The First 100 Cases of Parathyroid Tumor from Charity Hospital of Louisiana

EDWARD T. KREMENTZ,* M.D., RODRIC YEAGER,** M.D.
WILLIAM HAWLEY,*** M.D., RUDOLPH WEICHERT,† M.D.

From the Department of Surgery, Tulane University School of Medicine and Charity Hospital of Louisiana, New Orleans, Louisiana

THIS is a report of the first 100 patients with parathyroid tumors who were admitted to the Charity Hospital of Louisiana from January, 1942, through June, 1970. The experience in this large general hospital for the indigent people of Louisiana differs from that obtained by an individual consultant, a private clinic, or a community hospital. The overall results have been satisfactory, although some complications and fatalities have occurred and it is hoped that this review may prevent similar problems in this and other teaching institutions.

Fifty-three of these cases were previously presented by one of us at the Southern Surgical Association in 1966.[13] In the ensuing 4½ years, 47 cases have been added to the review including hyperplasias as well as adenomas. These cases have been obtained through the aid of the Tumor Registry at Charity Hospital whose records date back to 1948 and the Charity Hospital Record Room where the coding system can identify diagnoses made since 1942.

Seventy-five of these patients have been classified as surgical cases. The disease in these patients was diagnosed and treated by operation (Fig. 1). Twenty-five cases were discovered at autopsy. During this period admissions to Charity Hospital ranged between 50,000 to 60,000 per year. The Tulane service contributed 52 surgical cases and 19 autopsy cases, the LSU service contributed 23 surgical cases and four autopsy cases, and the now-discontinued Independent service provided two autopsy cases.

In the first 9 years of the series only one case was diagnosed in a patient with renal stones whose adenoma was removed in 1942 (Fig. 1). The first successful operation for parathyroid adenoma had been performed 17 years before by Mandl in Vienna in 1925.[18] Twenty instances requiring operation were diagnosed in the second 10-year period from 1951 through 1960, while five cases of parathyroid tumors previously undiagnosed were confirmed at autopsy. In the last 10 years from 1961 through 1970, reliable and accurate serum calcium determinations have been responsible for diagnosis of 54 instances requiring operation. The pathologists have found an additional 20 tumors at autopsy. Parathyroid tumors are more commonly diagnosed as a result of multichannel biochemical autoanalyzers used for screening all admissions, thereby detecting patients with hypercalcemia indicating investigation.[8] Indeed, this has raised the problem of whether neck explo-

Presented at the Annual Meeting of the Southern Surgical Association, December 7–9, 1970, Boca Raton, Florida.

* Professor of Surgery.

** Instructor in Surgery and Clinical Research Trainee supported by National Cancer Institute Grant 5T4 CA-5108 during a portion of the time devoted to this study.

*** Associate Clinical Professor of Medicine and Chief of Research Services, U.S.P.H.S. Hospital in New Orleans.

† Assistant Professor of Surgery.

Supported in part by U.S.P.H.S. Grants 5T4 CA-5108 and 5PO2 CA-05837.

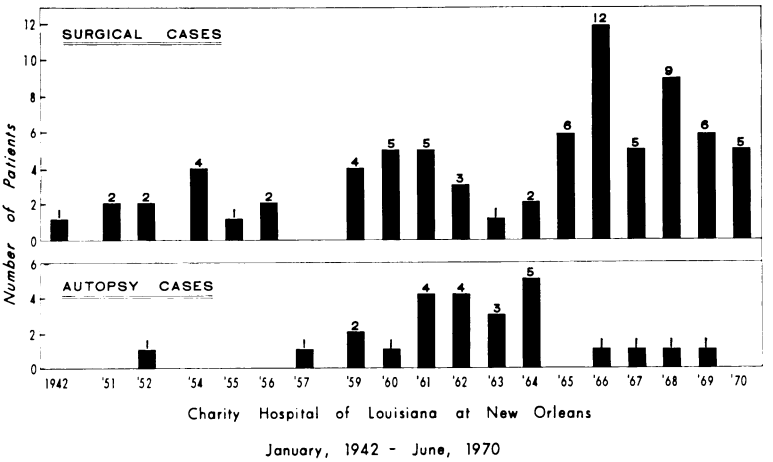

FIG. 1. One hundred patients with parathyroid tumors. (Surgical cases—75; autopsy cases—25.)

ration for adenoma is justified in patients with hypercalcemia and no related symptomatology. The multichannel analyzer has only been in use at Charity Hospital for the past 6 months and has not contributed to the detection of cases in this report.

One patient in the surgical group is an 80-year-old woman with an elevated serum calcium in whom it has been decided to defer operation as the surgical risk outweighs the potential benefits. Of the surgical cases, eight patients with adenomas were found incidentally at operations for other conditions. Seven operations were for disease of the thyroid, usually nodular goiters or adenomas. One parathyroid adenoma was found incidentally at prophylactic neck dissection for carcinoma of the tonsil. These patients had no symptoms of hypercalcemia nor had they had serum calcium determinations and the adenomas were considered asymptomatic. Of the autopsy cases, 14 patients had no symptoms of parathyroid disease recorded in their charts. Thus, 19 patients were found to have adenomas without symptomatology.

Distribution by Age

The youngest patient in this series was a 15-year-old boy who had renal stones and the oldest was a 92-year-old woman in whom adenoma was found incidentally at autopsy (Fig. 2). In the last 4 years, in five patients under 20, the disease was diagnosed with a variety of findings in marked contrast to the past when most patients fell in the older age groups and had renal stones or bony pathology. They had had hypercalcemia long enough to produce obvious findings. The greatest number of cases (30) were found in the sixth decade. In 69 of the patients the disease was diagnosed between their 41st and 70th year. The patients brought to autopsy were invariably in the older age groups.

Distribution by Race and Sex

Thirty-eight white patients and 62 Negro patients were in the series (Fig. 3). During the same period about 70% of the hospital admissions were Negroes, but if obstetrical, premature, and newborn admissions were deleted, the average number of

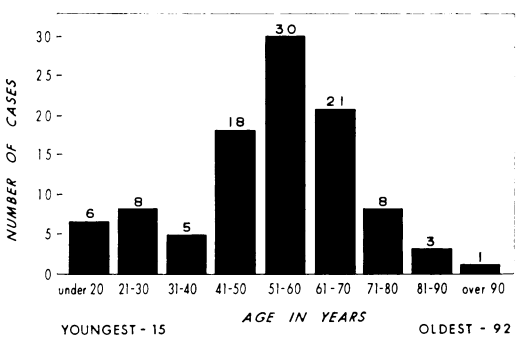

FIG. 2. Age incidence.

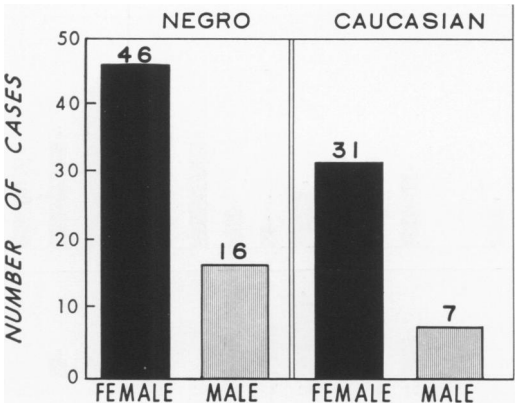

FIG. 3. Sex/race incidence.

Negro admissions decreased to about 60% so there was no greater racial incidence in our experience. The tumors occur more commonly in women. Seventy-seven of our patients were women while 61% of the hospital admissions were female.

Number and Types of Tumors

Of the 100 patients with parathyroid tumors, there were 96 with adenomas, three with hyperplasias, and one with carcinoma. Of the patients with adenomas, 86 had single adenomas, five had two adenomas, three had three adenomas, one had multiple adenomas, and one was not explored. This report is somewhat different from Cope's series in which 250 cases contained 34 patients with hyperplasia and 14 patients with parathyroid cancers.[3]

Three of the patients with single adenomas had hyperplasia in one other gland. Of the three patients with hyperplasia, two had involvement of four glands, one had involvement of three glands and one normal gland. Of the patients with four hyperplastic glands, one was a case of tertiary hyperparathyroidism occurring in a 30-year-old man who underwent a related donor renal transplant in March, 1967. By September, he had developed bone pain and osteoporosis. Work-up revealed elevated serum calcium levels and findings compatible with hyperparathyroidism. Exploration of the neck in October, 1967, revealed four hyperplastic parathyroid glands. Three and one half glands were removed. Calcium levels returned to normal and the patient is asymptomatic. This situation occurs in patients with renal failure, chronic uremia and resultant poor absorption of calcium. Persistent hypocalcemia results in compensatory hyperplasia of the parathyroid glands. Following correction of the uremic state by successful renal graft, tertiary hyperparathyroidism may persist characterized by chief cell hyperplasia, high serum calcium and low serum phosphorus which produces renal stones, bony and other pathologic changes. In some patients after successful renal transplant the hyperplasia regresses, in others it persists requiring operative correction. The first such case was reported by McPhoul[16] in 1964. By 1970, the 18th case manifested by renal stones and acute hyperparathyroidism was reported by Latimer *et al.*[14]

The single patient with carcinoma died of parathyroid poisoning. A tumor thought to be an adenoma was removed at another hospital because of persistent hypercalcemia. Two years later the patient underwent reoperation because of recurrent elevated serum calcium and a second large parathyroid gland was removed. The patient was transferred to Charity Hospital because of persistent hypercalcemia where she died shortly after admission. At autopsy a recurrent mass which proved to be a low grade parathyroid carcinoma was found in the region where the first tumor had been removed. It was felt on review of the sections that the original gland and the recurrence were carcinoma and that the second gland was a normal parathyroid.

It is not possible to accurately classify the histologic characteristics according to cell type of the tumors without having a single pathologist review the sections in each case. The pathology reports do not describe the cell type in most cases. How-

ever, when review has been carried out, the symptomatic cases generally have been of the chief cell type. There were seven oxyphil adenomas, all in non-functional occurrences and three functional clear cell adenomas described. The hyperplasias were chief cell or mixed oxyphil and chief cell type.

Anatomical Location

It has been difficult to determine the anatomical location of the tumors in many of the older charts particularly among the autopsy cases. The three cases of hyperplasia involved three or more glands which were all in normal positions. The locations of 84 adenomas in 76 patients were recorded and are depicted in Figure 4.

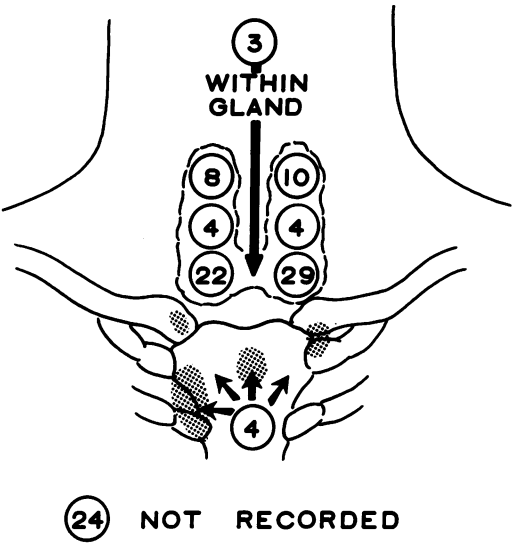

FIG. 4. Eighty-four adenomas in 76 patients.

Fifty-one of the adenomas were located behind the lower lobes of the thyroid gland receiving blood supply from the inferior thyroid arteries. Twenty-two were found on the right side, 29 on the left side. Eighteen adenomas were found posterior to the superior lobes of the thyroid associated with the superior thyroid artery, eight on the right and ten on the left. Four glands on each side were located in an intermediate position between the upper and lower lobes so that it was not possible to classify the position of the adenoma. Three adenomas were found within the thyroid gland. One was found by the pathologist after routine thyroidectomy, the exact place was not recorded although it was within the gland. The second lesion was found within the isthmus of the gland and was large enough to be palpated at exploration. The third lesion was found within the right lobe of the thyroid after subtotal thyroid resection which was carried out for persistent hypercalcemia after previous exploration of the neck failed to reveal an adenoma. Four adenomas were found in the upper anterior mediastinum and are shown in Figure 4. Two were removed at the time of neck exploration, one was in the tracheo-esophageal groove and one was behind the junction of the clavicle and sternum on the right side. The remaining two adenomas were found at mediastinotomy, both at the second stage operations for persistent hypercalcemia following previous negative neck explorations.

Associated Cancer

In reviewing the cases, a large number of concurrent cancers were found in these patients. Table 1 reveals that there were 21 carcinomas found in 18 of the 100 patients. There were six thyroid carcinomas, four pancreatic, two prostate, and two colon carcinomas. The rest were in various other sites as listed. There were 19 adenocarcinomas and two epidermoid carcinomas. The only explanation of the apparent increased incidence of cancer is that a large percentage of these patients are in the cancer age groups.

Associated Thyroid Disease

Associated thyroid disease occurred in 21 patients in conjunction with parathyroid tumors. Table 2 lists 15 patients with goiters,

TABLE 1. *Twenty-one Concurrent Carcinomas Found in 18 of 100 Patients with Parathyroid Tumors*

Type of Carcinoma	No. Cases
Thyroid	6
Pancreas	4
Prostate	2
Colon and rectum	2
Penis	1
Salivary gland	1
Ovary	1
Uterus	1
Stomach	1
Esophagus	1
Gallbladder	1

TABLE 2. *Twenty-five Associated Thyroid Diseases in 21 of 100 Patients with Parathyroid Tumors*

Thyroid Disease		No.
Goiter		15
Nodular (euthyroid)	13	
Colloid (hyperthyroid)	2	
Carcinoma		6
Papillary	2	
Follicular	1	
Sclerosing	1	
Medullary*	1	
Hurthle cell*	1	
Adenoma		3
Follicular	2	
Hurthle cell	1	
Thyroiditis		1

* Both lesions found in the same patient.

TABLE 3. *Presenting Findings in 80 Patients with Parathyroid Tumors*

Renal stone and nephrolithiasis	51
Weakness, fatigue, malaise	23
Peptic ulcer and related symptoms	17
Hypertension	6
Lethargy, confusion, psychosis	5
Pancreatitis	3

including 13 with nodular goiters without evidence of hyperfunction, and two with diffuse toxic goiters that had undergone involution at the time of removal as a result of appropriate preoperative medical therapy. Six carcinomas of the thyroid were found; two papillary, one follicular, one sclerosing, and in one patient a medullary and Hurthle cell carcinoma was found in the same gland. Three adenomas were found, two follicular and one Hurthle cell. One patient had histologic evidence of thyroiditis.

Presenting Complaints

Eighty patients had complaints suggestive of adenoma or hyperplasia. Fourteen of the autopsy cases had no symptoms relating to parathyroid disease, and eight instances were found incidentally to other surgical treatment. A number of patients had multiple complaints and were included separately so that the total complaints listed exceeds the number of patients with complaints (Table 3).

The most common complaints were related to symptoms produced by renal stone or nephrocalcinosis and occurred in 51 patients (Table 3). The next most common complaint was the syndrome of weakness, fatigue, and malaise with 23 patients. When this syndrome is looked for it is easily elicited. The classic complaint of "tripping over the rug" from leg weakness is not uncommon.

Seventeen patients had complaints referable to peptic ulcer. When peptic ulceration is found in patients with hyperparathyroidism, a search for other endocrinopathies should be made. The multiple endocrine adenopathy syndrome (MEA syndrome) described by Wermer in 1954, includes parathyroid adenoma and seven patients in this series had tumors or hyperplasias of other endocrine glands in addition to parathyroid tumors. Actually, islet cell hyperplasia or adenopathy (Zollinger-Ellison syndrome) may be the actual cause of the peptic ulceration, or the ulceration may be related directly to the effects of the parathyroid adenoma. Donegan and Spiro [5] reported that hypercalcemia stimulates gastric secretory activity with increases in acid concentration, pepsin content and volume. Barreras and Donaldson [1] have shown that an increase in serum calcium from 9.3 to 12.3 mg./100 ml. produced a 450% increase in gastric free acid and a 300% increase in pepsin secretions. Three of the patients

TABLE 4. *Six Patients Developing Acute Hyperparathyroid Crisis of 100 Patients with Parathyroid Tumor*

Age	Sex	Maximum Serum Calcium	Pathology	Operation	Outcome
69	F	8.0 mEq./l.	Hyperplasia + adenoma	No	Fatal
48	F	9.9 mEq./l.	Carcinoma	No	Fatal
64	F	12.0 mEq./l.	Adenoma	No*	Fatal
64	F	7.8 mEq./l.	Adenoma	Yes	Asymptomatic (18 mo.)
26	M	10.0 mEq./l.	Adenoma	Yes	Asymptomatic (30 mo.)
62	F	6.4 mEq./l.	Adenoma	Yes	Asymptomatic (24 mo.)

* Patient had a total thyroidectomy and radical neck dissection for thyroid cancer and 3 days later developed an acute parathyroid crisis from a residual mediastinal adenoma.

with MEA syndrome had adenomas or hyperplasia of the islet cells, all died as a result of the disease.

Only eight of our patients had bone disease, five patients had Von Reckinghausen's disease or osteitis fibrosis cystica and three had pathologic fractures, two resulting from bone cysts and one due to osteoporosis. A not uncommon complaint was deep-seated bone pain and a number of patients had evidence of osteoporosis. The classic x-ray signs of erosion of the radial aspect of the middle phalanges, the tufts of the distal phalanges, the distal one third of the clavicle and/or the lamina dura surrounding the teeth were occasionally seen.

Six patients had hypertension, four of whom had strokes. The association of hypertension with primary hyperparathyroidism has been recognized by others in as many as one-third of the patients. Madhaven, Frame, and Block [17] have pointed this out in a recent report of 80 cases of primary parathyroidism including 14 with hypertension. Eight had hypertension related to renal impairment, but six had no evidence of renal impairment. The hypertension regressed in seven patients after removal of the adenomas, three of those without renal impairment and four with renal impairment.

In five patients, lethargy, confusion, anxiety, or frank psychosis were noted. One patient had been previously hospitalized in a state mental institution and was found with hypercalcemia in the psychiatric wards at Charity Hospital. After removal of the adenoma, the patient's mental status cleared and he has been fully rehabilitated. A number of patients, after removal of the adenoma, become more responsive, alert, cooperative, and pleasant, in marked contrast to their preoperative dull, sluggish, irritable state.

Three patients had pancreatitis which is related to primary hyperparathyroidism. In addition polydypsia and polyurea or constipation have been common complaints.

Six patients had acute hyperparathyroidism and are listed in Table 4. This is a semi-emergency which develops when the usual slow progressive, often remitting symptoms of parathormone excess, becomes acute and causes a rapid fatal outcome. This condition may be brought on by dehydration, immobilization, or operation. Most authors [19] feel that serum calcium levels over 7.5 mEq./l. are necessary for the diagnosis, but we feel that clinical symptoms must be considered with calcium levels.[27] In the past few years, we have had a number of patients with calcium levels of

7.5 mEq./l. or above without acute symptoms, yet the 6th patient with acute symptoms was admitted to the psychiatric service with a diagnosis of severe depression with psychomotor retardation and her highest calcium level was 6.4 mEq./l. The patient improved on hydration with intravenous normal saline and oral sodium phosphate and subsequently recovered completely after removal of an adenoma.

These acutely ill patients are often semicomatose and the diagnosis may be obscure. Any seriously ill patient with a high serum calcium level and an elevated BUN should be considered to have acute hyperparathyroidism. Radiologic evidence and good past history are needed for confirmation. Time is usually not available for detailed diagnostic tests. If other conditions which provoke hypercalcemia such as cancer, hypervitaminosis D, milk-alkali syndrome, or sarcoidosis can be eliminated, operation is indicated. If the adenoma is not found, or if a second one is overlooked, the patient will, in all probability, die as a result of the operation. On the other hand, successful operation is life saving. Of the six patients treated at Charity Hospital, operation was deferred in the first because of the severe illness and she failed to respond to medical treatment. The second patient was not seen by the surgeons and failed to respond to treatment. The third patient was explored but operation for thyroid cancer took precedence and a mediastinal adenoma was overlooked. Acute hyperparathyroidism occurred and was complicated by acute pancreatitis leading to the patient's demise. In the remaining three patients the disease was properly diagnosed and cured with an appropriate operative procedure.

Diagnosis

The indication for operation in patients with primary hyperparathyroidism is hypercalcemia after other causes of elevated serum calcium have been excluded. The widespread adoption of serum calcium determinations by atomic absorption spectroscopy has lowered the normal range for serum calcium. We presently consider serum calcium levels of 5.3 mEq./l. as highly suspicious. Previously we had used persistent serum calciums of 5.6 mEq./l. as the critical level warranting exploration. The role of routine calcium determinations in asymptomatic patients has not been established. Our early impression is that the increased use of automated multiphasic biochemical profiles will detect primary hyperparathyroidism in many asymptomatic patients. However, the autoanalyzer calcium determination has a wider normal range and is subject to frequent spuriously high results. The frequency of false-positive determinations and the resultant cost to patient and physician may discredit the procedure or negate its value as a useful routine screening procedure.

Elevated serum calciums in patients with multiple myeloma, sarcoidosis and vitamin D intoxication will fall to 5.0 mEq./l. or less after 150 mg. of cortisone acetate has been given by mouth for 7 to 10 days. Serum calcium of 5.0 mEq./l. or less on 2 consecutive days after the second dose has been given is significant and the test may be discontinued. Suppression of hypercalcemia of primary hyperparathryroidism is rare. Cortisone does not consistently suppress hypercalcemia in patients with the milk-alkali syndrome or malignant disease. Primary hyperparathyroidism should be suspected in milk-alkali syndrome if the serum calcium does not fall to 5.0 mEq./l. within 2 weeks after adequate hydration and withdrawal of alkali and remain below that level for the next several months.

The tubular reabsorption of phosphorus test aids diagnosis of hyperparathyroidism in patients with borderline hypercalcemia and should be done before the cortisone suppression test, as use of cortisone may affect renal function.[7] This 4-hour test should be done in the morning after the

patient has had 3 days of high phosphate intake to exaggerate renal loss of phosphate. Values below 78% are considered abnormal.

With the isolation of pure parathyroid hormone [6] the development of a specific and sensitive radio-immunoassay became possible.[2] Many technical difficulties have precluded the development of the assay in most laboratories. Two groups have reported their experience in localizing parathyroid adenomas using the radio-immunoassay; one utilizing selective venous catheterization [22] and the other using the increment in serum parathyroid hormone levels before and after neck massage.[21] Experience with specific assays in other hyperfunctioning endocrinopathies has shown that significant increases in the circulating hormone are not always demonstrable and the diagnostic usefulness of the assay depends on the ability to combine the determination with some physiologic or mechanical manipulation as suggested above.

No test of function or immunologic assay differentiates hypercalcemia due to parathormone from that due to a parathormone-like substance. At present a thorough search must be made for malignant disease as a cause of hypercalcemia before operation is done for parathyroid adenoma.

Preoperative Localization of the Adenoma

A great deal of effort has gone into the preoperative localization of the parathyroid adenoma. The most simple method of carrying out this determination, but the most unrewarding, is physical examination. In the entire series, only two patients had preoperative palpable parathyroid adenomas confirmed at operation. In a number of instances tumors have been palpated but have proven to be thyroid nodules and two have proven to be thyroid carcinomas. One technic is to have the patient lie in a 30° head down position and perform a Valsalva's maneuver. This may push an adenoma superiorly and anteriorly out of the tracheo-esophageal groove into a palpable position. Radiologic technics have included soft tissue planograms of the neck or examination by barium swallow x-ray looking for extrinsic pressure on the esophagus from an adenoma. In our hands these technics have not been rewarding. Some groups have effectively localized parathyroid adenoma by arteriography as introduced by Sedlinger.[23] We have used this technic in only a few cases and although helpful, a fatal complication deterred our use of this method. A four-vessel angiography carried out by retrograde bilateral brachial arteriograms with 50% hypaque in a 33-year-old woman caused immediate stroke and subsequent death.

One interesting case, proving the value of arteriography, was seen in an elderly woman with proven hypercalcemia. Arteriography revealed a space occupying mass in the upper mediastinum in the tracheo-esophageal groove. The patient was operated upon for parathyroid adenoma and after the parathyroid glands were identified and appeared to be normal, the space occupying mass was found and removed. This lesion proved to be a 3 cm. node replaced with epidermoid carcinoma which subsequently was found to come from a small undetected primary lesion in the esophagus. Removal of the metastasis resulted in temporary lowering of the serum calcium, but the patient's malignant disease progressed and she died within a 2-month period. Autopsy confirmed the diagnosis of carcinoma of the esophagus with secondary hypercalcemia.

Our experience with selenomethionine (SE-75) scintograms to identify the site of the hyperfunctioning parathyroid tissue has been disappointing. Although we have observed uptake of isotope in several specimens, the amount has not been sufficient to identify the site on the scintogram. The principle difficulty is that the ratio of the concentration of Se-75, determined by spe-

cific activity in the parathyroid tissue to that of surrounding thyroid or thymic tissue has never exceeded three to one. Because of the relative size of the masses present, selective concentration in the parathyroid tissue must be at least tenfold that elsewhere before differentiation of the scintogram is satisfactory.

These results with selenomethionine scintograms do not necessarily reflect the experience of others.[9, 10] We have not had the opportunity to evaluate recent modifications in parathyroid scanning technics which utilize computer analysis of multiple scans with more than one radioisotope.[15, 20] The early reports suggest a significant improvement in the ability to localize functioning parathyroid adenomas.

Operative Localization of Adenomas by Vital Stain

The use of toluidine blue as a selective vital stain during operation to identify the parathyroid glands was first reported by Klopper and Moe.[12] Subsequent reports by Hurvitz and co-workers[11] described the use of this technic. In 1968 before this association, we reported our experience in 18 patients using both intravenous and intra-arterial injections of the dye which produces a bluish coloration in normal, adenomatous and hyperplastic parathyroid glands.[26] Experience with the dye revealed that myocardial depression, as evidenced by T-wave depression, negative chronotropic effect, myocardial irritability and A-V node depression may accompany its use in patients with arteriosclerotic heart disease, or in dosages above 7 mg./Kg. body weight. We feel that it is safe to use the dye in patients with normal renal and caordiovascular function. Following induction of anesthesia, an infusion of 7 mg./Kg. body weight of toluidine blue in 500 cc. of physiologic saline is given intravenously over a period of 60 to 90 minutes. This can be discontinued when the tumor and the glands are identified. Another effective way is to give the infusion in the hour prior to the onset of the operation. The reason for this is that while the parathyroids stain first, the thyroid also takes up the dye, but the color differential may be very slight. The thyroid gland clears quickly so that if the dye is given prior to operation, the thyroid usually has regained normal color leaving the parathyroids stained for several hours. All of the adenomas and hyperplastic parathyroids have stained in our experience, but in a few instances, normal or atrophic parathyroids have not taken up the dye. Whether the failure to stain is due to interference with blood supply at the time of operation or due to the atrophy and fatty infiltration of depressed glands is not known. Thyroid cysts stain selectively and lymph nodes occasionally take up the dye. In one patient with carcinoma of the thyroid, the tumor and lymph glands replaced with carcinoma stained readily. This raises a problem with the use of the dye in operations for thyroid cancer if both the parathyroid and the lymph nodes in the tracheo-esophageal groove of the involved side stain. Obviously, on the involved side all stained tissue needs to be removed. On the uninvolved side, biopsy of stained tissue would be necessary prior to its removal to differentiate between parathyroid and carcinoma. At the present time, we have toluidine blue ready for parathyroid operations and are prepared to go ahead with the infusion if needed providing there are no contra-indications. The contra-indications consist of heart disease, cardiac arrhythmias, or compromised renal function as the dye is cleared through the kidney. We routinely use the dye for a second exploration. mediastinotomy for adenoma, or for a radical resection for thyroid carcinoma.

Surgical Experiences

Of the 75 surgical cases, eight adenomas were found incidental to other operations. These patients were asymptomatic and all did well after removal of the tumors. Of

the 67 instances diagnosed before operation, 61 patients were cured at first operation. Three were cured at second operation, one by subtotal thyroidectomy for a suspected intra-thyroid adenoma, and two at mediastinotomy after negative neck exploration at first operation. Two patients died after operation from complications arising from undetected adenomas. In one instance, the patient had a MEA syndrome undetected at the time of operation for hypercalcemia. One parathyroid adenoma was found and removed. Postoperatively the calcium remained high, and a peptic ulcer exacerbated due to the islet cell tumors and an overlooked parathyroid adenoma. Severe bleeding from the ulcer followed and subtotal gastric resection was carried out. The bleeding continued postoperatively from further ulceration and the patient died. If the full extent of the disease had been recognized preoperatively, if both parathyroid adenomas had been found at the first operation, or if a total gastrectomy had been performed at the second operation, a more satisfactory outcome might have resulted. The remaining patient was operated upon because of a nodular goiter and hypercalcemia. The nodule proved to be a thyroid carcinoma and a total thyroidectomy and a unilateral neck dissection were carried out. A normal parathyroid was also removed. Postoperatively, the patient developed acute pancreatitis which resulted in a fatal outcome. At autopsy a parathyroid adenoma was found which was thought to be related to development of acute pancreatitis. Operation on the remaining patient has been deferred for the present.

Surgical Technic

The points that we wish to emphasize regarding operation for parathyroid tumors include careful dissection and complete hemostasis. Adequate exposure in most instances is easy to obtain as the thyroid gland is usually normal. In approximately 20% of the cases, concurrent thyroid pathology may cause technical difficulties. Division of the strap muscles and mobilization of the upper lobes of the thyroid by dividing the superior thyroid vessels may be carried out electively to provide good exposure.

Rolling the lateral thyroid lobes forward by the use of carefully placed traction sutures following division of the lateral thyroid veins will permit satisfactory visualization of the tracheo-esophageal groove, the recurrent laryngeal nerve, the inferior thyroid artery, and the parathyroid glands. We feel that each parathyroid gland or adenoma should be identified by careful exposure so that the vasculature will not be injured and require that biopsy and frozen section be done to confirm the diagnosis. In a small or atrophic gland, biopsy may require delicate technic and the use of iris scissors and fine forceps will eliminate injury to the gland. Pressure is preferred to control bleeding after biopsy rather than by application of a hemostat.

The enlarged inferior thyroid artery frequently may indicate the path to the parathyroid adenoma, as has been pointed out by State.[24] If the adenoma cannot be found and if all four cervical parathyroids have been identified, we prefer to perform an 80% subtotal thyroidectomy. In our experience, three adenomas have been found within the thyroid gland and have been removed by subtotal thyroidectomy. If the serum calcium does not return to normal after thyroidectomy, then an exploration of the mediastinum should be carried out. In a few instances, an adenoma may be found by palpation and inspection of the superior mediastinum through the cervical incision as was possible in two of our cases. In cases of hyperplasia, we follow the generally accepted plan of removing 3½ of the glands We have not removed grossly normal parathyroid glands thus far and have no reason to change our approach despite the observation of Haff, Block and Ballinger.[8] In

situations in which the residual parathyroid tissue may be insufficient to prevent tetany, the technic described by Cope [3, 4] is useful. A small amount of parathyroid adenoma or hyperplastic parathyroid tissue is transplanted into an accessible area where it can provide necessary parathormone if needed and can easily be resected in case the serum calcium does not return to normal.

Postoperative Complications

Sixteen patients developed hypoparathyroidism, 12 were temporary and four were persistent. If the patient develops signs of hypoparathyroidism, they are given intravenous calcium gluconate. In some instances the hypocalcemia will be corrected as the remaining atrophic glands return to normal function. If the hypoparathyroidism is more persistent, the patients are maintained on oral calcium intake for 4–6 weeks. This allows the remaining parathyroid tissure to develop to supply the needs of the patient. If all of the parathyroid tissue is absent, then persistent hypercalcemia will result and will require continued administration of the calcium and vitamin D or a homologous transplant. The remaining complications were wound infection in six cases, laryngeal nerve injury in two patients (one temporary and one persistent).

Comments

Parathyroid tumor has been diagnosed with a high degree of accuracy and this credit is due the internists and endocrinologists associated with these cases. The number of negative explorations, although not accurately known, is small and usually has followed a casual work-up. The operative procedure is a relatively simple, gratifying, exercise and it is only in the unusual case that technical difficulties arise. This occurs in patients undergoing second explorations or when the tumors are abnormally located. In these instances, surgeons experienced in the vagaries of the disease can prevent disastrous results. Most of our serious complications occurred when unexpected situations were encountered such as in patients with MEA syndromes in whom parathyroid operations precipitate exacerbation of other difficulties. For example, patient with islet cell tumors and parathyroid adenomas or in situations when thyroid carcinoma is found and treatment of adenomas is overlooked. Here again, previous experience with the situation may avoid a fatal outcome. Consequently, it is our recommendation particularly in teaching hospitals that clinicians experienced in the diagnosis and treatment of parathyroid tumors should participate in the therapeutic team.

Summary

From January, 1942, through June of 1970, 100 patients with parathyroid tumors were treated at the Charity Hospital of Louisiana. Seventy-five were clinical cases and 25 were found at autopsy. Sixty-six diagnoses were confirmed at operation, eight adenomas were found incidentally to other operations on the neck and one patient remains under observation. Fourteen of the patients brought to autopsy had no symptoms of parathyroid tumors. Forty-three clinical patients were treated since 1965, while only four instances were found at autopsy indicating an improved diagnostic record.

There were 96 cases of adenoma, three of hyperplasia, and one of carcinoma. Three patients with adenomas had hyperplastic glands as well. Three adenomas were within the capsule of the thyroid gland and four were found in the upper mediastinum. Renal stones, peptic ulcer, weakness, increased fatigability and mental confusion were the most prominent complaints. There were six patients with acute parathyroid crisis. Three survived after operation.

Seven patients had MEA syndrome, five are dead of the disease or complications subsequent to operation relating to the syndrome including one of the patients with acute parathyroid crisis.

Twenty-one patients had associated thyroid disease including 15 who had goiters and five with thyroid cancer. In all, 18 patients had 21 concomitant cancer disease. Of 66 patients in whom the disease was diagnosed and treated surgically, 61 were cured at first operation and three were cured at second operation; an adenoma was removed from the mediastinum in two instances and at thyroidectomy an intracapsular adenoma was removed in the third patient. One died from complications after failure to remove a second undetected adenoma. Another died from complications, after failure to remove an adenoma, when attention was directed to treatment of a concurrent thyroid cancer.

Postoperative complications consisted of 12 cases of temporary and four cases of permanent hypocalcemia. Six patients had wound infection and two patients had laryngeal nerve injury, one was permanent.

References

1. Barreras, R. F. and Donaldson, R. M.: Effects of Induced Hypercalcemia on Human Gastric Secretion. Gastroenterology, **52**:670, 1967.
2. Berson, S. A., Yalorv, R. S., Aurbach, G. D. and Plott, J. T., Jr.: Immunoassay of Bovine and Human Parathyroid Hormone. Proc. Nat. Acad. Sci., M.S., **49**:613, 1965.
3. Cope, O.: The Thyroids and Parathyroids, *in* Warren, R.: Surgery. W. B. Saunders, 1963.
4. Cope, O.: The Story of Hyperparathyroidism at Massachusetts General Hospital. New Eng. J. Med., **274**:1174, 1966.
5. Donegan, W. L. and Spiro, W. M.: Parathyroids and Gastric Secretion. Gastroenterology, **38**:750, 1960.
6. Eliel, L. P. and Thomsen, C.: Urinary Excretion of Parathyroid Hormones in Man; Effects of Calcium Loads, Protein Free Diets, Adrenal Cortical Steroids and Neoplastic Diseases. J. Clin. Endocr., **25**:445, 1965.
7. Gonder, F., Brannan, W., Ochsner, M. G. and Riddick, F. A., Jr.: Primary Hyperparathyroidism at the Ochsner Clinic: Experiences with 100 Cases. South. Med. J., **63**:1329, 1970.
8. Haff, R. C., Black, W. C. and Ballinger, W. F., II: Primary Hyperparathyroidism: Changing Clinical, Surgical, and Pathological Aspects. Ann. Surg., **171**:85, 1970.
9. Haynie, T. P., Otte, W. K. and Wright, J. C.: Visualization of Hyperfunctioning Parathyroid Adenoma using Se^{75}-Selenomethionine and the Photoscanner. J. Nuc. Med., **5**:710, 1964.
10. Howard, J. E., Follis, R. H., Jr., Yendt, E. R. and Conner, T. B.: Hyperparathyroidism: Case Report Illustrating Spontaneous Regression due to Necrosis of Adenoma, and Study of Incidence of Necrosis in Parathyroid Adenomas. J. Clin. Endocr., **13**:997, 1953.
11. Hurvitz, R. J., Perzik, S. L. and Morgenstern, L.: In Vivo Staining of the Parathyroid Glands. Arch. Surg., **97**:722, 1968.
12. Klopper, P. J. and Moe, R. E.: Demonstration of the Parathyroid during Surgery in Dogs, with Preliminary Report of Results in Some Clinical Cases. Surgery, **59**:1101, 1968.
13. Krementz, E. T., Race, J. L., Sternberg, W. H. and Hawley, W. D.: Parathyroid Adenoma: Problems in Diagnosis and Management. Ann. Surg., **165**:681, 1967.
14. Latimer, R. G., Renning, J., Stevens, L. E., Northway, J. D. and Reemtsma, K.: Tertiary Hyperparathyroidism Following Successful Renal Allografting. Ann. Surg., **172**:137, 1970.
15. Laughlin, J. S., Rotter, F. W., Dwyer, A. J., Mayer, K., Greenberg, E. G., Dunnick, A. B., Hasan, S., Rothschild, E. and Meyers, W. P. L.: Development and Application of Quantitative and Computer-analyzed Counting and Scanning. Cancer, **25**:395, 1970.
16. McPhaul, J. J., McIntosh, D. A., Hammond, W. S. and Park, O. R.: Autonomous Secondary (Renal) Parathyroid Hyperplasia. New Eng. J. Med., **271**:1342, 1964.
17. Madhaven, T., Frame, B. and Block, M. A.: Influence of Surgical Correction of Primary Hyperparathyroidism on Associated Hypertension. Arch. Surg., **100**:212, 1970.
18. Mandl, F.: Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis Fibrosa (unter besonderer Berucksichtigung der Therapie der letzteren). Arch. Klin. Chir., **143**:245, 1926.
19. Payne, R. L., Jr. and Fitchett, C. W.: Hyperparathyroid Crisis: Survey of the Literature and a Report of Two Additional Cases. Ann. Surg., **161**:737, 1965.
20. Potchen, E. J.: The Pre-operative Localization of Parathyroid Tumors. Progress in Clin. Ca., **4**:160, 1970.
21. Reiss, E. and Canterbury, J. M.: Primary Hyperparathyroidism. New Eng. J. Med., **280**: 348, 1969.
22. Reitz, R. E., Pollock, J. J., Wang, C. A., Heischli, D. J., Cope, O., Murray, T. M., Deftos, L. J. and Potts, J. T., Jr.: Localization of Parathyroid Adenomas by Selective Venous Catheterization and Radioimmunoassay. New Eng. J. Med., **281**:348, 1969.
23. Seldinger, S. I.: Localization of Parathyroid Adenoma by Arteriography. Acta Radiol., **42**:353, 1954.
24. State, D.: The Enlarged Inferior Thyroid Artery, A Valuable Guide in Surgery of Parathyroid Adenomas. Surgery, **56**:461, 1964.
25. Wermer, P.: Genetic Aspects of Adenomatosis of Endocrine Glands. Amer. J. Med., **16**:363, 1954.
26. Yeager, R. M. and Krementz, E. T.: Toluidine Blue in Identification of Parathyroid Glands at Operation. Ann. Surg., **169**:829, 1969.
27. Yeager, R. M. and Krementz, E. T.: Acute Hyperparathyroidism. Southern Med. J. (In Press).