Changing Diagnostic Criteria for Hyperparathyroidism *

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THIRTY-TWO years ago, when Mandl first removed a parathyroid adenoma from a patient with generalized osteitis fibrosa, bone disease was considered to be the chief manifestation of hyperparathyroidism. Parathyroid over-function was soon found to be associated with hypercalcemia, hypophosphatemia, and hypercalcuria. With the passing of time, bone lesions became less common and nephrolithiasis accounted for the majority of the diagnosed cases. In addition, some patients were found to have hyperparathyroidism without nephrolithiasis or bone disease, and most recently, with only minimal chemical abnormalities.

Although elevated serum calcium is still the most important single laboratory finding in this disease, the degree of elevation may be only slight. This consideration, together with the demonstration of normal serum phosphate levels in surgically proved cases, has stimulated us to evaluate other diagnostic procedures which might be of help.

Early diagnosis and surgical treatment are essential if we are to prevent the irreversible hypertension and uremia that have, in previously reported cases, resulted in the patient's death despite removal of the causative tumor.

We, therefore, studied the measurement of tubular reabsorption of phosphate, the effect of a standardized dietary phosphate deprivation, and the calcium tolerance test. Chemical investigations have been carried out in patients with nephrolithiasis, nephrocalcinosis, bone lesions, the clinical syndrome of acute hypercalcemia, peptic ulcer, and occasionally in patients with no symptoms.

During the last 23 years we have had 33 cases of surgically proved hyperparathyroidism, of which 23 were seen during the last two years (Fig. 1). This increased recognition of the disease followed the establishment of a laboratory for the accurate chemical screening of patients with nephrolithiasis, bone disease, or other clinical syndromes suggestive of hyperparathyroidism. Of the patients studied during the first 21 years of this 23-year period, all but one had skeletal disease. Of the 23 patients seen during the past two years, only two (9 per cent) had bone disease as demonstrated by roentgenogram, hyperphosphatasemia, and bone biopsy. Eighteen of the 23 patients had nephrolithiasis; one had nephrocalcino-

* Presented before the American Surgical Association, Chicago, May 8–10, 1957.

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Grateful acknowledgment is made to the many physicians who have kindly permitted us to study their patients with nephrolithiasis, thus enabling us to accumulate the data reported here. Financial support for these studies was obtained from Ayerst Laboratories, Inc., New York, N. Y.; The Elise and Walter Haas Award; G. D. Searle and Co., Chicago, Ill.; and an institutional grant (The McKee Fund) administered by the Committee on Research, University of California School of Medicine.

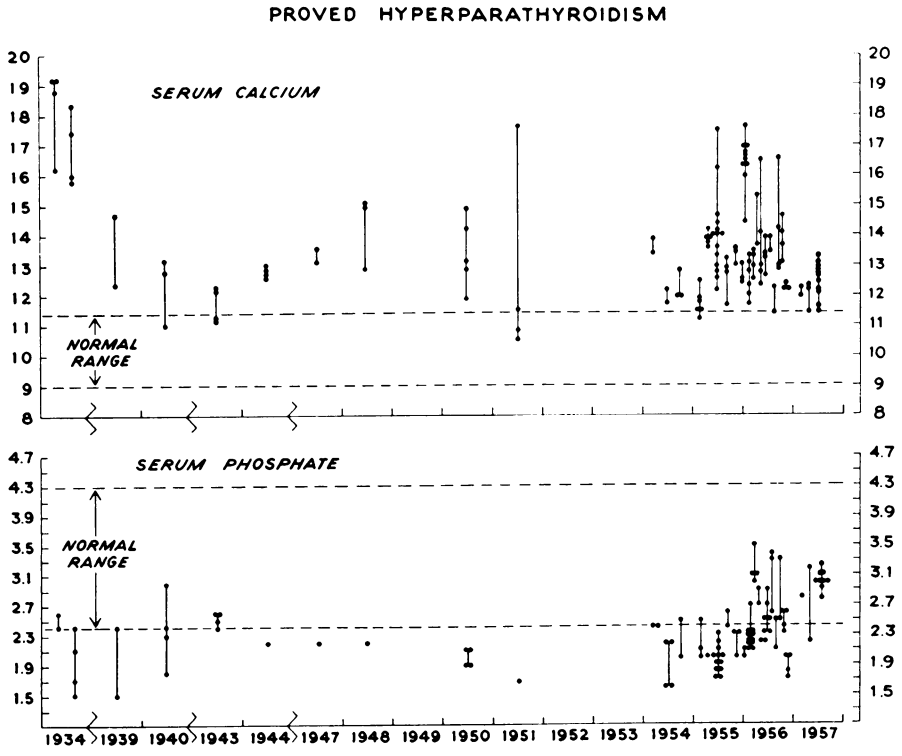

FIG. 1. Blood calcium and phosphate levels in surgically proved cases of hyperparathyroidism. Each vertical line represents one patient. Each point on the line indicates a calcium or phosphate level. Note the increased frequency of cases, the relative infrequency of severe hypercalcemia, and trend to higher serum phosphate levels in recent years. (Phosphate levels are omitted in two cases of uremia.)

sis, and two patients had no symptoms whatsoever! This distribution of clinical syndromes shows even fewer cases of skeletal disease than Hellström's 26 per cent;[5] it may in part reflect the cooperative attitude of urologists in our vicinity who have referred their patients with renal calculi to us for investigation. Seven per cent of all patients with nephrolithiasis associated with hypercalcuria who were studied in our laboratory have been found to have hyperparathyroidism.

MINIMAL HYPERCALCEMIA

The serum calcium content was determined by the method of Kramer and Tisdall,[2] as modified by Clark.[3] This method recovers 100 ± 2 per cent of standard calcium solutions. Although this technic yields values about 1 mg. higher than those reported from the Massachusetts General Hospital or the Mayo Clinic, our range of normal is practically the same width.

The normal calcium level, as determined by studies on 303 normal subjects, ranges from 9 to 11.4 mg./ml.[2] (Fig. 2). Because several patients had only slightly elevated serum calcium levels during this last two-year period, a need was felt for some type of corroborative determination. The wide spread and the highest values for serum calcium in a few patients may be explained on the basis of periods of immobilization.

NORMOPHOSPHATEMIA IN HYPERPARATHYROIDISM

Hyperparathyroidism was recognized in our early cases only when hypophospha-

temia was present. This early experience agreed with Fuller Albright's [1] observations that hyperparathyroidism was necessarily associated with a low serum phosphate level unless renal insufficiency supervened. Our recent experience has caused us to deviate from this concept, inasmuch as 60 per cent of our patients with proved hyperparathyroidism seen during the past two years had serum phosphate levels within the range of normal (Fig. 3).

This altered concept evolved during the early part of 1956, when we studied a 65-year-old woman * who had passed a renal calculus one year previously and then developed a gastric ulcer. This patient's serum calcium concentrations ranged from 11.6 mg./100 ml. to 13.2 mg./100 ml. (Six determinations) in the presence of normal serum protein; her serum phosphate level varied from 3.0 to 3.5 mg. per cent, a value which was confirmed in three other laboratories. At this time we were investigating the calcium tolerance test of John Eager Howard *et al.*[6] The patient was studied by this technic and responded in a way typical of hyperparathyroidism. Her renal tubules reabsorbed only 68.4 per cent of the phosphate filtered by the glomeruli (normal range, 80 to 90 per cent.)[2] With this evidence, and despite the normophosphatemia, she was operated upon, and an adenoma of the right superior parathyroid gland, measuring 2.8 × 2.6 × 0.3 cm. and weighing 1.3 Gm., was removed.

After this singular experience we were able to confirm the diagnosis of hyperparathyroidism in 14 patients with hypercalcemia and normophosphatemia. Only one of the 23 patients had uremia (which raises serum phosphate levels) during this time, which left 13 patients with normal serum phosphate levels of the 22 with normal renal function.

* Referred by Drs. Joseph D. Wilson of Stockton, California, and Norman J. Sweet of San Francisco.

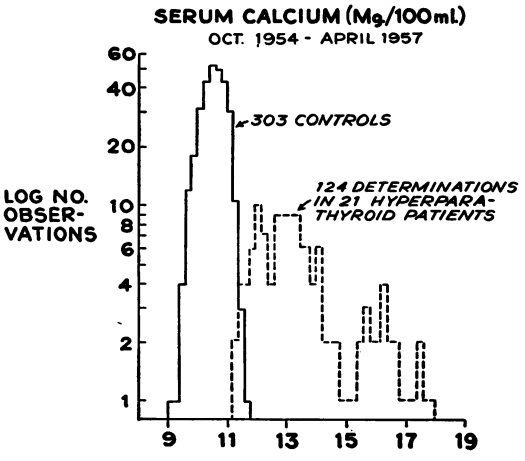

FIG. 2. Distribution of serum calcium levels in normal subjects and in patients with surgically proved hyperparathyroidism. Note slight overlap.

Normal serum phosphate levels in hyperparathyroidism can be explained by several possible mechanisms. At the present time there are two known actions of the parathyroid hormone; one, the mobilization of calcium from the skeleton, and the other, the inhibition of reabsorption of filtered phosphate by the renal tubules. It is now established that these two mechanisms are independent of each other.[8] An excess of the

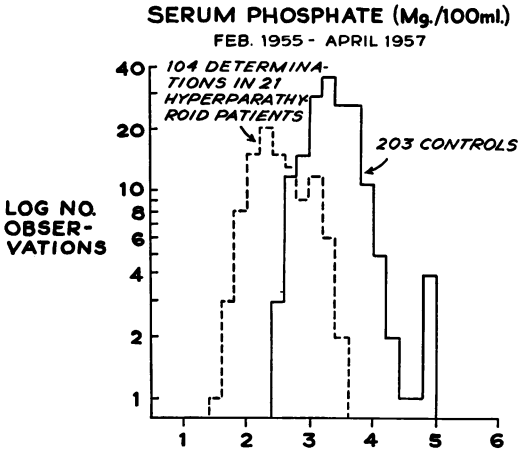

FIG. 3. Distribution of serum phosphate levels in normal subjects and in patients with surgically proved hyperparathyroidism with normal renal function. Note large area of overlap.

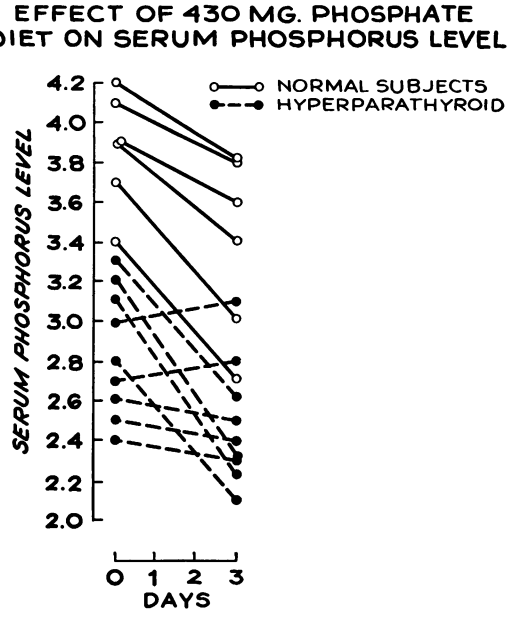

FIG. 4. Effect of a low-phosphate diet on serum phosphate levels of six normal subjects and nine patients with hyperparathyroidism, normal serum phosphate levels, and normal renal function.

hypercalcemic factor without excess of the phosphate-diuretic factor might explain the presence of hypercalcemia without hypophosphatemia. Such an explanation can be excluded from this group of patients, since direct measurement of the tubular reabsorption of phosphate proved to be low in every case.

Another possible explanation for the normal serum phosphate levels in patients with hyperparathyroidism and normal renal function is that an increased appetite for phosphate compensates for the urinary phosphate leak.[9] To test this, patients who had normal serum phosphate levels despite subsequent proved hyperparathyroidism were given a diet low in phosphate (430 mg. per day).

As seen in Figure 4, this dietary restriction lowers the serum phosphate in normal individuals, but not below 2.7 mg./100 ml. In contrast, such a restriction in normophosphatemic, hyperparathyroid patients produced a maximal depression of the serum phosphate level within three days; hypophosphatemic levels were reached in five of nine tested patients. Since four patients maintained normal serum phosphate levels despite the continued renal phosphate leak and curtailed phosphate intake, a third mechanism must be involved. Skeletal and muscular breakdown, causing release of endogenous phosphate stores, seems to be a likely possibility in these patients.

TUBULAR REABSORPTION OF PHOSPHATE (TRP)

Normally, the renal tubules reabsorb 80 to 90 per cent of the phosphate filtered through the glomeruli[2] (Fig. 5). Sirota,[11] and Schaaf and Kyle[10] have demonstrated that this figure is considerably reduced in hyperparathyroidism, thus accounting for the hyperphosphaturia typical of this condition. In our experience, simple measurement of the 24-hour urinary phosphate excretion does not suffice for this purpose, since many normal subjects excrete more phosphate in the urine than do patients with hyperparathyroidism.

Direct measurement of the TRP is done simply by simultaneous determination of phosphate and creatinine concentrations in the blood and urine. To determine the amount of phosphate reabsorbed by the tubules, it is necessary to measure the quantity of phosphate filtered by the glomeruli and to subtract the amount found in the urine. The quantity of phosphate filtered equals the volume of plasma filtered per minute (glomerular filtration rate, determined by measurement of the creatinine clearance), multiplied by the serum phosphate concentration. The measurement of creatinine clearance would ordinarily require exact timing and complete collection of urine during the clearance period.

Fortunately, however, exactly the same amount of time and volume of urine are

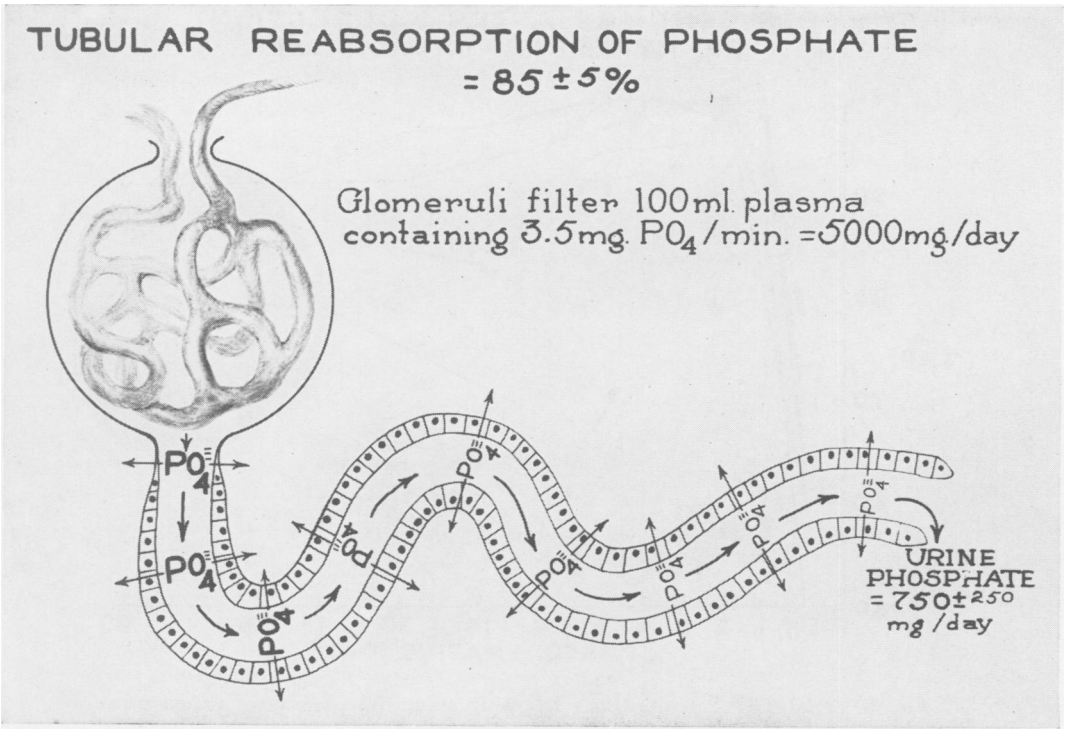

FIG. 5. Schematic representation of phosphate filtration by the glomeruli and reabsorption by the renal tubules. Note that 80 to 90 per cent of the filtered load is reabsorbed in the tubules, so that normally only 10 to 20 per cent appears in the urine.

used for the urinary excretion of phosphate. Thus, the timing and urine volume cancel out so that the final formula requires neither figure.[2]

One need know only the serum (S) and urine (U) concentrations of phosphate (P) and creatinine (C) to calculate the TRP by the formula:

$$TRP = 1 - \frac{UP \times SC}{UC \times SP}$$

Practically, this must be done at a time when the serum phosphate level is not fluctuating. Since the serum phosphate level falls after each meal, we have found it convenient to have the urine collected during the night and to take the blood sample at the end of this period, while the patient is fasting. The urine may be collected for a period as long as 12 hours, i.e., 8 p.m. to 8 a.m. Periods of less than four hours probably should not be employed.[12]

Of 22 patients with proved hyperparathyroidism, 21 had a distinctly and consistently lowered TRP. One patient had a TRP of 82 per cent, which is within normal range. This could have been explained by the fact that she had been given a diet greatly restricted in phosphate (Shorr regimen for nephrolithiasis) during the time of the test. It has been shown previously [2] that in normal subjects a stringent restriction of dietary phosphate raises the TRP to 90 per cent or more, but in patients with hyperparathyroidism this diet raises the TRP up to 85 per cent. Thus, the patient's TRP of 82 per cent falls within the range found in phosphate-starved hyperparathyroid pa-

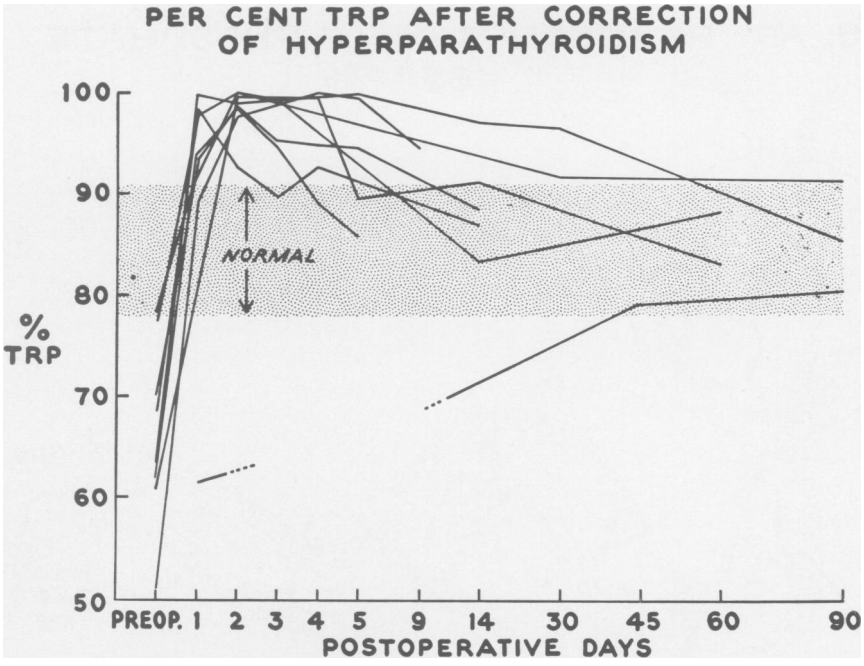

FIG. 6. Serial TRP determinations following successful excision of excess parathyroid tissue in 10 patients with hyperparathyroidism and normal renal function. (Previously published in J. Clin. Endocrinol. and Metab., 16: 1513, 1956.)

tients, but below that of normal subjects similarly treated.

In our experience, the TRP is uniformly lowered in hyperparathyroidism, but a low TRP is not specific for this condition. Renal phosphate leaks also occur in osteomalacia, sarcoidosis, and rarely, in multiple myeloma —as well as in the Debré-de Toni-Fanconi syndrome ("phosphate diabetes"). We have also encountered six cases of idiopathic phosphate leaks. These, however, could be curtailed by the low phosphate diet, unlike the low TRP of hyperparathyroidism. Finally, since the technic depends upon the use of creatinine clearance as an index of the glomerular filtration rate, the test is not applicable in the presence of uremia.

In addition to its diagnostic value, the TRP is also useful as an indication of adequate correction of the hyperparathyroid state. Following resection of all excessively functioning parathyroid tissue, the lowered TRP rises virtually to 100 per cent, as is shown in Figure 6. This is a mathematical way of saying that almost all the filtered phosphate is reabsorbed by the tubules so that practically none appears in the urine. The reason cannot be, as might be supposed, that the phosphate is disappearing into the bone, because the filtered phosphate load in the kidney is actually increasing. The serum phosphate level rises rapidly and the glomerular filtration rate also rises in many cases, so that the filtered phosphate load may double within the first 48 hours. Despite the greatly increased amount of phosphate filtered through the glomeruli, very little of it appears in the urine. We believe that the high TRP, after successful removal of excess parathyroid tissue, is caused by a temporary hypoparathyroidism which removes the parathyroid restraint

upon tubular reabsorption of phosphate. In three to 19 days, the rate of tubular reabsorption of phosphate returns to normal.

In three patients of the entire group studied by this method, the TRP remained at a low level postoperatively. The persistently low TRP, plus the persistent hypercalcemia, gave corroboration to the conclusion that hyperfunctioning parathyroid tissue had been left behind. With later adequate surgical removal, the TRP reverted to normal in two of these patients. The third patient, who had hyperplasia of four parathyroid glands which had caused acute parathyroid poisoning, still has a low TRP level and mild hypercalcemia despite almost complete excision of the parathyroid tissue. From this experience, we believe that a postoperative rise of TRP is welcome evidence of a successful operation.

CALCIUM TOLERANCE TESTS

In 17 patients, calcium tolerance tests performed by the method of J. E. Howard (using a dose of 12.4 to 18.6 mg./Kg.*), showed abnormal results in only 11. When the results were abnormal, these ancillary data were of particular value in making the correct diagnosis in normophosphatemic patients. However, normal responses are not inconsistent with hyperparathyroidism. In this test, a calcium salt is infused in a saline solution over a period of four hours; the rise of the serum phosphate level and the urinary phosphate excretion are measured. In normal subjects, the serum phosphate level rises at least 0.9 mg./100 ml. and a phosphate antidiuresis occurs.[2]

In 11 of 17 hyperparathyroid patients, the serum phosphate rise was subnormal and no antidiuresis occurred. In the other six patients, the results of the test were normal despite subsequent proof of the diagnosis by operation. Since positive results were obtained in only 11 of 17 patients, it is apparent that this test is not as diagnostic as the demonstration of hypercalcemia and low TRP.

Despite the ever increasing recognition of hyperparathyroidism, we feel that further diagnostic tests are needed. We now have under observation five patients with kidney stones, hypercalcuria, borderline or intermittent hypercalcemia, normal serum phosphate levels, and borderline TRP values. The response to phosphate deprivation is also borderline. For example, the TRP, which rises above 90 per cent in normal subjects but rarely over 85 per cent in hyperparathyroid patients, has risen into the borderline range between 85 and 90 per cent. At the moment, these patients are being observed to see if they will develop more typical chemical abnormalities diagnostic of hyperparathyroidism. We have preferred to establish the diagnosis by chemical means whenever possible, rather than to carry out a surgical exploration in a doubtful case. For this reason, we have begun to use additional tests. Currently, the use of an infusion of non-radioactive strontium appears to be of value as an indicator of the rate of skeletal deposition.[4] The rate has been found to be accelerated in the proved cases of hyperparathyroidism we have studied thus far.

SUMMARY

Increasing experience in the diagnosis of hyperparathyroidism has led to the following conclusions:

1. The accurate chemical screening of patients with nephrolithiasis, nephrocalcinosis, acute hypercalcemia, or skeletal disorders has resulted in the recognition of more patients with this disease.

2. Hypercalcemia is now often minimal,

* Two-thirds to 1.0 ml. of 20 per cent calcium gluconogalactogluconate (Neo-calglucon®), generously supplied by Mr. Harry Althouse, Sandoz Pharmaceuticals, San Francisco, California.

requiring frequent determinations and corroboration by other tests.

3. In contrast to the previously emphasized hypophosphatemia, the serum phosphate levels have been normal in most of our recent cases of surgically proved hyperparathyroidism.

4. The tubular reabsorption of phosphate measured by a simplified technic was uniformly subnormal. This test was of diagnostic value in those patients with minimal hypercalcemia and normal phosphate levels.

ACKNOWLEDGMENT

Acknowledgment is made to Jeanette Arakawa, B.S., Thomas Mintz, M.D., and David Meltzer, M.D., for technical assistance.

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DISCUSSION

DR. ROYSTER: I enjoyed this paper very much, since we certainly need more methods to diagnose this condition when there are borderline states. I have one question I would like to ask of Dr. Goldman. In these cases of borderline disease, where this test proved to be confirmatory, what did the pathology of the glands show?

I am reminded of a statement by Dr. Cope, in which he was writing of the thyroid gland as well as of the parathyroid, that when the endocrine gland is out of balance and produces disease, it is usually possible in most every case to find the cellular change indicating that there is actual disease. Also, I would like to point out another thing, that there are many causes of changes in the phosphorus excretion and in the test of tubular reabsorption. There have been studies to show that there is an increased excretion of calcium under various conditions, with or without the presence of hyperparathyroidism, and that when the patient is excreting calcium in excess, the calcium takes phosphorus with it. Therefore hyper-