Primary Hyperparathyroidism:

Changing Clinical, Surgical and Pathologic Aspects

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ON July 1, 1966, a 12-channel serum auto-analyzer was installed at Barnes Hospital, St. Louis, Missouri. Since that date, all patients entering this hospital have had routine serum calcium determinations. In the 30 subsequent months 47 patients have undergone operations for primary hyperparathyroidism, many as a result of this screening test followed by other appropriate studies. This constitutes a remarkable increase in the frequency of such operations; there having been only 39 patients so treated in the previous 10 years.[13] Twelve patients were asymptomatic prior to the detection of hypercalcemia by routine screening. Eleven were found to have symptoms of hyperparathyroidism only in retrospect after discovery of hypercalcemia. Clinical records and pathologic specimens of these patients were examined to assess the incidence of operations for asymptomatic primary hyperparathyroidism, to define the reasons for the increase in surgical experience with this disease, and to determine the nature of the pathologic lesions involved. An attempt was also made to correlate histologic diagnoses with the pre- and postoperative clinical and biochemical findings.

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Clinical Material

In the 30-month period July 1, 1966 to December 31, 1968, approximately 87,500 patients were admitted to Barnes Hospital, St. Louis, Missouri. All had serum samples examined at the time of admission on a 12-channel analyzer (SMA 12 Technicon, Inc.). Information was obtained concerning the history and presenting complaints in 47 patients operated upon for primary hyperparathyroidism. X-ray evidence of renal stones or bone changes, serum calcium and phosphorus concentrations, and values for blood urea nitrogen, alkaline phosphatase and tubular reabsorption of phosphate were tabulated. In many cases, data concerning creatinine clearance and serum creatinine concentrations were available. The results of more sophisticated tests of parathyroid function such as the glucagon infusion test, parathormone bioassay, and phosphate loading tests were available in a few patients, but not in sufficient numbers to be significant.

Surgical specimens were reviewed. The number, size and appearance of excised or biopsied glands were tabulated. This information was then correlated with the pre- and postoperative course of each patient.

Results

Analysis of the screening technic using the SMA 12 Autoanalyzer, previously per-

TABLE 1. *Patients without Symptoms of Hyperparathyroidism. Total Patients—12.*

	Mean	Median	Range
Age	61 yrs.	61 yrs.	45–79 yrs.
Highest serum calcium, normal diet	12.7 mg./100 ml.	12.5 mg./100 ml.	11.6–14.2 mg./100 ml.
Lowest serum phosphorus, normal diet	2.3 mg./100 ml.	2.3 mg./100 ml.	1.8–2.8 mg./100 ml.
Tubular resorption of phosphorus, normal diet, %	72%	76%	60%–81%

formed at Barnes Hospital by Daughaday and associates, shows that approximately 40 patients per 1,000 studied have serum calcium concentrations of over 10.5 mg./100 ml., while four per 1,000 have serum calcium concentrations of 11.5 mg./100 ml. or higher.[6] The diagnosis of hyperparathyroidism in these patients is generally based on persistently elevated serum calcium and depressed phosphorus concentrations, demonstration of depressed tubular reabsorption of phosphorus, and the elimination of other causes for hypercalcemia. Twenty-four of the 47 patients were admitted because of symptomatic primary hyperparathyroidism. Eleven had incidentally discovered symptomatic hyperparathyroidism and twelve, or approximately one fourth of the group were asymptomatic. There were nine women and three men who were asymptomatic, both as to initial admission diagnostic impression, and upon retrospective analysis of clinical signs and symptoms (Table 1). None had symptoms suggestive of hyperparathyroidism or hypercalcemia related to renal, osseous, central nervous, or gastrointestinal systems. Any symptoms or findings, including osteoporosis in elderly patients, led to exclusion from this group. The average age was 61 years. The serum calcium concentrations averaged 12.7 mg./100 ml. (range 11.8–14.2 mg./100 ml.) and serum phosphorus concentrations averaged 2.3 mg./100 ml. The average tubular reabsorption of phosphorus on normal diet was 72% (normal 80–90%). Seven of the twelve asymptomatic patients had three parathyroid glands excised at operation, one had three and one half parathyroids removed, and three had two glands removed. The twelfth had only one parathyroid resected. Six patients had histologic diagnoses of chief cell hyperplasia, five had parathyroid adenomas, and in the remaining patient tissue was insufficient for diagnosis.

Postoperatively hypercalcemia persisted in three patients. Parathyroid tissue excised in these three showed chief cell hyperplasia. None of these three patients has

TABLE 2. *Patients Admitted with a Complaint Unrelated to Hyperparathyroidism Who Had Symptoms of Hypercalcemia Only in Retrospect and Found Symptomatic Only in Retrospect. Total Patients—11.*

	Mean	Median	Range
Age	58 yrs.	58 yrs.	31–74 yrs.
Highest serum calcium, normal diet	12.8 mg./100 ml.	12.5 mg./100 ml.	11.4–15.6 mg./100 ml.
Lowest serum phosphorus, normal diet	2.5 mg./100 ml.	2.4 mg./100 ml.	1.7–3.9 mg./100 ml.
Tubular resorption of phosphorus, normal diet, %	68%	70%	45%–92%
Duration of symptoms, in years	3.9	5.0	0.3–10.0

TABLE 3. *Patients Admitted because of Symptoms of Hyperparathyroidism. Total Patients—24.*

	Mean	Median	Range
Age	47 yrs.	53 yrs.	16–70 yrs.
Highest serum calcium, normal diet	12.1 mg./100 ml.	12.2 mg./100 ml.	10.0–14.6 mg./100 ml.
Lowest serum phosphorus, normal diet	2.6 mg./100 ml.	2.5 mg./100 ml.	1.8–4.0 mg./100 ml.
Tubular resorption of phosphorus, %	69%	74%	24%–88%
Duration of symptoms, in years	6.5	6.0	0.3–20.0

been reoperated upon and none has developed symptoms of hyperparathyroidism.

Eleven patients were mildly symptomatic and the disease was incidentally detected (Table 2). This group comprised one man and ten women. The average age was 58 years. All were admitted for conditions unrelated to hyperparathyroidism such as elective herniorrhaphy, acute cholecystitis or thrombophlebitis. In no patient was the diagnosis of hyperparathyroidism considered before admission and before screening of serum calcium. Symptoms of hyperparathyroidism were elicited retrospectively, however, from each patient. Five had mild central nervous system symptoms (minimal lassitude, mental depression, headache), four had nephrolithiasis from 2 to 5 years prior to admission, one had a peptic ulcer 20 years previously and one had vague abdominal pain together with lassitude and weakness.

The average serum calcium concentration in this group was 12.8 mg./100 ml. and the mean serum phosphorus value was 2.5 mg./100 ml. The average TRP on regular diet was 68%. Four patients from this group had three glands removed, four had two glands excised, and three had one parathyroid excised. Chief cell hyperplasia was found in three patients, and adenomas in seven, and in one tissue was insufficient for diagnosis. Three patients in this group, at last follow-up, had recrudescent or persistent disease. One had three parathyroid glands excised; the diagnosis was chief cell hyperplasia. Two months later the serum calcium concentration was 13.3 mg./100 ml. A second patient with persistent disease had three glands removed, one was believed to contain a parathyroid adenoma and two were microscopically normal parathyroids. Electron microscopy of the two "normal" glands showed chief cell hyperplasia. The cells from these glands contained large quantities of highly structured rough surfaced endoplasmic reticulum and extensive Golgi vesicles containing secre-

TABLE 4. *Pathologic Diagnoses Related to Clinical Presentation*

Diagnosis	Clinical Status			
	Asymptomatic	Mildly Symptomatic	Symptomatic	Total
Parathyroid adenoma	5	7	7	19
Chief cell hyperplasia	6	3	14	23
No diagnosis*	1	1	3	5
	12	11	24	47

* Only small quantities of tissue available for study, and histologic features distorted following surgical manipulation.

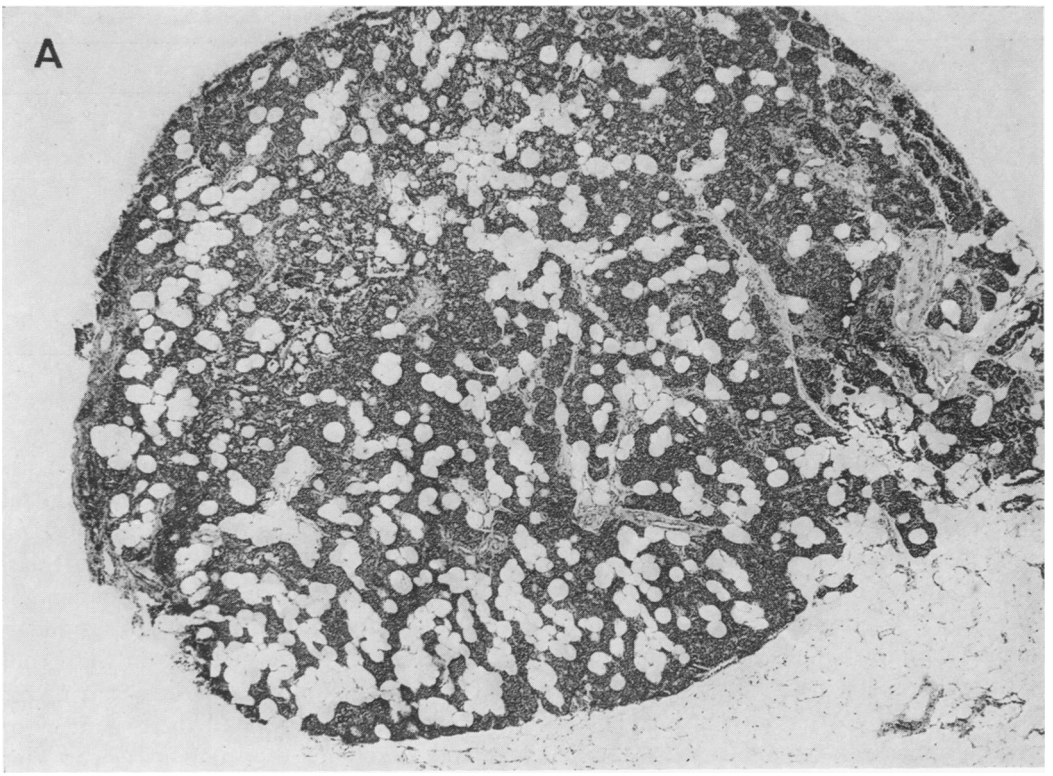

FIG. 1A. A normal parathyroid gland incidentally removed from an adult during thyroid surgery. The gland weighed 35 mg. and is composed of evenly distributed fat cells and small chief cells. ×138.

tory material. These morphologic findings suggest functional activity and are identical to those seen in patients with typical chief cell hyperplasia. Serum calcium in this patient was 11.7 mg./100 ml. five weeks postoperatively. This patient was the only fatality in this series and died of subarachnoid hemorrhage two months subsequent to parathyroidectomy. The third patient also had three glands showing chief cell hyperplasia excised and had an elevated calcium two months postoperatively. None of these patients has been reoperated upon.

Twenty-four patients were admitted and evaluated because of symptoms directly related to hyperparathyroidism (Table 3). There were 14 women and 10 men in this category with an average age of 47 years. Seventeen had nephrolithiasis, nephrocalcinosis or both. Two patients had bone pain with radiographic verification of osseous changes related to hyperparathyroidism. Five patients in this group had multisystem involvement of the urinary, skeletal, central nervous and gastrointestinal systems.

The average calcium concentration of this group was 12.1 mg./100 ml. Three patients never had elevated serum calcium values, but during evaluation because of nephrolithiasis, had hypercalcuria and elevated parathormone levels. The average serum phosphorus concentration in this group was 2.6 mg./100 ml., while the average alkaline phosphatase value was 15.7 King-Armstrong units, and the average tubular reabsorption of phosphorus on normal diet was 69%.

At operation, three patients in this group had three and one half glands removed. Nine had three glands excised or biopsied

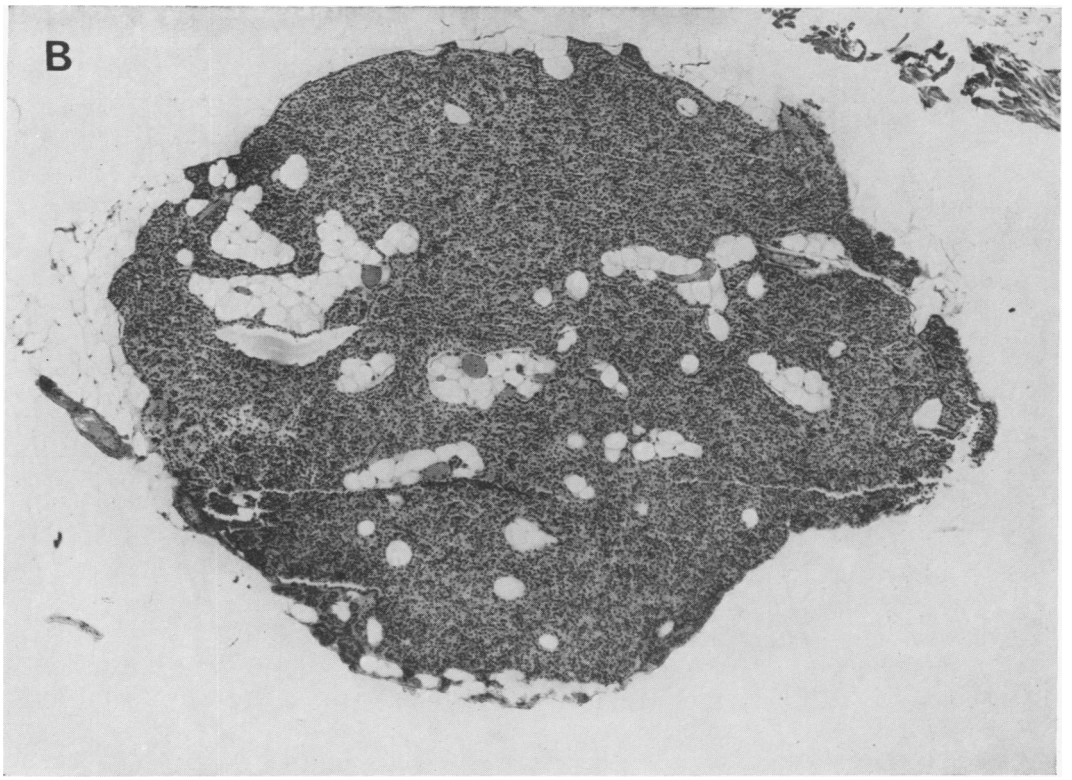

FIG. 1B. This enlarged 80 mg. gland was removed from a 40-year-old adult with laboratory findings of hyperparathyroidism. Fat content is reduced, and a diagnosis of equivocal hyperplasia was made. ×200.

and ten had two glands resected. Two patients had only one gland removed. Thirteen of these patients had histologic diagnoses of chief cell hyperplasia, seven had adenomas, and in three, no definite diagnosis could be made. Two patients had persistent or recrudescent disease. One, who was operated upon three times, developed recrudescence six weeks subsequent to the last operation. The glands had been altered by surgical manipulation, and no histologic diagnosis could be made other than hemosiderosis secondary to trauma. The remaining patient, who subsequently had a mediastinal exploration for persistent symptomatic hypercalcemia had no identifiable parathyroid disease.

Table 4 lists the histologic diagnosis in each of the three groups of patients.

Some histologic problems in identifying minimally hyperplastic parathyroid glands are illustrated in Figures 1 (A–D).

Discussion

No differences in biochemical analyses or microscopic evaluations of resected glands could be determined among the three groups of patients. There was a tendency for asymptomatic patients to be older than those with symptoms, and for those who were asymptomatic with chief cell hyperplasia to have smaller glands than symptomatic patients with this form of disease. However, the ranges in age and gland size were considerable, and overlapping values were common.

The incidence of hypercalcemia from all causes in hospitalized patients is in the range of 40:1,000. It has been suggested that the incidence of hyperparathyroidism is approximately 1:1,000 in patients under-

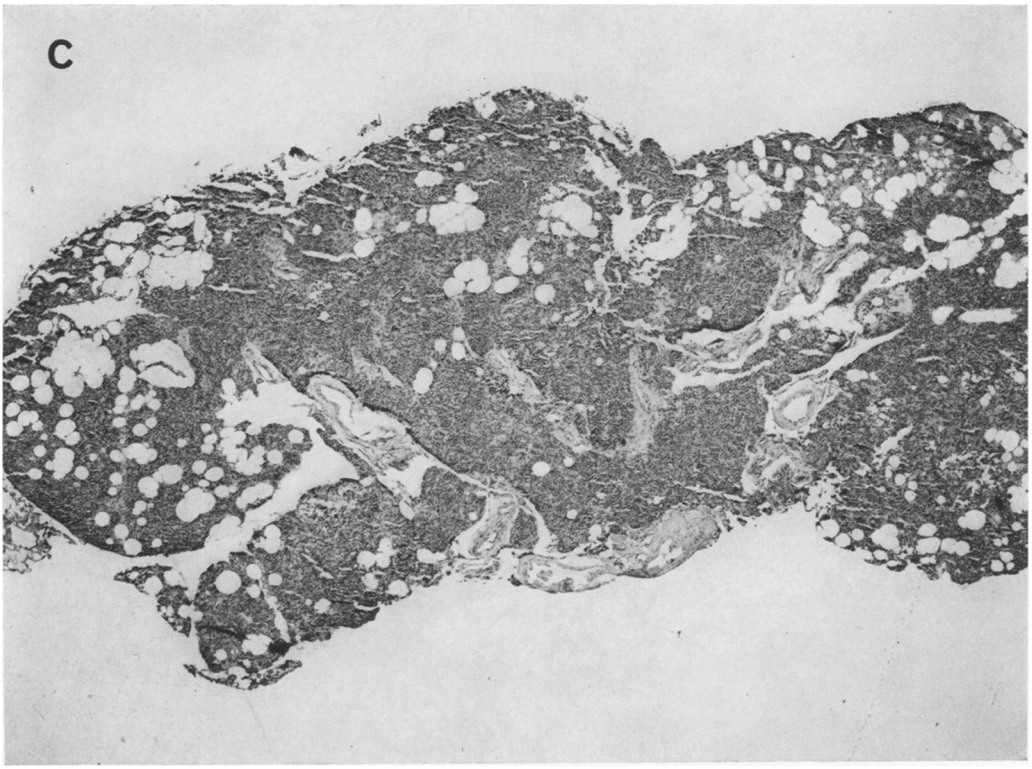

FIG. 1C. This 100 mg. parathyroid was removed from another adult with apparent hyperparathyroidism. The central area has reduced fat, but we are not certain that this gland is hyperplastic. ×60.

going routine admission serum screening tests.[2] Our figure is 1:2,000 or approximately one half of this suggested incidence. It is, however, three and one half times higher than the reported incidence of primary hyperparathyroidism in patients who have symptoms.[14] The fact that one fourth of these instances of presumed primary hyperparathyroidism were asymptomatic at the time of operation prompted this study. This incidence of asymptomatic hyperparathyroidism is in striking contrast with reported series in which routine analyses for serum calcium levels were not performed.[3, 13]

The frequency of symptomatic patients in this study is increased three- to fourfold over the preceding decade in this hospital. This is in large part due to earlier diagnosis, as shown by the decreasing number of patients with symptomatic osseous disease.

Several questions have been raised by the frequency of asymptomatic patients in this series. First, when in the natural course of the disease does hypercalcemia first produce symptoms? It is as yet impossible to state how long hyperparathyroidism must be present to lead to renal lithiasis, nephrocalcinosis, pancreatitis, or bone changes. Dent[7] stated that patients without osteitis fibrosa cystica are capable of continuing for 30 to 40 years with hypercalcemia secondary to hyperparathyroidism before of renal function is disturbed in spite of nephrolithiasis. Patients with bone disease have a much more rapid course, with early renal failure and nephroclacinosis. A second question raised by Dent's study and by our experience concerns the feasibility of a prospective study of patients who have

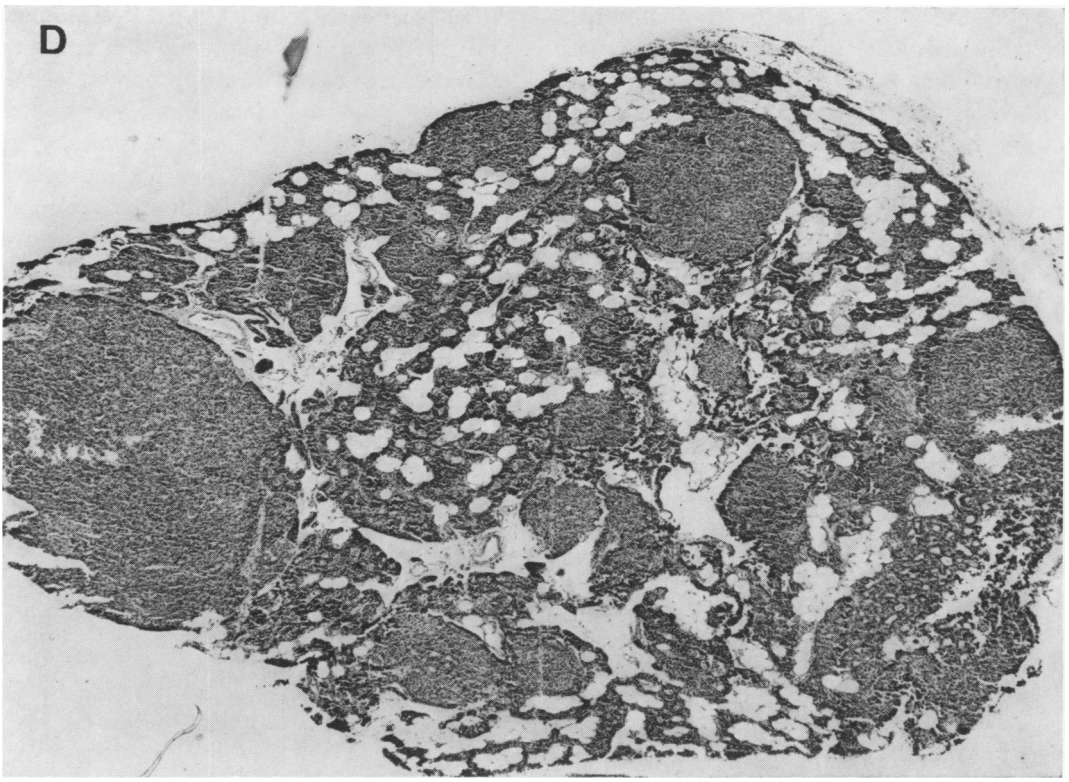

FIG. 1D. This 85 mg. parathyroid was removed from a patient with well documented chief cell hyperplasia. Note the nodular foci of chief cell proliferation and compare with (B) and (C). ×120.

asymptomatic hypercalcemia due to primary hyperparathyroidism and who refuse operation. From such an investigation it might be possible to determine when, if ever, hypercalcemic patients become symptomatic.

At present, we believe that all patients with hypercalcemia due to hyperparathyroidism should be operated upon in view of limited knowledge of the natural history of persistent hypercalcemia. This policy is based on the known tendency of nephrocalcinosis to result in subtle renal damage prior to the onset of other symptoms. In 1962, Riddich and Reiss,[12] advocated operation in asymptomatic patients to avoid these permanent changes. Others have subsequently supported this position.[10, 11]

Due to the increasing use of laboratory screening procedures, it is probable that the number of operations for hyperparathyroidism will increase. Screening calcium determinations lead to earlier detection of asymptomatic patients with hyperparathyroidism. As a consequence, incipient and subtle histologic changes in parathyroid glands are difficult to interpret.

Review of tissue sections from asymptomatic and "early" symptomatic patients suggests that there is a stage of the disease in which there is significant hypercalcemia but little pathologic change. Ultrastructural studies have shown hyperplasia (extensive ergastoplasm and Golgi, etc.) and hyperfunctional activity, despite normal light microscopic appearance.

Copp and others suggested that a deficiency of calcitonin may lead to relative hyperparathyroidism.[4] The antagonistic relation of calcitonin and parathormone has been verified.[9] Some form of imbalance in

this or other aspects of calcium homeostasis may be involved in certain patients with hypercalcemia and hyperparathyroidism.

Several points, made in other reports, should be emphasized.[3, 13] First, a thorough operative exploration of the neck must be carried out and effort should be made to expose four glands. The distinction between adenoma and chief cell hyperplasia is difficult if not impossible by frozen section. Because of the frequency of recurrence with chief cell hyperplasia, and because of the difficulty in diagnosis at operation, we are approaching the position taken by Block *et al.*[1] that extirpation of three and part of the fourth gland may be required in all patients. When four glands cannot be found subtotal thyroidectomy and removal of cervical fat pads in hope of removing aberrant parathyroid tissue is recommended. Should this fail to produce biochemical changes, mediastinal operative exploration should be undertaken at a subsequent procedure, in symptomatic patients.

The delay before biochemical recurrence in some patients is similar to that previously reported, and emphasizes the need for long follow-up.[1, 5] The fall in serum calcium levels following apparently unsuccessful operations, with recrudescence of hypercalcemia in a few weeks, has been reported by Dent,[8] and reemphasizes the necessity for prolonged observation of these patients.

Summary

Forty-seven patients were operated upon for primary hyperparathyroidism in the Barnes Hospital, St. Louis, Missouri in a period of 30 months. Only 39 patients with this disease were similarly treated at this hospital in the past decade. This increase is attributable to routine screening of serum calcium levels in all patients admitted during the 30-month period. Of 47 with hyperparathyroidism twelve were asymptomatic (with reference to that disease), a higher incidence than previously reported. Another 11 were found to be symptomatic only in retrospect following the discovery of hypercalcemia. Thus, approximately half of these patients would not have had an early and correct diagnosis of primary hyperparathyroidism had not routine admission blood calcium determinations been obtained. Clinical and pathologic features of symptomatic and asymptomatic patients were reviewed and indicate few differences in the groups as to preoperative signs and symptoms, preoperative calcium levels, and the nature of parathyroid tissue removed. Several questions related to the natural history of hyperparathyroidism are raised by experiences with these patients.

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