of patients with hyperparathyroidism the hypertension being related to impaired renal function. Although the blood pressure may show a transient fall when the hyperparathyroidism is corrected, it usually persists (Watson, 1974).

Polyuria, due to disturbance of tubular function, may in severe cases mimic diabetes insipidus (Pyrah *et al.*, 1966). Only 10% of our patients complained of polyuria although 41% had nocturia, presumably an earlier manifestation of the same symptom.

The serum calcium was the most important diagnostic index exceeding 11 mg/100 ml in every case in this series. The normal range is stated to be 9 mg to 11 mg/100 ml (2·25-2·75 mmol/l.). A true normal range should be determined by each laboratory by sampling from the normal population. When this has been done in centres with a special interest in calcium metabolism the normal range has been much narrower, with lower upper limits. If the wider limits are accepted then marginal hypercalcaemia will be missed. 30% of the patients in our series had normal serum calcium levels at times before the diagnosis was made. Similar findings have been reported by others (McGeown and Morrison, 1959; Riddick and Reiss, 1962). Repeated calcium estimations are therefore necessary in all patients with stones.

In a review of 138 patients, Lloyd (1968) reported a definite correlation between tumour size and serum calcium levels. Also, in his patients with overt bone disease, the tumours were larger, the serum calcium higher and the history shorter than in patients with stones. We were only able to find some relationship between serum calcium and tumour size.

Hypercalciuria was common although approximately 1 in every 5 patients had normal levels. Parathyroid hormone has been shown to promote significant tubular reabsorption of calcium (Nordin and Peacock, 1969). In patients with hyperparathyroidism this action of parathyroid hormone compensates for the increased filtered load of calcium resulting in normal calcium excretion in some of these patients. Hypercalciuria was also a poor diagnostic index owing to the overlap with other stone formers, approximately one-third of whom have hypercalciuria (Fig. 5; Williams and Chisholm, 1974).

The plasma chloride may be useful in the differential diagnosis of patients with hypercalcaemia. Parathyroid hormone acts on the renal tubules to promote bicarbonate loss resulting in a hyperchloraemic acidosis in primary hyperparathyroidism. Hypercalcaemia due to other causes promotes potassium and chloride loss. Serum chloride levels above 102 mEq/l. have been found in hyperparathyroidism and below this level in patients with hypercalcaemia due to other causes (Wills and McGowan, 1963).

The serum radioimmunoassay of parathyroid hormone was introduced by Berson *et al.* (1963) and early reports suggested that all patients with hyperparathyroidism had elevated levels (Reiss and Canterbury, 1969). However, it is our experience and that of others (Watson, 1974) that in a proportion of cases elevated levels cannot be detected. Sampling from the large neck veins has improved the technique (Reitz *et al.*, 1969) and permitted localisation of some tumours. However, owing to the variability of the venous drainage of the parathyroids and streaming of blood, this technique is less reliable than might be expected (O'Riordan, Kendall and Woodhead, 1971). We have no experience of thyroid vein catheterisation which is said to improve the results (Shimkin *et al.*, 1972). The technique of venous catheterisation is not without risk and should be reserved to help localisation in patients who have undergone previous neck surgery.

Surgical exploration can be difficult (Davies, 1974). We have been fortunate in relieving the hyperparathyroidism in 95% of patients following the first operation. Methylene blue is a useful adjunct to finding the abnormal glands.

The histology is similar to that described in other large series. The oxyphil cell adenoma is of some interest. Christie (1967) reviewed the oxyphil cell and noted its rarity in the infant parathyroid and its increasing numbers with age and in chronic renal failure. He thought that the oxyphil cell adenoma was not associated with a clinical syndrome. Oxyphil cell adenomas have, however, been reported in association with hyperparathyroidism (Selzman and Fechner, 1967) and were found in 8% of our series.

The majority of tumours involve the lower parathyroids (Nicholson, 1969). We have found no reference in the world literature to the difference in lateralisation between the sexes noted in our series.

Primary hyperparathyroidism has been considered to be a rare disease but this may be that until recently we have only observed the clinical tip of a biochemical iceberg. In large-scale screening programmes of apparently healthy populations, biochemical hyperparathyroidism has been diagnosed in 0·1% (Boonstra and Jackson, 1971; Watson, 1974). With the increasing use of multichannel analysers it is likely that primary hyperparathyroidism will be diagnosed with increasing frequency and the treatment of asymptomatic cases will become a problem. There can be no doubt that correction of the condition reduces the high recurrence rate of stone formation. The treatment of asymptomatic cases without stones is a difficult problem which will be resolved only by long-term prospective trials keeping such patients under review.

Summary

73 patients with primary hyperparathyroidism are reviewed.

The elevated serum calcium was the main diagnostic index but estimation of the parathyroid hormone was useful confirmatory evidence when raised. A normal level does not exclude the diagnosis being found in 32% of patients.

Intravenous methylene blue was a useful adjunct to surgery.

95% of the patients had relief of their hypercalcaemia after a single operation.

78% of patients had stones and there was a marked reduction in further stone formation after surgery.

We are particularly indebted to Mr C. H. Talbot, who operated on a large number of patients in this series, to Professor T. J. Martin for his helpful comments and for the parathyroid hormone assays, and to the following surgeons who kindly allowed us to include their patients in this series: Professor R. G. Clarke; Mr Miles Fox; Mr P. Muller; Mr D. J. Robertson; and Mr J. T. Rowling.

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