INTERMITTENT HYPERPARATHYROIDISM

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Functioning parathyroid tumors are usually considered to be continuously hypersecreting. In the absence of a specific assay for parathyroid hormone in blood, the finding of persistent hypercalcemia remains the most reliable biochemical guide reflecting excess circulating hormone in patients with primary hyperparathyroidism.[1-4] Furthermore, careful study of these patients has usually shown remarkable stability of the hypercalcemia with serum calcium concentration rarely varying more than 2.0 mg.%.[2] It is generally agreed that *normal* values for serum calcium properly exclude the diagnosis of parathyroid hyperfunction with rare exceptions.[1-7]

Within the past few years, we have observed four patients with surgically proved hyperparathyroidism who were studied for periods of one to fifteen months prior to removal of a parathyroid adenoma. In each instance, following a period of documented hypercalcemia, normal values for serum calcium were observed on two or more occasions before removal of a parathyroid adenoma. We interpret these changes as indicative of intermittent hypersecretion of hormone by the tumors.

Materials and Methods

Each patient was studied in the hospital on diets low in gelatin and calcium content. Serum calcium was determined by the method of Campbell[8] using an EDTA-murexide titration with electrophotometric determination of the end point. In one patient, the oxalate precipitation and permanganate titration of Clark-Collip[9] was used, but since 1960 we have used the EDTA-murexide method exclusively. Serum phosphorus and creatinine and urinary calcium were performed by standard methods.[9-11] Urinary hydroxyproline was estimated by the method of Prockop and Udenfriend.[12]

All serum calcium determinations were performed in duplicate in the research laboratory. Normal serum calcium values using the EDTA-

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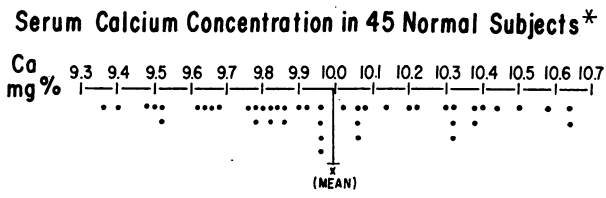

FIG. 1. Includes 39 male and 6 female subjects between 22 and 40 years of age

murexide method, ranged between 9.36–10.64 mg.% (Fig. 1).* In the single patient in whom the Clark-Collip method was used, a value of 11.0 mg.% was considered as the upper level of normal.[1, 9] However, by using a modification of this latter technique Keating considered serum calcium values greater than 10.6 mg.% as abnormal.[2] Serum albumin and globulin were obtained at frequent intervals in all patients and were always normal, so that disturbances in serum protein concentration need not be considered in the interpretation of these results.

A few comments about hydroxyproline seem in order. This urinary constituent is probably derived in major part from bone collagen and has been found elevated in hyperparathyroidism by a number of investigators.[15-17] In addition, administration of parathyroid hormone to normal subjects causes an immediate rise in urinary hydroxyproline with prompt return to normal values following cessation of hormone administration.[16, 18] We have found urinary hydroxyproline elevated in 14 of 17 patients with hyperparathyroidism and consider it a useful aid in the diagnosis of this disorder. We have also noted significantly greater elevations of urinary hydroxyproline in those patients with radiographic evidence of bone disease. In 27 *normal adults* receiving low gelatin diets, urinary hydroxyproline ranged between 20–55 mg. with a mean value of 37 mg. per day.

* This group has been expanded to 60 normal subjects and the same range has been maintained with a mean value of 9.974 ± 0.344 mg. %. Furthermore, repetitive determinations of serum calcium over a period of weeks in several individuals in this group revealed remarkably little variation and all results remained within the normal range listed in Figure 1.

We believe, that previous studies, such as those of Danowski[13] reporting wider fluctuations in serum calcium concentration in normal subjects bear reinvestigation under standardized conditions. This is further emphasized by the work of Dent[3] and Radcliff and associates[14] who recently observed that muscle exercise and/or prolonged venous stasis can sometimes produce spurious elevations in serum calcium levels in healthy volunteers. These observations also serve to remind the clinician of the great care and caution required in assessing the significance of "borderline" elevations of serum calcium concentration.

Results

Case 1: E.S., a 68-year-old female, who was seen in 1959 with a history of polyuria, passage of gravel in the urine, anorexia, constipation, arthralgia and fatigue of 5–10 years duration. In 1953–54 following removal of a benign thyroid adenoma, two serum calcium values of 12 mg.% had been obtained, but apparently were disregarded as laboratory error because hypocalcemia was expected.

In 1959 the patient was hospitalized because of the chronicity of her complaints, and serum calcium was found to be 11–12 mg.% with serum phosphorus 2.5–3.2 mg.%. The physical examination was unremarkable except for evidence of mild weight loss. Renal function was normal and no calculi were seen on I.V. pyelogram. Mild generalized osteoporosis was found by x-ray examination. Intravenous calcium infusion studies performed according to the technique of Howard, Hopkins and Connor[19] revealed no change in serum and urinary phosphorus on the infusion day. Hyperparathyroidism seemed likely with such a long duration of hypercalcemia, but because of the patient's age, the mild nature of the disease and a story suggesting poor cardiac reserve, surgery was postponed. During the next 15 months, the patient was followed in the Out-Patient Clinic and then re-admitted to the hospital in November 1960. The results of this patient's studies are outlined in Figure 2.

On several occasions in August 1959 serum calcium values were recorded between 10.5 and 10.8 mg.% by the Clark-Collip method. From September 1959 to July 1960 consistent hypercalcemia was present. In November 1960 the method for estimation of serum calcium was changed to the EDTA-murexide technique with upper normal value of 10.6 mg.% (Fig. 1). Two days before surgery, serum calcium of 10.4 mg.% was obtained. Note also, in this and subsequent patients, that the normal or near normal serum calcium values generally occurred together over a period of several days.

Serum phosphorus and urinary calcium frequently were observed in the normal range. Two urinary hydroxyproline determinations were distinctly elevated. On November 23, 1960 a parathyroid adenoma, weighing 4.0 gm. was removed. Histologic examination of the tumor revealed a very cellular chief cell adenoma with no evidence of necrosis, scarring, or cyst formation. Transient hypocalcemia occurred after operation, but there was a complete disappearance of symptoms over the next several months. During a four-year period of follow up, the patient has been asymptomatic and serum calcium and phosphorus remain normal.

Case 2: M.H., a 58-year-old woman was admitted July, 1963 because of flank pain and bilateral staghorn calculi were found. Urinary

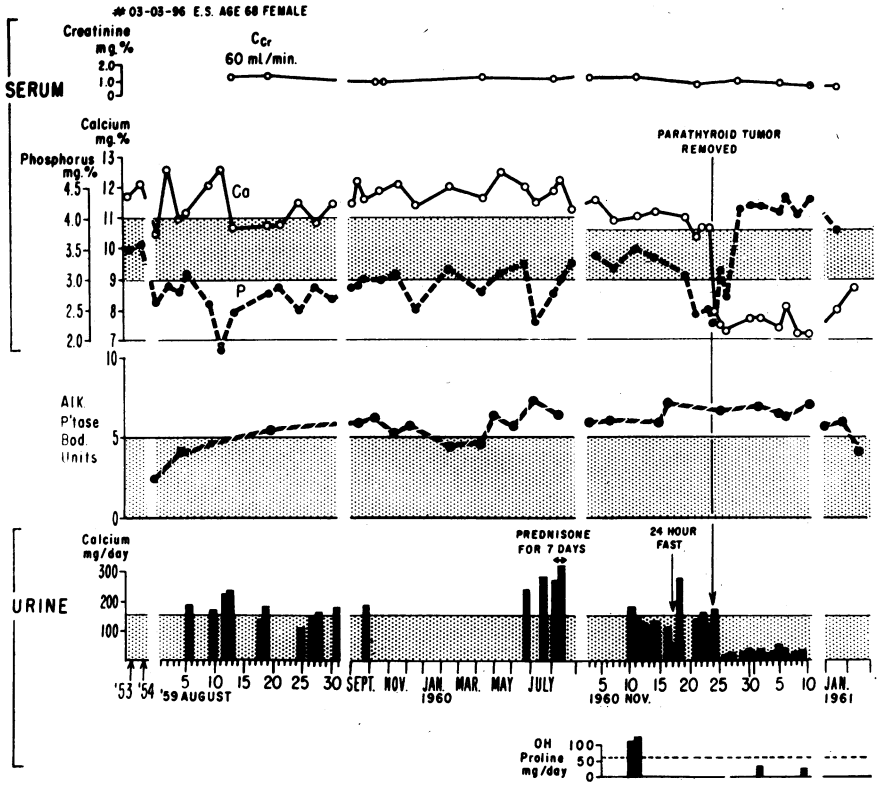

FIG. 2. *Case 1.* Results obtained between 1953–61, with patient hospitalized during August '59 and November '60. The shaded areas represent the normal range for each measurement listed. Note the change in normal range for serum calcium in November, 1960 when a new method of estimation was used (see text).

symptoms dated back only 6 months and except for fatigue and nocturia, the patient was asymptomatic. The physical examination revealed no abnormalities. Proteus organisms were cultured from the urine. Mild azotemia was present and creatinine clearance was reduced to 47 ml./min. No evidence of bone disease was found by x-ray examination and alkaline phosphatase was always normal.

Initially, mild hypercalcemia was observed with serum calcium values of 11.1–11.5 mg.% (Fig. 3). Surprisingly, a few days after nephrolithotomy, serum calcium was 9.9 and 9.7 mg.% and serum phosphorus had returned to normal. Transient azotemia occurred, but this probably had no bearing on the return of serum calcium to normal since the phosphorus concentration never rose above 3.9 mg.%. This was soon followed by a gradual rise in serum calcium to distinctly elevated levels,

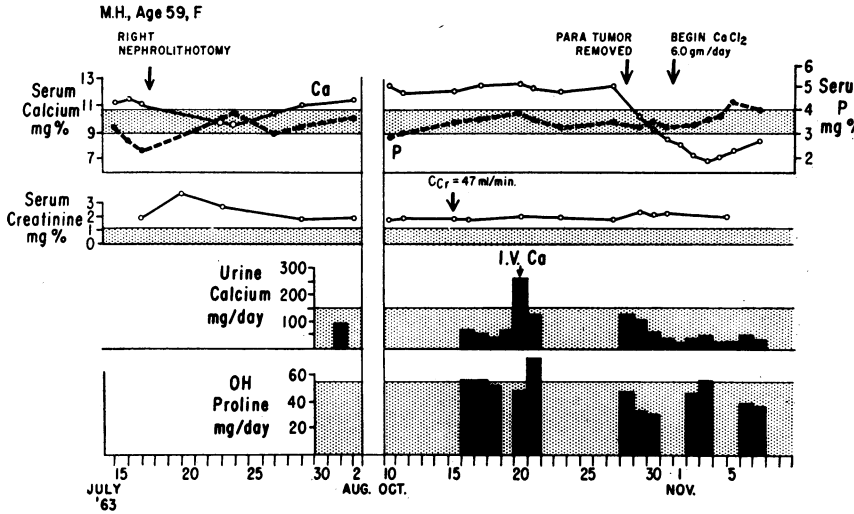

FIG. 3. *Case 2.* All studies were carried out during two separate periods of hospitalization in 1963. Intravenous calcium infusion was performed on October 20 (see text). Oral calcium supplements were begun on the fourth day after the parathyroid tumor was removed.

10 to 15 days after operation. This response suggested a temporary reduction in parathyroid hormone secretion. The patient's post-operative course was uncomplicated and intravenous fluids were not given after the first post-operative day, so that changes in hydration cannot explain these blood chemical alterations.

The patient returned in October '63 when persistent hypercalcemia was demonstrated over a 2-week period (Fig. 3). Urinary calcium was usually reduced, whereas hydroxyproline was either normal or slightly elevated. Intravenous calcium infusion test yielded a response typical of hyperparathyroidism.[19] On October 29 an 800 mg. parathyroid adenoma was removed. Histologic examination of the tumor revealed one tiny area of scarring with hemosiderin deposits, in the periphery of the tumor which might be interpreted as previous evidence of necrosis, though its very small size made this of doubtful significance.

Hypocalcemia occurred postoperatively and the patient continues to require calcium chloride supplements two years after operation to maintain serum calcium at 8 to 9 mg.%. Mild azotemia also persists, but there has been no recurrence of renal stones.

Case 3: T.F., a 41-year-old surgeon, was entirely asymptomatic. Hypercalcemia was found in November 1964 when serum calcium was measured because the patient's father and sister had surgically proved

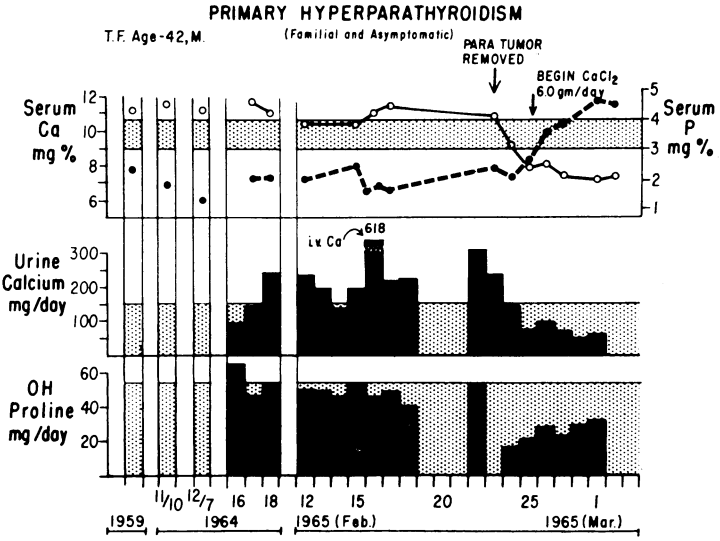

FIG. 4. *Case 3.* Note the change in time scale on the abscissa. Patient was studied on the Research Ward in December, 1964 and February, 1965. Serum calcium represented by open (○) circles and serum phosphorus by closed (●) circles. "I.V. Ca" indicates intravenous calcium infusion study (see text). Oral calcium chloride supplements were begun on the third post operative day.

hyperparathyroidism 33 and 25 years previously.† In further review, serum calcium of 11.2 mg.% with phosphorus of 2.1 mg.% had been found in this patient in 1959 at another hospital, so these chemical abnormalities had presumably existed for five years. Physical examination was normal and no evidence of bone disease was evident by x-ray examination, though alkaline phosphatase was slightly elevated at 5 to 6 Bodansky units. Renal function was excellent as measured by creatinine clearance of 100 ml./min. and normal concentrating power after 15 hours of water deprivation.

During three months of observation in late 1964 and early '65 serum calcium was always elevated (Fig. 4). However, after admission to the hospital in February '65, normal serum calcium values were observed. Urinary calcium was modestly elevated though urinary hydroxyproline was variable. Intravenous calcium infusion studies[19] revealed no change in urine phosphorus excretion on the test day, adding further support to the diagnosis of hyperparathyroidism. At operation in February 1965, a parathyroid adenoma weighing 804 mg. was found behind the left lobe

† The clinical details of the relatives' illnesses were reported by Shallow and Fry in 1948.[20]

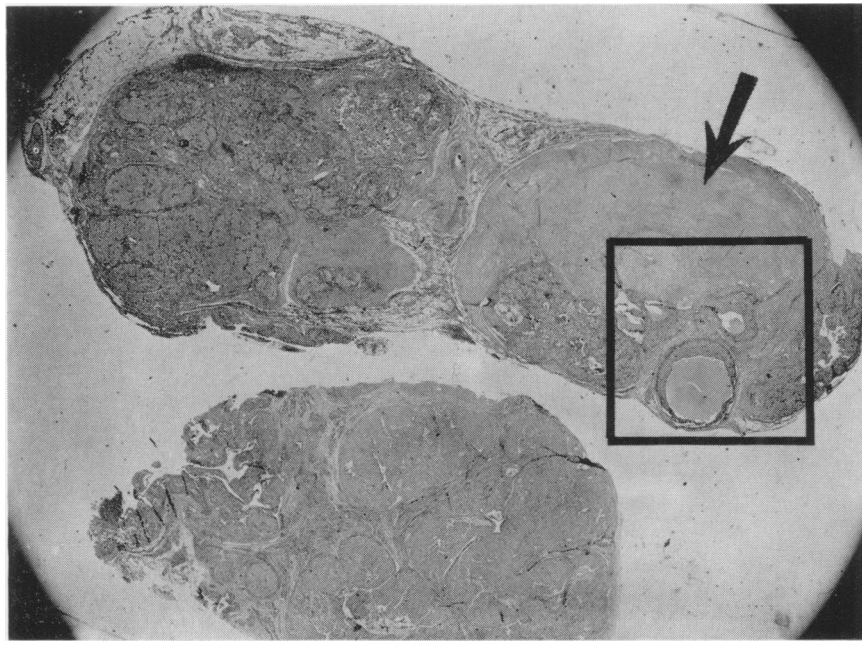

FIG. 5. (× 10)—Low power view of cross section of parathyroid tumor from Case #3 to demonstrate extent of scarring and cyst formation. The arrow points to the large scar. The area within the black square is seen in higher magnification in Figure 6.

of the thyroid. On cut section, burgundy-colored fluid exuded from the tumor and multiple cysts and scars were seen suggesting probably healed areas of previous infarction (Fig. 5 and 6). Because of the family history, all parathyroid glands were biopsied, and in addition to the tumor shown (Fig. 5), two other glands were considered adenomatous by microscopic examination though grossly they were of *normal* size. The fourth gland was normal, grossly and histologically. Post operatively, the patient developed hypocalcemia with tetany and continues to require calcium chloride supplements to maintain serum calcium at 8 to 9 mg.%.

Case 4: T.M. was a 22-year-old mentally retarded boy who had a kidney stone removed in 1962. He had also noted persistent fatigue, polyuria and constipation. Pain in the right thigh developed in 1964 and he was admitted to University Hospital, January 1965. On admission, serum calcium was 16 mg.% and serum phosphorus 2.9 mg.%. Normal blood urea nitrogen and creatinine clearance estimations were found. Alkaline phosphatase was moderately elevated at 8–10 Bodansky units. Bone survey revealed only mild generalized demineralization without specific evidence of sub-periosteal resorption. Physical examination was

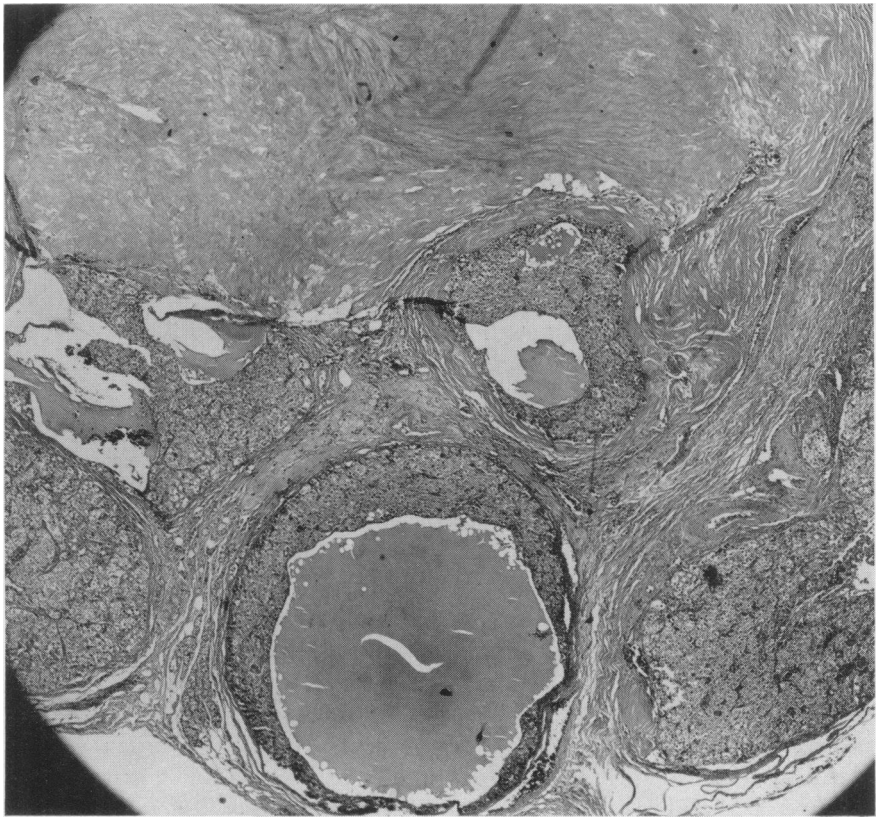

FIG. 6. (× 30)—Higher magnification of tumor from case 3 to show scarring and microscopic cysts lined by chief cells.

negative except for B.P. 180/100 and a palpable 4 x 3 cm. mass adjacent to the left lobe of the thyroid. Barium swallow revealed a deviation of the esophagus to the right in this region.

The patient was studied for three weeks on the Research Ward while on a constant diet containing 455 mg. calcium and 1280 mg. phosphorus daily. For the previous several years the patient had consumed large quantities of milk (averaging 1 gallon daily) and this was stopped on entry to hospital. In Figure 7 note that shortly after admission there was a gradual fall in serum calcium and a rise in serum phosphorus to the normal range.‡ Urinary calcium was unusually low, while hydroxyproline was constantly elevated.

‡ It seemed unlikely that the reduction in calcium intake caused by the withdrawal of milk from the diet was responsible for the return of serum calcium to the

On 2/5/65 the patient's neck was explored and a 6 x 3 cm. brown tumor was found pushing the esophagus to the right as the x-ray film had indicated. On cut section, the tumor consisted of a dark red gelatinous mass and *no* parathyroid tissue could be identified on multiple frozen sections. Later, permanent microscopic sections revealed tiny remnants of viable parathyroid tissue in the capsule with massive recent hemorrhagic necrosis of the remaining tumor (Figs. 8–9).

This patient clearly had a massive spontaneous destruction of the parathyroid tumor which could readily account for the abrupt pre-operative changes in serum calcium and phosphorus concentration. However, complete inactivation of the tumor probably did not occur prior to surgery, since serum calcium never fell below 10.5 mg.% and urinary phosphorus did not show the characteristic marked reduction usually evident immediately following removal of a parathyroid tumor (Fig. 7).

Of additional interest was the transient *rise* in urinary calcium and calcium clearance§ in the immediate post-operative period, in association with a fall in serum calcium and a reduced filtered load of calcium. This unusual finding can be explained by the work of Kleeman and associates[22] who demonstrated that parathyroid hormone excess *reduced* the renal clearance of calcium, whereas hypoparathyroidism was associated with a relative *increase* in the clearance of calcium.

Note also in Figure 7 that the elevated urinary hydroxyproline values decreased only transiently following operation and gradually returned to normal in the ninth post-operative week. We have observed a similar delay in return of urinary hydroxyproline to normal following removal of a parathyroid tumor in other patients with advanced bone disease and believe it may reflect continued bone collagen turnover during a stage of rapid new bone formation.[16] This response emphasizes that urinary hydroxyproline may not be a reliable measure of an *acute* decrease in parathyroid activity, especially if bone disease is present.

Serum alkaline phosphatase was initially elevated at 8 to 10 Bodansky units but fell to normal just *before* parathyroid surgery. Following operation, the serum alkaline phosphatase remained constantly between

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normal range in this patient. Though the dietary change may have been a factor, Albright and Reifenstein[21] have previously shown that marked alterations in calcium intake had no significant effect on the serum calcium concentration in a patient with primary hyperparathyroidism.

§ The "clearance" of calcium was calculated as the ratio of the observed clearance to that of creatinine ([Cca/Ccr] × 100) according to the method of Kleeman and associates.[22] In these studies, the "clearance" represented at best only an approximation, since diffusible calcium was *assumed* to be 70% of the total serum calcium and all clearances were calculated on the basis of 24-hour excretion periods. Creatinine clearance remained unusually constant before and after operation.

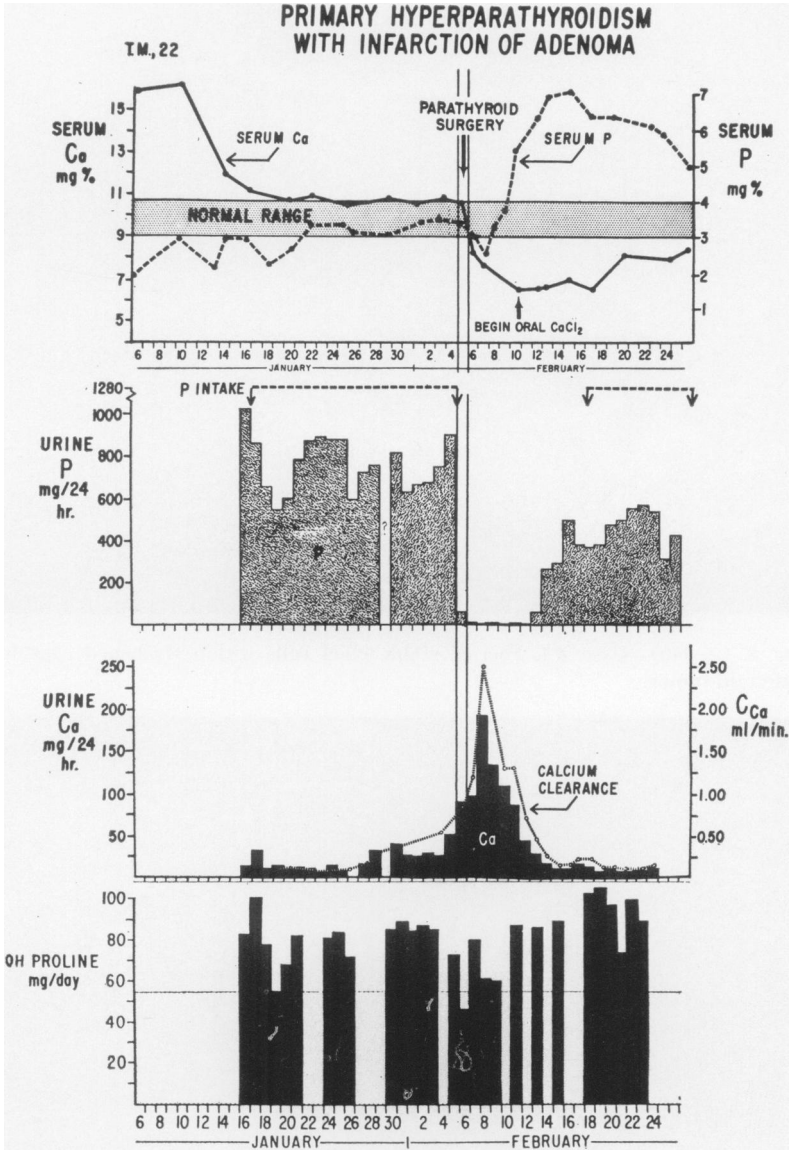

FIG. 7. *Case 4.* Constant diet was begun on January 17 and continued until day of parathyroid surgery. This same diet was resumed eleven days after surgery. Calcium chloride, 6.0 gm./day was begun on the 5th post operative day. Note also that urine phosphorus showed no impressive reduction until immediately after parathyroid surgery (see text).

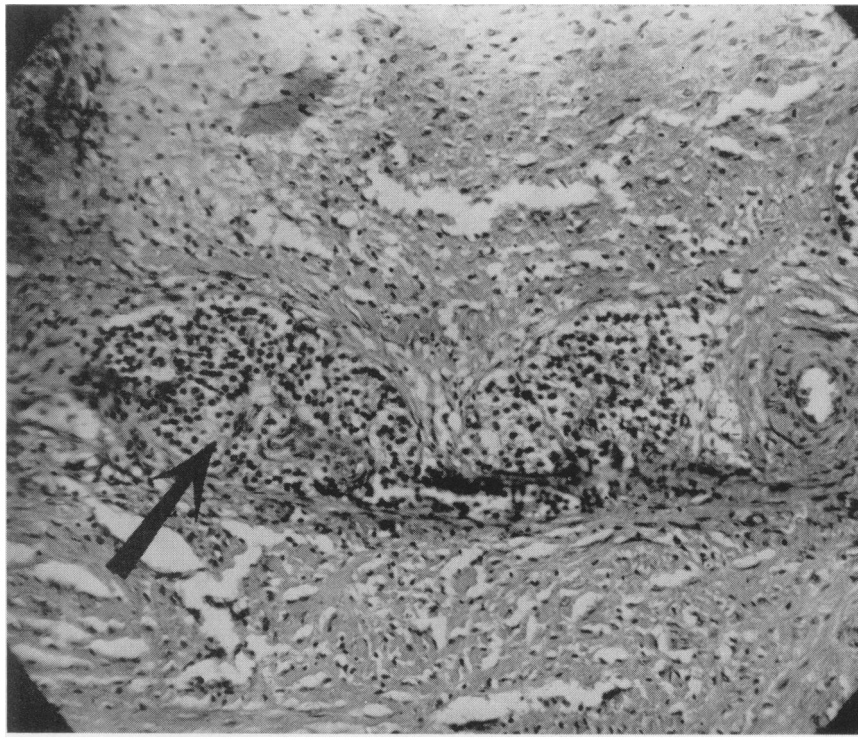

FIG. 8. (× 140)—Case #4. Foci of viable chief cells within thickened capsule of parathyroid tumor.

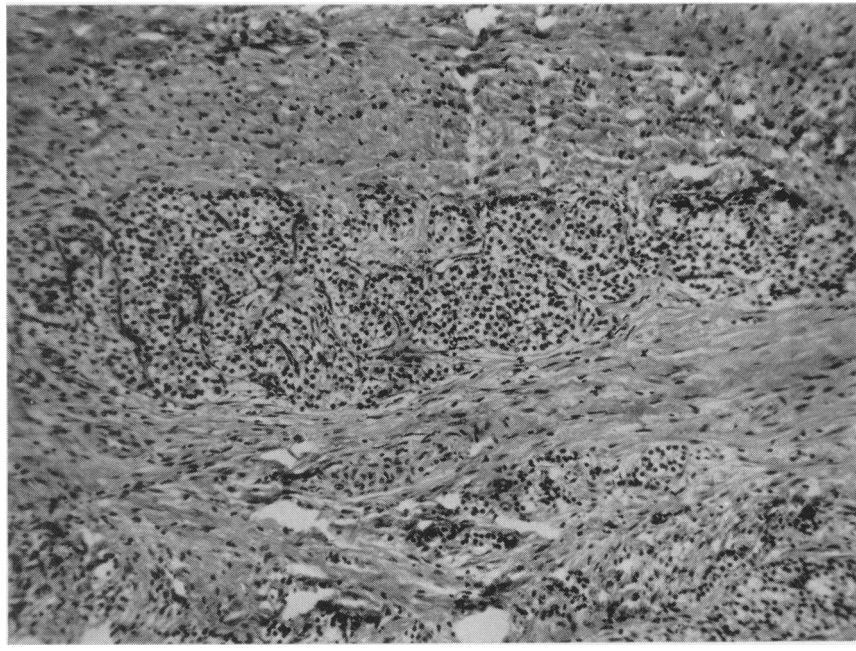

FIG. 9. (× 140)—Clump of chief cells surrounded by connective tissue adjacent to capsule of tumor. (Case #4.)

4.0 and 5.2 Bodansky units. This return of alkaline phosphatase to near normal levels in the face of continued elevation of urinary hydroxyproline excretion has also been seen previously,[16] thus indicating that these two indices of bone metabolism may not always parallel one another.

Discussion

Soon after hyperparathyroidism was first recognized in this country, nearly forty years ago, an occasional instance of spontaneous remission was reported, though convincing bio-chemical proof was usually lacking in these cases.[23, 24] In 1953, the first unequivocal documentation of this phenomenon was reported by a member of this Association, Doctor John E. Howard and co-workers.[25] These authors described a patient whose serum calcium concentration fell gradually from 20 to 8 mg.% over a 10 day period, and at surgery one week later, a necrotic parathyroid adenoma was removed. In a review of 35 previously removed parathyroid tumors, these investigators found evidence of large scars with hemosiderin deposits in three, suggesting previously healed infarctions. Since that time, other reports of infarction of parathyroid adenomata have appeared.[26-28]

During the past 10 years, a few investigators have reported an occasional patient with hyperparathyroidism who was found to have an *isolated normal* value for serum calcium occurring in association with otherwise *elevated* determinations prior to removal of a parathyroid adenoma.[29-31] Such observations suggested to these authors the possibility of intermittent hyperactivity of some parathyroid tumors. However, the *single* isolated normal serum calcium value always cast some doubt on this notion, since the possibility of laboratory error could not be entirely excluded.

In 1959 and 1963 McGeown[7, 32] commented on the spontaneous fluctuations in serum calcium that sometimes occurred in hyperparathyroidism and emphasized that occasional normal values may be seen. In 1961, Keating reviewed the experience of the Mayo Clinic with this problem.[2] In 380 cases of surgically proved hyperparathyroidism, only 13 patients had occasional serum calcium values below 10.3 mg.% and all but one case had average values of multiple serum calcium determinations *above* 10.5 mg.%. Keating was especially impressed with the remarkable stability of hypercalcemia in these patients. He suggested that "random variation" and occasional spurious laboratory determinations, rather than varying output of parathyroid hormone, was the more likely explanation for the occasional normal serum calcium values found in these few patients.

In the four patients presented in this report, the intermittent hypercalcemia is not likely due to faulty technique in the laboratory, for reasons previously outlined. Rather, we interpret the spontaneous alterations in serum calcium concentration as evidence supporting the concept of intermittent hypersecretion of hormone by these tumors. In two patients, this thesis is further strengthened by anatomical evidence seen in the excised tumors. In Case #4 a massive recent necrosis was found and in Case #3, impressive evidence of recent and previous destruction within the tumor was demonstrated. Cystic change and scarring in parathyroid tumors is not a rare finding, as previously reported by other investigators.[33-35]

It is well known that other hormone-producing tumors, such as pheochromocytoma and insulin-secreting neoplasms of the pancreas, characteristically may be associated with periodic hypersecretion of hormone, and, on the basis of the present results we believe some parathyroid tumors behave similarly. In our own small series of 32 patients with hyperparathyroidism, this phenomenon has been demonstrated in four instances—an incidence of 12.5%.

It is apparent that there were no unique clinical features to distinguish these patients from others with primary hyperparathyroidism, except for the intermittent hypercalcemia. In general, the disease was clinically mild, though three of the patients had a history of renal calculi and varying degrees of muscle weakness and fatigue. Radiographic skeletal surveys were normal except for a modest degree of rarefaction in Case 1 and 4. Slight elevation of alkaline phosphatase was noted in three patients (Cases 1, 3, 4). Urinary hydroxyproline was elevated at some time before operation in all patients, though in two, (Cases 2 and 3) normal values were also seen. Urinary calcium excretion was highly variable. Intravenous calcium infusion studies measuring the serum and urine phosphorus response was abnormal in each patient and was of distinct help in the diagnosis.

Convincing proof that the intermittent hypercalcemia, described in these patients reflects varying hormone output by the tumors, must await reliable and reproducible measurements of parathyroid hormone in plasma. In the meantime, it is apparent that in suspected patients, a few normal serum calcium values do not necessarily exclude the diagnosis of hyperparathyroidism, and the physician must continue to rely on his clinical judgment and repeated serum calcium determinations to recognize this disorder.

Summary

1. Four patients with primary hyperparathyroidism have demon-

strated intermittent hypercalcemia prior to surgical removal of the hyperfunctioning tissue.

2. These changes in serum calcium probably reflect intermittent hypersecretion of hormone by the tumors.

3. In two of the patients, anatomical evidence of destruction of a large segment of the tumor was found, whereas in the remaining two cases no significant evidence of previous infarction was seen.

4. Intermittent hyperparathyroidism is not a rare phenomenon and can best be detected by repeated serum calcium estimations in patients suspected of harboring the disorder.

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DISCUSSION

DR. FRANCIS C. WOOD (Philadelphia): Is it your impression that these tumors ought to be removed in these patients?

DR. CONNOR: Yes Dr. Wood. Three of these patients (Case #1, 2 and 4) had significant disability including recurrent renal calculi, polyuria, mild muscle weakness and fatigue. These features disappeared following correction of parathyroid hyperfunction by surgery.

However, Case #3 raises different questions. How should one manage the patient with asymptomatic hyperparathyroidism? Should such a patient be subjected to surgical exploration if he is living so well with his disease and there is no evidence of renal or skeletal injury? I must say we debated at some length as to the wisdom of surgery in this patient and actually favored close medical supervision with periodic blood chemistries and assessment of renal function once a year. However, the patient (a physician) urged operation on the basis of his family history and the likelihood that he would get into trouble some time in the future when he might not be the best surgical risk.

Another disturbing feature about these patients was the development of apparent permanent hypoparathyroidism in two of them (Cases #2 and 3). This is very unusual in our experience following surgery for hyperparathyroidism and was probably related to the extensive exploration that was required, e.g., necessity for biopsy of all four parathyroid glands in case #3 in view of the striking family history of multiple adenomas and recurrent hyperparathyroidism.[20]

I should add that in each of these latter patients, hypocalcemia is well controlled with twice daily doses of oral calcium chloride and vitamin D therapy has not been required. Both of these patients (one now age 60) are back at full-time productive occupations and remain asymptomatic.