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Hyperparathyroidism—epidemic or endemic?

Diagnosis and treatment

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DURING the eleven-month period between January 1 and December 1, 1969, 25 operations for hyperparathyroidism were performed at the Cleveland Clinic Hospital. In the previous year, 11 were performed, and a decade ago only five were done (*Fig. 1*).

Why has the incidence of operations for hyperparathyroidism increased so strikingly? Does this represent an epidemic or is it a local phenomenon? What have we learned from our increasing experience in the diagnosis and treatment of the disease?

Definitions

Secondary hyperparathyroidism is distinguished from primary in that usually the serum calcium is not increased in the former. The patient has an underlying condition that is causing the hyperparathyroidism, such as chronic renal failure. If the secondary hyperparathyroidism becomes autonomous, it is said to be tertiary hyperparathyroidism and usually the serum calcium is increased.

Causes of increasing incidence of hyperparathyroidism

Increased diagnosis by means of SMA-12. In 1968, the Cleveland Clinic installed a 12-channel AutoAnalyzer (SMA-12) that is able to analyze a sample of blood for 12 chemical constituents as fast and as economically as in the past had been done for any two constituents. Within a few months the staff physicians appreciated the advantages of this broad-spectrum type of chemical examination and began to make use of its vast potential. By January 1969, 200 blood samples a day, six days a week, were being analyzed in the SMA-12 for calcium and 11 other constituents. This volume of analyses is in contrast to 20 calcium determinations daily in 1967, when a calcium analysis had to be specially ordered. At the same time, AutoAnalyzers were being introduced elsewhere in the country with the result that serum calcium values were being determined for about 10 times as many patients as ever before.

In this way, many patients who had none of the typical symptoms of hyperparathyroidism were found more or less accidentally to have an increased

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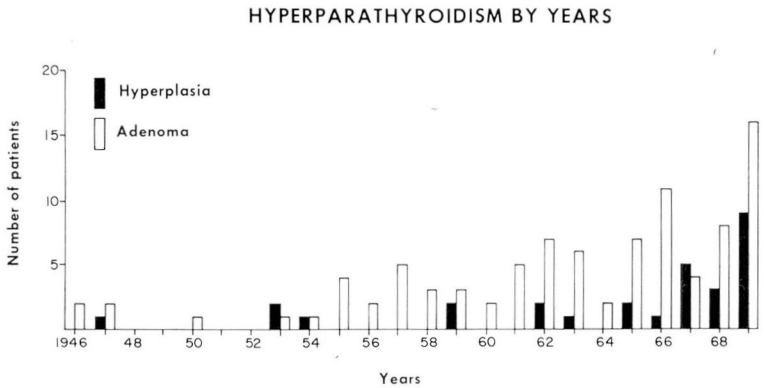

Fig. 1. Graph showing number of patients with hyperparathyroidism diagnosed at the Cleveland Clinic from 1946 through December 1, 1969.

serum calcium and were being referred to us for surgical treatment. In the last 11 months, of 16 patients with parathyroid adenomas, 12, clinically unsuspected, were diagnosed from routine laboratory tests. One is tempted to speculate as to what happened to such patients in the past. Did renal or bone disease ultimately develop, or did they go through life with mild symptoms of fatigue and depression?

Renal failure and chronic dialysis. The Cleveland Clinic has a large renal dialysis and kidney transplantation program that attracts many patients in renal failure. These patients often have increased serum phosphorus content as a result of renal failure. They may suffer from renal osteodystrophy (*Fig. 2*), causing bone pain, fractures, and precipitation of calcium in muscle and connective tissue. These changes are often reversible when the renal failure is corrected by a successful kidney transplant, but they are dramatically reversed by removal of parathyroids.[1] For this reason we have been removing the parathyroids of most patients in the dialysis program who have severe bony changes or extensive deposits of calcium in the soft tissues. Occasionally, after a successful transplant in patients with renal failure, hypercalcemia may develop. Those patients are thought to have tertiary hyperparathyroidism, and in that event it is usually believed that parathyroid surgery is necessary to correct the problem. Of the 25 patients with hyperparathyroidism operated on in the recent 11-month period, eight are in this category. This accounts for the increased number of operations done for hyperplasia of the parathyroids.

Diagnosis of hyperparathyroidism

The SMA-12 has taught us nothing new about the diagnosis of hyperparathyroidism. None of the complicated urinary excretion tests has contributed significantly to the diagnosis. Sometimes, when both calcium and phosphorus serum values are high, a trial on steroids to establish the presence or ab-

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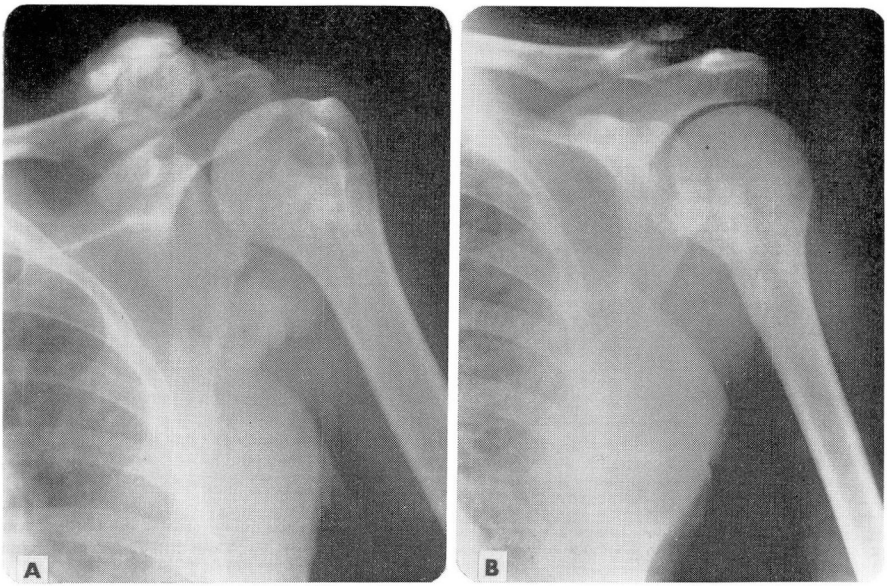

Fig. 2. Roentgenograms of the left shoulder. A, Showing calcification of soft tissues, a change due to secondary hyperparathyroidism. B, Showing the regression that occurred after parathyroidectomy.

sence of sarcoid is worthwhile, but the results of this trial can be misleading in both directions. When serum calcium is high and phosphorus low, no other tests are needed; the patient almost always has hyperparathyroidism. When there is renal failure, and serum phosphorus is high, true hyperparathyroidism may or may not be present.

Recently there has been developed an interesting test for determining, by immunologic assay, the amount of circulating parathormone. This test promises to differentiate between hyperparathyroidism due to hyperplasia of the parathyroid and that due to parathyroid adenoma. In hyperplasia, giving calcium intravenously results in a rapid fall in the amount of circulating parathormone; whereas, when there is an adenoma that functions autonomously, giving calcium causes no decrease. It is thought that when an adenoma is present, massaging the patient's neck on the side of the adenoma causes an increase in the amount of circulating parathormone, thus helping to determine in which side of the neck the adenoma is. Despite all refinements, however, there are two truisms about the diagnosis of hyperparathyroidism. One fact is that if the serum calcium is more than 11 mg per 100 ml, and the serum phosphorus is low or normal, in three or more tests, the patient has hyperparathyroidism. The other fact is that when at operation the parathyroids cannot be quickly and clearly identified, they are atrophic due to the presence of an adenoma, and the surgeon is obligated to search until he finds the tumor or proves histologically the presence of all four parathyroids.

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Multiple adenomas of the parathyroid are rare. When a typical adenoma is found, the other parathyroids are small and hard to identify. We have never seen a patient who had a second adenoma in such circumstances. However, when in addition to the adenoma one or two enlarged parathyroids are identified, then it is necessary to identify all of them. Probably they are enlarged as a result of chronic renal failure; and when this is the case, more than one of them could be functioning autonomously like an adenoma.

Treatment of hyperparathyroidism

Parathyroid adenomas. There is no operation easier to perform than that for parathyroid adenoma, provided that the tumor is reasonably large and placed in its usual position. When the tumor is small, or tucked away in some ectopic location, there is no operation more vexing. The surgeon knows that an adenoma is present, from the fact that he can find no parathyroids, or because the ones that he does see are atrophic. When the lower parathyroid glands are not readily found in the neck, we have found examination of the thymus most helpful. The thymus and the lower parathyroid glands share a common embryogenesis, and thus when the adenoma is in the mediastinum it is almost always within or near the thymus. The technic of thymectomy from a cervical approach has been described in prior reports.[2, 3]

Primary hyperplasia. The rarest of the parathyroid diseases is primary hyperplasia unassociated with demonstrable disease of the kidneys. The best treatment seems to be to leave only half of each of two of the parathyroids intact.

Secondary hyperparathyroidism. When severe hyperparathyroidism secondary to renal disease causes extreme changes in bone, and deposition of calcium in soft tissue, the hyperparathyroidism is most easily reversed by total ablation of all four parathyroids. When the changes are mild it is acceptable to remove two of the parathyroids and all but a small part of each of the other two.

Treatment of tertiary hyperparathyroidism. When the patient is in renal failure the parathyroids become enlarged and overactive, and they eventually may function autonomously. The situation is similar to that observed in the thyroid when hyperplasia originally induced by iodine deficiency may result in the formation of adenomas and these in turn may function autonomously and cause hyperthyroidism. In the case of the parathyroid, the best treatment is to remove all grossly adenomatous-looking parathyroids, or when all are diffusely enlarged remove all but half of each of the two smallest ones. This makes possible a tissue diagnosis of all four parathyroids. There is no reason to search further, for we have never encountered a patient with more than four parathyroids. It is important to look at the vessels of each parathyroid carefully before removing any part of it, for if necrosis of the

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remnant is to be avoided, then the part removed should be the end away from the one where the artery enters.

Hyperparathyroidism associated with polyglandular disease. Occasionally, a parathyroid tumor is associated with Zollinger-Ellison tumors of the pancreas, diarrhea, hypercalcemia, and hypokalemia. We removed a large parathyroid adenoma from one patient with this disease complex, after which all symptoms subsided and the serum calcium value decreased. At the time of the operation the other parathyroids had been identified and were not large. Within three months, though, the hypercalcemia recurred, and on reexploration a second fairly large adenoma was found and removed. The serum calcium value again decreased to normal, but the diarrhea and hypokalemia did not subside until the pancreatic tumor was removed.[4]

One of us (G.C., Jr.) has also followed the progress of another patient with a Zollinger-Ellison tumor who has had two parathyroid tumors removed. The reason for their formation is not known; but the possibility of removing most of the parathyroid tissue should be considered in patients with these polyglandular diseases.

Summary

In the last year there has been a striking increase in the incidence of hyperparathyroidism. The increase is attributed to prolongation of lives of the patients with renal failure, and to the accidental discovery of asymptomatic hypercalcemia as a result of increased use of the SMA-12 AutoAnalyzer.

Diagnosis and treatment of the different types of hyperparathyroidism are outlined.

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