Hyperparathyroidism

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SUMMARY

The changing clinical presentation of primary hyperparathyroidism from the 'overtly symptomatic' to the 'symptomatic in retrospect' and, finally, the 'asymptomatic discovered on routine 12-channel auto-analyser', is discussed.

The increasing incidence of primary chief cell hyperplasia, which is probably both relative and absolute, is stressed and the problems of diagnosis both macroscopical and microscopical, emphasised. Hyperparathyroidism is probably best considered as an interrelated hyperplastic and neoplastic state which may occur in the same patient, in the same gland or in multiple glands. We therefore believe that the best initial surgical approach is removal of the abnormal gland and biopsy of one other gland. If the biopsy of the second gland is normal, nothing further should be done, but if this is abnormal, 2 more glands should be removed. To date this policy has proved to be most rewarding.

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There is an increased incidence of primary hyperparathyroidism, and with this an increasing number of questions and problems arise. This paper reports the clinical spectrum, diagnostic tests, pathological findings and treatment at the University of Cape Town teaching hospitals during two periods. The first was from 1953 to 1969 when 36 cases were reported[1] and the second from 1970 to 1972 when there were a further 13 cases.

Hyperparathyroidism is classified as primary, secondary and tertiary or autonomous. This discussion refers mainly to primary hyperparathyroidism.

There was a wide age range of patients with hyperparathyroidism in our series, the youngest being a girl of 10 years (Table I). There was a preponderance of females —33 females and 16 males.

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PATIENTS

Clinical Presentation

There are 3 types of clinical presentation: overtly symptomatic, symptomatic only in retrospect, or asymptomatic. The presenting features are subdivided into those due to bone disease, renal disease, hypercalcaemia, other disorders, e.g. pancreatitis, peptic ulcers, and asymptomatic or incidental (Table II). Asymptomatic or incidentally discovered primary hyperparathyroidism used to be a relatively rare disease, but has increased significantly since the introduction of the 12-channel auto-analyser.

TABLE II. PRESENTING FEATURES

	Number of cases		
	Group I (36)	Group II (13)	Total (49)
Bone disease			
Pain	4	2	6
Fracture	1	1	2
Renal disease			
Colic, stone, infection	23	5	28
Renal failure	0	1	1
Hypertension and stones	2	1	3
Hypercalcaemic symptoms	7	1	8
Other			
Peptic ulcer	0	2	2
Pancreatitis	1	1	2
Asymptomatic	3	4	7

The frequency of primary hyperparathyroidism in patients whose serum calcium is determined on routine examination has been estimated at 1:1 000[2] to 1:2 000.[3] This is 3 to 4 times higher than the incidence of primary hyperparathyroidism in patients presenting with symptoms.[4] Nevertheless, malignant disease is still the commonest cause of a raised serum calcium, while hyperpara-

TABLE I. AGE DISTRIBUTION OF 49 CASES OF HYPERPARATHYROIDISM

	Age group (years)								
	0 - 10	11 - 20	21 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 - 80	81 - 90
Group I (1953 - 69)									
No. of cases	1	—	6	6	9	6	6	1	2
Group II (1970 - 72)									
No. of cases	—	—	1	2	3	5	—	—	—

thyroidism is a poor second. In Ballinger and Haff's series,[3,5] 50% of cases had unsuspected primary hyperparathyroidism discovered on routine serum calcium estimations. In their group I there were only 3 patients, but in group II, consisting of 13 patients, 4 were asymptomatic and 4 were symptomatic only in retrospect.

Investigations

The diagnostic triad of hyperparathyroidism comprises hypercalcaemia, hypophosphataemia and hypercalciuria. The great number of tests reported in the literature, however, attests to the variability and inconsistency of this triad. In our patients, hypercalcaemia was regarded as an essential prerequisite for surgery, but we kept in mind that cyclical episodes of normocalcaemia and even hypocalcaemia may occur.

Increases in serum calcium are due to the direct effect of the parathyroid hormone on bone, gastro-intestinal tract and kidney. All our patients had an elevated serum calcium, above 11,0 mg/100 ml, which is our current upper limit of normality. In group I the highest levels were associated with bone disease, but in group II the highest level was in an asymptomatic female.

The morning serum phosphorus value was below 2,5 mg/100 ml in approximately half of the patients in both groups. Alkaline phosphatase was elevated in 11 of 49 patients. All these patients had bone disease.

The hypercalcaemia of hyperparathyroidism is usually, but not always, resistant to cortisone. Cortisone usually abolishes the hypercalcaemia of sarcoidosis and of vitamin D overdosage and also of about one-half of the cases with bone malignancies. In 25 out of 26 of our patients in whom the test was performed, there was no suppression.

Other investigations carried out in our patients included the percentage tubular reabsorption of phosphate, urinary calcium, plasma electrophoresis, serum electrolytes, renal function tests, radiography of bones and barium swallows. Unfortunately, radio-immunoassay of parathyroid hormone in serum is not yet available as a routine in our laboratory. This provides a direct laboratory diagnosis of hyperparathyroidism. Arteriography of the thyrocervical trunk may reveal a tumour 'blush' if the adenoma is large enough (Fig. 1). Radio-isotope scanning with selenomethionine, which is claimed as a useful diagnostic aid, was not carried out. Also, operative identification and localisation of parathyroid glands by pre-operative intravenous infusion of methylene blue (which does not have the myocardial toxicity of toluidine blue) which has been reported as being useful, was not done.

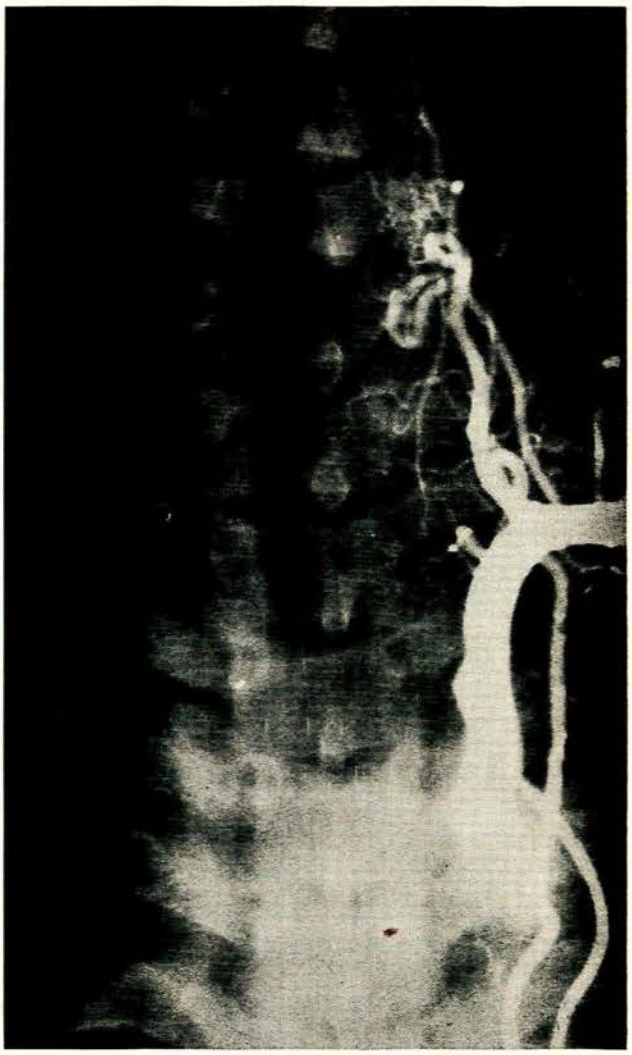

Fig. 1. Selective arteriography of thyrocervical trunk showing tumour 'blush'.

Treatment

Pre-operative preparation is necessary if acute hypercalcaemia, electrolyte imbalance, renal damage or dehydration is present.

The definitive treatment of hyperparathyroidism is operative removal of all excess functioning parathyroid tissue, at the first operation if possible. The surgeon must spend time on a careful exploration of the entire surgical region and must be aware of the embryology, anatomy, pathology, appearance and possible positions of normal parathyroid glands.

The thyroid gland is exposed with meticulous, dry-field dissection. All 4 parathyroid glands in the normal or ectopic situations must be identified, while it should be remembered that the number of glands is variable, from 3 to 6.

Surgical Pathology of Parathyroid Tumours

In our series most of the adenomas were situated in the right inferior gland and the rest were evenly distributed in the right superior, left superior, left inferior and mediastinal sites (Table III). In group I, there were no cases of hyperplasia. During the last 3 years, 4 out of 13 patients in group II presented with hyperplasia, i.e. an incidence of 30%.

TABLE III. SURGICAL PATHOLOGY OF PARATHYROID TUMOURS

	Number of cases		
	Group I (36)	Group II (13)	Total (49)
Single adenoma			
Right superior	4	1	5
Left superior	5	0	5
Right inferior	10	3	13
Left inferior	2	2	4
Mediastinum	4	2	6
Other	1	0	1
Unspecified	5	1	6
Total	31	9	40
Multiple adenoma	1	0	1
Hyperplasia	1	4	5
Carcinoma	0	0	0
Extra parathyroid hormone production	3	0	3

The pathologist's problem of differentiating hyperplasia from adenoma was demonstrated in 4 of the 13 cases. In the first case, the initial frozen section and permanent section were diagnosed as adenoma, but on review the diagnosis was changed to chief cell hyperplasia. In a second case, the frozen section appearances were those of hyperplasia, but on review the diagnosis was chief cell adenoma. The third case was found to have 4 macroscopically normal parathyroid glands. Biopsy specimens of 3 glands were interpreted as either hyperplasia or adenoma. However, the hyperparathyroidism persisted and at re-exploration via a midline sternotomy, a pigeon egg-sized adenoma was excised, with a dramatic cure of the condition. The fourth case presented with a duodenal ulcer of 5 years' duration and was found to have an elevated serum calcium level. She belonged to the group of asymptomatic cases diagnosed in retrospect. At operation 4 normal parathyroid glands were found; the 2 on the right only after the right lobe of the thyroid was removed. Postoperatively the hypercalcaemia persisted. Two months later the mediastinum was explored but no obvious parathyroid gland was found. The thymus, as well as pericardial, anterior and superior mediastinal fat, was removed, and in this tissue an adenoma was found. A review of the previous 4 glands showed hypoplasia. The postoperative calcium level returned to normal.

The cell type of both the adenomas and the primary hyperplastic glands has mostly been chief cell. Only one oxyphil adenoma was found and this presented in an asymptomatic patient with the highest recorded pre-operative serum calcium of 16,2 mg/100 ml—a most unusual association.

DISCUSSION

The most interesting difference between our two groups of patients is to be found in the increased incidence of parathyroid hyperplasia in the patients operated on since 1970. In this context, a diagnosis of 'hyperplasia' has been assigned to patients in whom there is gravimetric and histological evidence of cellular overactivity in more than one gland, be it hyperplasia alone, adenoma coexisting with hyperplasia or nodular hyperplasia.

Utley and Black[6] have shown that a rim of compressed normal parathyroid tissue around the abnormal cells is not as reliable a feature in the diagnosis of an adenoma as was formerly claimed.

The absence of hyperplasia in our group I cases may not be significant, since the histology of more than one gland was not available in most of the cases, whereas biopsy specimens were indeed obtained in 11 out of 13 patients in group II (84%).

The other interesting feature in our series is the sex incidence of primary chief-cell hyperplasia. There were 2 females and 2 males, i.e. a ratio of 1:1. This has been noted previously.

It is unrealistic to group the morphological manifestations of hyperparathyroidism into distinct and separate states in the parathyroid tissue, viz. primary hyperplasia, adenoma and carcinoma. It would be more meaningful to consider a spectrum of change with the four categories as convenient diagnostic resting places along the sequence (Fig. 2).

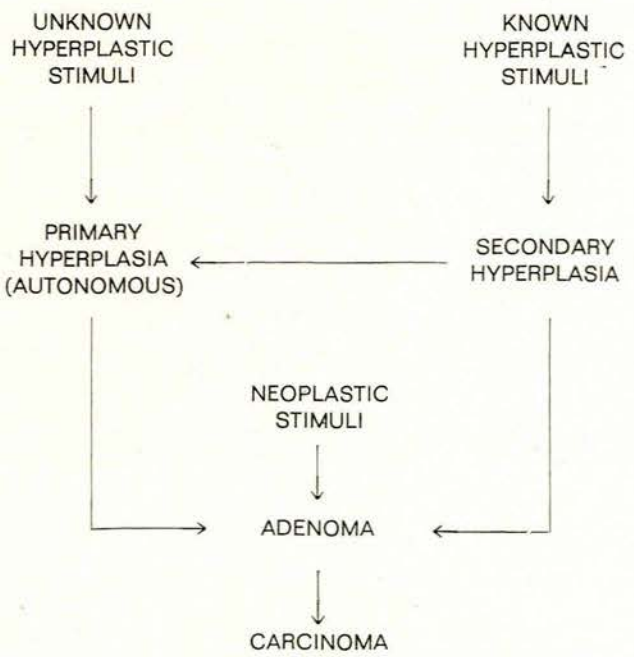

Fig. 2. Relationships between the hyperplastic and neoplastic parathyroid conditions.[7]

For the proper interpretation of the parathyroid state of an individual, 3½ parathyroid glands should be removed and examined histologically. This near-total parathyroidectomy assures a more accurate assessment of a patient's parathyroid state and provides less chance of recurrence.[7]

Haff and Ballinger[3] routinely remove 3½ parathyroid glands because of the difficulty of establishing the diagnosis of hyperplasia (chief-cell hyperplasia) grossly and by frozen section at the time of operation, i.e only 30 - 50 mg of parathyroid tissue are left behind. When 4 parathyroid glands cannot be found, a subtotal thyroidectomy is carried out and the cervical and upper mediastinal fat pads are removed in the hope that aberrant parathyroid tissue will be included. Exploration of the mediastinum at a later stage is performed as a second procedure only after a thorough search of the excised cervical tissue and if symptoms of primary hyperparathyroidism persist.[3,5]

The efficacy and safety of this policy is apparent from the data published by Haff and Ballinger.[3] Only 1 of 38 patients treated at initial operation by a resection of 3 or more glands developed recurrent hyperparathyroidism. Two cases of prolonged hypoparathyroidism were easily controlled with supplementary calcium. In contrast, 8 of 36 patients who had less than 3 glands completely excised, developed recurrent disease. There is a need for long and continued follow-up to show the delayed biochemical recurrences. The follow-up data of Haff and Ballinger[3] indicate the great importance of recognising the entity. Six of their 9 patients with recurrent disease had chief-cell hyperplasia.

A more exacting and aggressive approach toward parathyroid resection for primary hyperparathyroidism has been adopted by us over the past 3 years. This change in attitude was prompted by the reports of recurring or continued disease after successful removal of a parathyroid adenoma, coupled with the realisation that parathyroid hyperplasia frequently cannot be distinguished visually from normal parathyroid glands. The need for such a more aggressive approach would not be as great if the true incidence of primary parathyroid hyperplasia was indeed as low as the frequently quoted figure of 3 - 8% in patients with hyperparathyroidism. However, for reasons which are not entirely clear, the incidence of primary parathyroid hyperplasia is increasing. The latest reported incidence varies from 25% to 50%, and in our series it is 30%.

Our policy at present is to excise the so-called 'adenoma' or abnormal gland and to do biopsy on one normal gland. The tissue is submitted for frozen section. If the abnormality of one gland is confirmed and if the second gland is normal, no further procedure is carried out: but if it is abnormal, the other 2 glands are removed, i.e. a 3½ gland parathyroidectomy is performed. In our 13 patients we have only had 1 case of prolonged hypocalcaemia with tetany due to severe skeletal depletion ('hungry bones'), which responded satisfactorily to calcium and vitamin D. It would appear more desirable to be left with a few patients with hypoparathyroidism (which can be successfully managed today) than several patients with subclinical continuing hypercalcaemia and insidiously developing nephrocalcinosis and renal failure. Theoretically, the incidence of postoperative hypoparathyroidism should increase when near-total parathyroidectomy is carried out, but Straus and Paloyan's short-term follow-up does not confirm this.[7]

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