Primary Hyperparathyroidism in the 1990s
Choice of Surgical Procedures for This Disease

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Many advances have occurred in recent years in the diagnosis, localization, and treatment of primary hyperparathyroidism. Several different operative choices for primary hyperparathyroidism also have been proposed—a unilateral approach versus the standard bilateral parathyroid exploration. The unilateral approach is based on the concept that if an enlarged parathyroid gland and a normal gland are found on the first side of the neck that is explored, then this is an adenoma and the second side should not be explored. Only if both glands on the initial side are recognized to be abnormal is the second side explored. The theoretical advantages of this unilateral approach are a decrease in operative morbidity rates—hypoparathyroidism and nerve injuries—and a decrease in operative time. Furthermore, proponents argue that if persistent hyperparathyroidism occurs, the second side can be easily explored because it was previously untouched. In the hands of several expert parathyroid surgeons, excellent results have been achieved. However, the unilateral approach has a number of disadvantages. It places considerable pressure on the surgeon and pathologist, for they have only one parathyroid gland other than the large one to examine. There is a significant potential risk of missing double adenomas or asymmetric hyperplasia because the second, ipsilateral parathyroid gland may appear normal or near normal in these conditions. This could lead to an increased incidence of persistent or recurrent hyperparathyroidism. Furthermore, a significant reduction of operative time may be questioned, especially when the time for performing special fat stains, which often are performed with unilateral explorations, is added. Finally, even if the intent is to perform a unilateral exploration, a bilateral exploration will be necessary about half of the time. The authors strongly recommend a bilateral parathyroid exploration for all patients undergoing an initial parathyroid operation. In cases of adenoma, bilateral visualization of normal parathyroid glands and careful biopsy of only one of them will minimize hypoparathyroidism. This operative approach will lead to better results, especially for the less experienced parathyroid surgeon.

Surgery for primary hyperparathyroidism (HPT) is usually one of the most gratifying of all operations; however, at times, it can be one of the most frustrating. Parathyroidectomy has been practiced for about 65 years. During that time, a great deal of knowledge of the anatomy, embryology, pathology, and physiology of this disease has been acquired. The measurement of circulating parathyroid hormone (PTH) by radioimmunoassay made the diagnosis much easier. The use of newer assays for parathyroid hormone (midmolecule and immunoradiometric assays [IRMA] assays) and for parathyroid hormone-related peptide (PTH-RP), which is elaborated by some nonparathyroid cancers, has made the diagnosis of primary HPT more exact and the chance of misdiagnosis far less common. Localization studies of enlarged parathyroid glands have improved in recent years, but problems of accuracy are still associated with their use. No single study in general use has been demonstrated to be more than about 80% accurate, and each procedure is associated with both false-positive and false-negative results of varying incidences.

In the face of these improvements, it is not surprising that changes in the philosophy and practice of parathyroidectomy have been suggested. Foremost among these is the use of unilateral neck exploration, often guided by localization studies, if the surgeon thinks that an adenoma is present on that side. This report surveys the potential strengths and weaknesses of this approach and compares it with bilateral neck exploration. Because a randomized study comparing these surgical approaches has not been performed, the following comments represent the opinions of the authors based on their personal experience and on a review of the literature. First of all, there is no substitute for experience. Although unilateral
parathyroid exploration has been practiced with great success by experts such as Professors C. A. Wang and Sten Tibblin, the authors believe that the chance of failure when practiced by less sophisticated parathyroid surgeons far outweighs any potential benefit. The use of bilateral neck exploration with careful, judicious use of parathyroid biopsy of only one normal appearing gland when an adenoma is present greatly decreases the chance of missing asymmetric hyperplasia or double adenomas, results in a low incidence of postoperative hypocalcemia, and gives superior results, especially for the less experienced parathyroid surgeon.

**Historical Perspective**

In 1925, the first parathyroidectomy was performed in Vienna on "Albert," the now famous trolley car operator. Albert had developed severe bone disease, a condition that was thought by many pathologists at that time to be due to parathyroid insufficiency. Only after failure of injections of parathyroid extract and the failure of a parathyroid transplant was surgical excision considered. In 1925, a parathyroidectomy was performed by a young surgeon, Dr. Felix Mandl. One large gland was removed, and the operation resulted in symptomatic improvement of Albert's condition for about 6 years; then his bone problems recurred. 

The first patient who was operated on in the United States for primary hyperparathyroidism was a merchant marine captain, Charles Martell. Over the years, Captain Martell had developed a debilitating bone disease, with severe pain, "brown tumors," fractures, and kyphoscoliosis. He was recognized to have hypercalcemia and hypophosphatemia. These blood abnormalities, it was noted, were similar to changes that occurred when parathyroid extract was given to children with chronic lead poisoning to mobilize lead from their bones. They too developed hypercalcemia and low circulating phosphate levels. Thus it was postulated that Martell had an overactivity of the parathyroid glands. Unaware of the successful parathyroidectomy in Vienna, doctors at Massachusetts General Hospital explored his neck in 1926. Unfortunately, only normal structures were found. Five other unsuccessful neck operations were performed over the following years until, in 1933, a large parathyroid gland was found in his mediastinum. Ninety per cent of it was resected; the remaining part was intentionally left in place to try to prevent tetany. Despite this, as might be expected in a patient with very severe bone disease, postoperative tetany occurred. Six weeks later, Charles Martell died in chronic renal failure after an operation to remove a kidney stone that had blocked his ureter.

How ironic it seems that the first two patients who were operated on for primary hyperparathyroidism had serious difficulties associated with their surgical therapies. The same problems still concern us even today. Albert appears to have demonstrated recurrent hyperparathyroidism. Charles Martell had an ectopic parathyroid adenoma and required multiple neck operations with removal of most, if not all, of his normal parathyroid glands before it was found in his chest. Severe hypocalcemia, which was difficult to treat, followed removal of most of this mediastinal tumor.

**Prevalence**

Primary HPT is no longer an uncommon disease. In fact, it appears to be the most common cause of hypercalcemia in nonhospitalized patients. It occurs in about 1 in every 500 women over 40 years of age and in about 1 in every 2000 men.

**Symptoms**

When first described, primary HPT was a disease of the bones. It soon became apparent, however, that kidney stones were more common than severe bone disease. Gradually other symptoms and signs were added to this syndrome, largely because of the work of Oliver Cope and his associates (Table 1). Later, an increased incidence of chondrocalcinosis, pseudogout, and gout was recognized as well.

As medical students, we all learned that primary HPT is associated with "painful bones, renal stones, abdominal groans, and psychic moans." Today many other individuals are discovered to have this disorder because of the recognition of hypercalcemia on multiphasic chemical blood screening tests. Many of these patients are thought to be "asymptomatic" by their physicians. By this designation, many physicians mean that they have none of the classical symptoms and signs that are listed in Table 1. However, a careful history often discloses subtle or even profound symptoms of fatigue, weakness, depression,
polyuria, polydipsia, arthralgia, or constipation. Further testing often shows an accelerated course of osteoporosis. Studies from Uppsala, for example, have documented that alterations in neurotransmitter levels comparable to those found in endogenous depression are present in patients with primary HPT. These abnormalities, they have shown, revert to normal after successful parathyroidectomy. Thus, the definition of "asymptomatic" in patients with primary parathyroidism often differs according to "the eye of the beholder."

Diagnosis

To be successful, the clinician must diagnose those individuals who have primary hyperparathyroidism and distinguish them from the many others who have hypercalcemia of other causes (Table 2). The diagnosis of primary HPT is usually made by findings of elevated serum calcium levels associated with elevated parathyroid hormone concentrations. The newer assays for circulating parathyroid hormone have made the diagnosis of primary HPT much more secure. In our laboratory, an elevation of midmolecular PTH in patients with hypercalcemia has correlated very well with primary hyperparathyroidism. The newer, double-antibody IRMA assays that measure intact PTH may be even more exact, for they are less influenced by the presence of renal failure or renal impairment. Using this new assay, it may be possible to measure changes in circulating PTH intraoperatively after removal of all abnormal parathyroid glands to assure that the operation has been curative. This procedure has not yet been perfected, however.

The importance of properly measured serum calcium values in the chemistry laboratory cannot be overemphasized. Sometimes hypercalcemia may be subtle, although symptoms such as repeated kidney stones may be severe. The better laboratories usually have upper levels of serum calcium concentrations of 10.3 mg/dL or less. In most such laboratories, the diagnosis of normocalcemic hyperparathyroidism is very uncommon. In cases of hypoproteinemia, an elevation of ionized calcium levels may be diagnostic of primary HPT in the face of normal total calcium levels.

Serum phosphate levels are low in about 80% of cases. Alkaline phosphatase values are not often elevated, only when severe bone disease is present. In virtually all cases of primary HPT, the urinary calcium output is 200 mg/day or greater when the patient eats a standard diet. Values lower than these are suggestive of familial hypocalciuric hypercalcemia, a condition that should not be treated surgically.

A list of the differential diagnoses of hypercalcemia is shown in Table 2. A detailed discussion of each disease state is beyond the scope of this paper. It should be observed, however, that although metastatic bone disease is the most common cause of hypercalcemia in hospitalized patients, primary HPT is the most common cause of hypercalcemia among outpatients and is the second most common cause in the hospital setting. An uncommon but difficult problem in the past has been the fact that some tumors elaborate a PTH-like peptide that is thought to be the cause of hypercalcemia. A recently discovered peptide, PTH-RP, can be measured in the blood of many such patients and can be used to differentiate them from others with primary HPT; thus inappropriate parathyroidectomy can be avoided.

Indications for Parathyroidectomy

The purpose of the parathyroidectomy in primary HPT is to restore the patient to a normocalcemic, euparathyroid state and to reverse the symptoms associated with this disease. With correction of the hyperparathyroid state, most but not all of the symptoms and signs of the disease are reversed (Table 3). Bone disease (osteitis) is universally benefited. Roentgenographic evidence is seen of healing of bone cysts; the "salt and pepper" osteolysis of the skull, and subperiosteal bone resorption are corrected. Patients with nephrolithiasis develop far fewer new stones. Renal function also has been shown to improve in some studies, but not in all. Malaise, fatigue, weakness, and depression, often classified as neuropsychiatric symptoms, improve or disappear in as many as three fourths of patients. Up to half of all peptic ulcers will improve or heal. Uric acid levels decrease in many individuals. Nausea, polyuria, polydipsia, and constipation are frequently relieved. Only hypertension, seen in many patients with this disease, is not benefited in most patients with primary hyperparathyroidism.

<table>
<thead>
<tr>
<th>TABLE 2. Differential Diagnosis of Hypercalcemia</th>
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<tbody>
<tr>
<td>Malignancy</td>
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<tr>
<td>Solid tumors with or without bony metastases</td>
</tr>
<tr>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Lymphomas and leukemias</td>
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<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
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<tr>
<td>Hyper- and hypothyroidism</td>
</tr>
<tr>
<td>Addison's disease</td>
</tr>
<tr>
<td>VIPomas, pheochromocytoma</td>
</tr>
<tr>
<td>Granulomatous disease</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Increased intake</td>
</tr>
<tr>
<td>Calcium</td>
</tr>
<tr>
<td>Vitamin D and vitamin A intoxication</td>
</tr>
<tr>
<td>Milk alkali syndrome</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Benign familial hypocalciuric hypercalcemia</td>
</tr>
<tr>
<td>Paget's disease with immobilization</td>
</tr>
<tr>
<td>Thiazides</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
</tbody>
</table>

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Because of the success of parathyroidectomy, most clinicians believe that if a patient is symptomatic and is not a prohibitive medical risk, a parathyroidectomy should be performed. Some differences of opinion exist about the value of parathyroidectomy for patients who are asymptomatic. Scholz and Purnell at the Mayo Clinic demonstrated, for example, that about half of the asymptomatic patients with clear hyperparathyroidism who could be successfully followed for 10 years developed some problem associated with their disease. They recommended parathyroidectomy in such patients because follow-up was difficult and the operation was very successful at their institution. Other studies have demonstrated the value of parathyroidectomy in patients with primary hyperparathyroidism and asymptomatic osteoporosis, as measured by bone densitometry. Not all investigators agree, however. Thus, the value of parathyroidectomy in truly asymptomatic patients is still being debated. All agree, however, that the most important prerequisite for success is an experienced parathyroid surgeon.

**Pitfalls for the Surgeon**

Difficulties associated with parathyroidectomy for primary HPT relate to the variability in the number of parathyroid glands, the different locations of normal and pathologic glands, and problems distinguishing normal glands from others that are subtly diseased. To be successful, a parathyroid surgeon must have an excellent knowledge of the anatomy, embryology, and pathophysiology of the parathyroid glands.

**Number of Parathyroid Glands**

Gilmour, in an extensive autopsy study, found that roughly 80% of individuals had four glands, 6% had five, and 13% had three. Two glands or six glands were present very rarely. Other anatomists and surgeons have found more than six glands to be present in some cases. This variability creates difficulties for the surgeon in several situations. First of all, four normal glands may be present in the neck, whereas a fifth, a supernumerary gland, which is adenomatous, may be present in the mediastinum. This situation occurred in 5 of 14 mediastinal parathyroid adenomas that were reported from the Mayo Clinic prior to 1970, for example.

A second example in which the number of glands plays an important role is in primary parathyroid hyperplasia. Particularly in the multiple endocrine neoplasia type 1 (MEN-1) or other familial syndromes, recurrent hyperparathyroidism occurs frequently, even after subtotal resection of parathyroid glands in the neck. A thymectomy must be included as part of the standard parathyroidectomy for this condition to remove other parathyroid glands that might be present in this tissue.

**Location of Parathyroid Glands**

**Embryology.** The upper parathyroid glands arise embryologically from the dorsal part of the fourth branchial pouches, along with the lateral lobes of the thyroid, the ultimobranchial bodies (Fig. 1). They descend only slightly during embryologic life along with the thyroid and continue to remain in close association with the upper portion of the lateral thyroid lobes. Because of their relatively circumscribed migration, their position in adult life remains quite constant.

The lower parathyroids arise from the dorsal part of the third branchial pouches along with the thymus and they descend with the thymus. Because they travel so far in embryologic life, they have a very wide range of distribution in the adult. They may be found all the way from just beneath the mandible anterior to the carotid artery bifurcation, to the pericardium (Fig. 2). When the

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**Table 3. Response of Symptoms and Signs to Parathyroid Surgery at 5-Year Follow-up**

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Preoperative Prevalence (%)</th>
<th>Long-term Improvement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ronni-Sivula and Sivula (n = 289)</td>
<td>Lafferty and Hubay (n = 100)</td>
</tr>
<tr>
<td>Osteitis</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Renal calculi</td>
<td>34</td>
<td>18</td>
</tr>
<tr>
<td>Neuropsychiatric*</td>
<td>61†</td>
<td>21</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>35</td>
<td>49</td>
</tr>
</tbody>
</table>

* Includes fatigue, lethargy, malaise, weakness, depression, headache, irritability, and confusion.
† Combines malaise, fatigue, and weakness in 46% plus depression in 15%.

Adapted from Lafferty and Hubay.
lower parathyroid gland descends into the mediastinum, it is almost always anterior to the recurrent laryngeal nerve.

**Location of Normal Glands.** The average weight of a normal parathyroid gland is 35 to 50 mg. Some may be slightly heavier. They can be thought of as being about half the size of one's little fingernail; thus they are small and they can be difficult to identify. Normal glands are usually yellowish-brown and sometimes look like fat, particularly to the inexperienced eye. They are also difficult to find because of their various possible locations.

In most cases, the normal upper gland may be found on the posterior portion of the middle third of the thyroid, usually toward the superior part of this area, either under a delicate fascia on the thyroid lobe or on a projecting nodule. In embryonic life and may end up anywhere along the course of the dotted line. When this gland is in the chest, it is nearly always in the anterior mediastinum. Reprinted with permission from Kaplan.

The normal inferior parathyroid glands are more variable (Fig. 3A, B). In somewhat more than 50% of cases, the lower parathyroid is found on the lateral or posterior surface of the lower pole of the thyroid gland, or not more than 0.5 cm below the lower pole. The next most common location, in 12.8% of the cases, is within 1 cm below the lower pole of the thyroid. In most of the remaining individuals, the lower parathyroid gland is found within the tongue of the thymus (called the thyro-thymic ligament). The tongue of the thymus usually can be identified just below the lower pole of the thyroid gland on each side, adjacent to the inferior thyroid veins. Less frequently, normal inferior parathyroids can be located in the superior mediastinum within the thymus. Finally, rarely they are found high in the neck, the so-called undescended parathyroid glands.

Gilmour found that the parathyroids occasionally are included within the thyroid capsule or lie beneath it.
FIG. 3. (Left) Most frequent locations for the normal parathyroid (anterior view). The locations for the upper parathyroid are shown at the left and for the lower at the right. The relative frequency with which the glands are found in the various locations is indicated on the diagram. (Below) Most frequent locations for normal parathyroid glands (lateral view). Reprinted with permission from Gilmour.\textsuperscript{21}
Sometimes, a parathyroid is completely covered by the thyroid. These intrathyroidal lesions usually involve the inferior parathyroid glands. Normal lower parathyroid glands are usually anterior to the recurrent laryngeal nerves, whereas the upper parathyroid glands are usually situated more posteriorly.

Abnormal Parathyroid Glands. When parathyroid glands enlarge and become adenomatous or hyperplastic, their position can change. Large upper parathyroid glands frequently fall back, posterior to the recurrent laryngeal nerve and under the inferior thyroid artery, and are found along the esophagus down into the posterior-superior mediastinum. Lower parathyroid glands are displaced into the anterior-superior mediastinum, either separately or along with the thymus gland. Usually they remain anterior to the recurrent laryngeal nerves.

Although 80% to 85% of parathyroid adenomas are found adjacent to the thyroid gland in their normal locations, 15% to 20% are ectopically placed. Ectopic glands can be found in the anterior-superior mediastinum, either within or outside of the thymus, along the esophagus into the posterior-superior mediastinum, or very rarely in the middle mediastinum. Uncommonly they can be found within the carotid sheath or even lateral to the carotid sheath. Rarely, an "undescended" lower parathyroid gland is found high up in the neck, anterior to the carotid artery bifurcation. Finally, 3% to 5% of all parathyroid adenomas are intrathyroidal, usually within the lower pole of the thyroid gland. Fortunately, most of these can be felt or recognized as a mass within the thyroid lobe, but in other instances they are found only after thyroid excision or thyroidotomy. Locating and removing ectopic parathyroid glands during the initial neck operation remains one of the major pitfalls to successful parathyroid surgery.

Pathology of Primary Hyperparathyroidism

One of the most difficult aspects for the surgeon is the recognition of the pathologic process that is present, for appropriate treatment is dependent on this. Primary hyperparathyroidism may be due to a parathyroid adenoma, to hyperplasia of the parathyroid glands, or rarely to a parathyroid carcinoma. The symptoms of the disease are similar regardless of the actual cause.

Originally in the treatment of hyperparathyroidism, all patients were believed to have either single or multiple adenomas or water clear hyperplasia, the latter being a condition rarely if ever diagnosed today. Primary chief cell hyperplasia was not recognized as an entity until Cope and co-workers described it in 1958. Hence, studies that include data from before this time are misleading, for multiple enlarged glands were usually called multiple adenomas instead of hyperplasia.

In the late 1960s and early 1970s, the difficulties of diagnosing mild chief cell hyperplasia pathologically became evident. As shown in Table 4, the prevalence of chief cell hyperplasia varied considerably in series from different institutions, from 3% to 65%. It was finally concluded that the pathologists were being greatly influenced by the operation that was performed. When subtotal parathyroidectomy was performed routinely, more hyperplasia was diagnosed. When a more conservative operation was performed with removal of a single gland, it was most likely called an adenoma. The importance of mild hyperplasia and the best way of diagnosing this condition are questions that still are being debated.

Today, however, it is generally agreed that primary HPT is caused by a single adenoma in 80% to 85% of cases and that chief cell hyperplasia is found in 15% to 20% of cases. In the MEN-1, MEN-2A and the familial hyperparathyroid-

### Table 4. Relative Frequency of Parathyroid Adenoma, Hyperplasia, and Carcinoma in Reported Series

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>No. of Patients</th>
<th>Adenoma (%)</th>
<th>Primary Hyperplasia (%)</th>
<th>Carcinoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldman et al., 1971</td>
<td>96</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kreamentz et al., 1971</td>
<td>96</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hoehn et al., 1969</td>
<td>93</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Davies, 1974</td>
<td>90</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Palmer et al., 1975</td>
<td>90</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myers, 1974</td>
<td>82</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Werner et al., 1974</td>
<td>84</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang, 1976</td>
<td>82</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Romanus et al., 1973</td>
<td>81</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block et al., 1974</td>
<td>80</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruining, 1971</td>
<td>60</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haff and Armstrong, 1974</td>
<td>57</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esselstyn et al., 1974</td>
<td>51</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haff and Balingher, 1971</td>
<td>50</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paloyan et al., 1973</td>
<td>33</td>
<td>65</td>
<td></td>
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Reprinted with permission.
roidism syndromes, hyperplasia is the rule. Parathyroid cancer is found in less than 1% of cases in many series, including the authors' experience, but makes up 3% to 5% of others. Perhaps it is being overdiagnosed in some institutions.

Classically, an adenoma has been defined pathologically as an enlarged gland with a rim of normal tissue. However, Roth and other pathologists state that this histologic appearance can be found in cases of hyperplasia as well, and that it is not possible to tell the difference between hyperplasia and adenoma from looking at only one gland; other glands must be examined.

The greatest differences of opinion relate to what constitutes mild hyperplasia and whether or not mildly hyperplastic glands are of physiologic importance. Some pathologists consider normal-sized or mildly enlarged glands to be hyperplastic if they do not contain enough extracellular fat. Others do not feel that such glands are necessarily abnormal, and consider the amount of intracellular fat to be the most important criterion in this differentiation. Some pathologists use fat stains or osmium stains at the time of frozen section to evaluate intracytoplasmic fat in normal-appearing or mildly enlarged glands. However, the validity of these techniques has not been accepted by all pathologists, and they present some technical complexities as well. Many pathologists and surgeons believe that the differentiation of a mildly hyperplastic from a normal gland by frozen section examination is very difficult.

The major problem for the surgeon at the time of operation is to differentiate an adenoma from chief cell hyperplasia, or single gland disease from multiglandular disease of the parathyroids. In general, most experienced surgeons think that by evaluating the size, shape, and color of the parathyroid glands at operation, they can distinguish normal glands from abnormal ones. If one gland is enlarged and the others are perfectly normal visually and by biopsy with frozen section, this is an adenoma. If all glands are enlarged this is hyperplasia (or multiglandular disease).

A significant difficulty at the time of operation is that the glands of parathyroid hyperplasia may be asymmetric; not all of the glands exhibit the same degree of enlargement. Some, in fact, may appear normal or near normal. Bruining has demonstrated that two and three gland enlargements were present in a number of his cases (Fig. 4) Each of these patients had one or more normal or near normal appearing glands. Most authors agree that double adenomas occur in 5% or fewer cases; however, others believe that this represents a form of multiglandular disease. Thus, because the microscopic differentiation of an adenoma from hyperplasia is difficult when examining one enlarged gland and because frozen section differentiation of mild hyperplasia from normal is also very difficult, most surgeons believe that they play the major role as diagnostician as well as therapist. Obviously, the more glands the surgeon can see and evaluate, the more reliable will be the diagnosis and, hence, the treatment.

Localization Procedures

Clark and Duh have written an excellent summary of the advances that have been made in the preoperative localization of parathyroid tumors. With experienced radiologists and modern equipment, about 75% to 80% of all parathyroid tumors can be localized using either ultrasonography, thallium-technetium scanning, magnetic resonance imaging (MRI) or computed tomography (CT). In the best studies, using multiple techniques, as many as 80% to 90% of single parathyroid tumors have been identified.

In every series, however, both false-positive and false-negative results have been obtained. The tests are best when a single parathyroid gland enlargement is present, when the tumor is larger than 1 g in weight, and when no thyroid nodules are present. Only 20% of multiple gland enlargements are correctly identified. Thus, localization studies of patients with hyperplasia can be very misleading. Other problems relate to the small size of many parathyroid tumors, their position deep in the neck or chest, and the fact that thyroid nodules are frequently...
present, especially in elderly female patients, the very individuals who have the highest prevalence of primary hyperparathyroidism.

Ultrasonography is very operator dependent. Although experts may localize 80% or more correctly, others with less experience correctly localize far less than half.8 This technique is good only in the neck, and is best when a 10-MHz real-time, small parts scanner is used. It usually cannot identify small lesions, especially those deep in the neck or behind the esophagus. It cannot be used for lesions under the sternum. In some centers, needle aspiration of the suspected tumor is performed under ultrasound guidance. Cytologic examination and parathyroid hormone measurement of the aspirate may add to the certainty of the findings. The appearance of an intrathyroidal parathyroid on ultrasonography is shown in Figure 5.

Thallium-technetium scanning, although done in many hospitals, is very difficult to do well. Thallium (201TI) is taken up by both the thyroid and by enlarged parathyroid glands, whereas technetium (99mTc) pertechnetate is taken up only by the thyroid. Images with each isotope are obtained and then the technetium scan is subtracted from the thallium scan by computer analysis. What remains is the image of the enlarged parathyroid gland.

Potential problems with this technique create false-positive results in 10% to 20% of the cases. The patient must not move; for this reason we use a harness. Thyroid nodules interfere with the subtraction procedure. We have found, however, that this scan, when done well, is excellent for imaging ectopic parathyroid glands, those away from the thyroid gland (Figs. 6 and 7).

Although we have used CT examinations less frequently, these can be of value especially for mediastinal, substernal tumors (Figs. 7 and 8). Magnetic resonance imaging examinations do not require contrast material, and parathyroid tumors are usually bright on T2-weighted imaging (Fig. 9). In our experience, small tumor size, movement of the carotid arteries, and technical difficulties associated with the lower neck and upper chest make MRI examination less rewarding.

Venous catheterization with blood sampling for parathyroid hormone has largely been replaced by the other modalities; however, it still plays a role in lateralizing the side of the disease in very difficult cases. Arteriography is rarely done in our experience because of the potential for severe complications. Finally, we have not found toluidine blue or methylene blue used intraoperatively to be of value.

**To Localize or Not To Localize**

There is no question that localization studies should be used before all reoperative parathyroidectomies, or when one is contemplating parathyroidectomy in a patient who has had extensive thyroid surgery in the past (Fig. 10). This latter situation is not uncommon, because low-dose radiation to the neck is known to be followed by an increased incidence of both thyroid cancer and primary HPT.36,37 The mean latency period for development of the hyperparathyroidism is longer than for thyroid cancer, so that a number of individuals who have had total or near-total thyroidectomy may later need a parathyroidectomy. Correct localization of the enlarged parathyroid gland before reoperative parathyroidectomy, as reported by Levin and Clark,38 was between 45% and 68% for the various tests. Combinations of tests were better. Thus, although not perfect, localization studies greatly aid the surgeon and are mandatory before reoperative surgery.

When operating in the "virgin neck," most surgeons agree that there is no need to do localization studies. Common localization studies are about 75% to 80% accurate when done well. Because virtually all expert parathyroid surgeons cure 95% or more of such patients although they have not had localization studies, one could...
argue that the best localization procedure is to find an excellent parathyroid surgeon. Furthermore, it has not been demonstrated uniformly that localization tests save time intraoperatively. Finally, the cost of both an ultrasound and a thallium-technetium scan at our institution is nearly $1100.00. On the other hand, by doing ultrasound preoperatively, a small number of intrathyroidal parathyroid adenomas may be localized, whereas a thallium-technetium scan may recognize the occasional "ectopic" gland. We use these studies especially in cases of hyperparathyroid crisis, for example. Thus, although not cost effective, preoperative localization tests may help a small number of patients.

There is a potential down-side, however, to the routine use of preoperative localization testing in patients who have not previously had surgery. Apparent localization of
one enlarged gland may serve as an invitation for the inexperienced surgeon to venture into the neck to remove that gland, perhaps not realizing that hyperplasia may be present. Remember that multiglandular disease is missed by localization studies in 80% of cases.\textsuperscript{38} The first exploration is the best time to cure the hyperparathyroid state; the second parathyroidectomy is always much more difficult and less successful than the first.

Strategy of the Initial Parathyroid Exploration

The role of the surgeon in the first parathyroid exploration is to remove the offending gland or glands and thus cure the disease, or to assure himself or herself that no abnormal parathyroid tissue remains in the neck or in any ectopic location that might be reached by this exposure at the conclusion of a negative exploration.

Subtotal Parathyroidectomy

In the early 1970s, the incidence of parathyroid hyperplasia was found to be very high in a number of series.\textsuperscript{26} Paloyan and Pickleman\textsuperscript{39} proposed that correction of this condition required \textit{subtotal parathyroidectomy} for all patients if persistent and recurrent hyperparathyroidism were to be prevented. Although this operation could be performed with very low morbidity rate by many of its proponents, in the hands of other surgeons, perhaps those less experienced, it resulted in a higher incidence of post-
operative hypoparathyroidism. The subsequent use of cryopreservation of parathyroid tissue with the possibility of later reimplantation, and the use of autotransplantation of parathyroid tissue at the time of the initial operation, have greatly diminished this problem. Perhaps as a reaction to the proposal that all patients require subtotal parathyroidectomy, however, other operations were proposed or reexamined.

Unilateral Neck Exploration for Adenoma

Unilateral neck exploration is now practiced in 17% of the major parathyroid centers around the world, but mostly in Scandinavia and other European centers. Wang and Tibblin et al. have long advocated that only one side of the neck be explored when an adenoma and a normal gland are found on the same side. These surgeons have considerable experience, and in their hands, the results of operation are excellent. They contend that the unilateral approach reduces operating time and hence, patient costs. Furthermore, they believe that the morbidity rate (recurrent laryngeal nerve injuries and postoperative hypoparathyroidism) is lessened, and the results of parathyroidectomy are just as good as with bilateral exploration. Reoperation, they believe, is not a problem, because the second side was untouched.

Wang recently presented data that demonstrated that he performed a unilateral exploration in 70% of 800 first-time parathyroid explorations for adenoma. In these operations, he had a 4% failure rate. In 30% of the time...
when an adenoma was present, (262 of 800 cases), he performed a bilateral operation, either because he explored the wrong side first, because the second gland on the ipsilateral side could not be identified, or because the adenoma was in an ectopic position. Six per cent of these 262 patients had persistent hyperparathyroidism, largely due to ectopic parathyroid adenomas in the mediastinum. This is clearly a superb series. If one adds the patients who had hyperplasia to the 30% who required exploration of both sides for adenoma, however, it should be noted that, in as many as 50% of all cases of primary HPT, Professor Wang performs a bilateral neck exploration.

Potential problems exist with unilateral neck explorations. These include failure to recognize hyperplasia. As shown in Figure 4, hyperplasia often may be asymmetric. The second gland might look very normal to the surgeon, especially to an inexperienced surgeon. The surgeon has only one gland other than the large one to evaluate and thus could easily misinterpret it. Wang proposes the use of a “gradient solution” in which a normal gland floats and a hyperplastic gland sinks. Tibblin et al.42 emphasize the use of fat stains during frozen section. There also may be a failure to recognize double adenomas, a setting in which the two other glands are perfectly normal. These occur in 2% to 5% of cases in some series43,45 and in 9% of patients over 65 years of age in the Michigan series.35 Both hyperplasia and cases of double adenoma are much easier to diagnose, opponents argue, if both sides are examined. It has been estimated that exploration of the second side adds only 12 to 20 minutes of operating time. Finally, the practice of using localization studies to determine the side of the enlarged gland followed by unilateral exploration on this basis8 may lead to increased numbers of patients with persistent or recurrent hyperparathyroidism, for localization tests only recognize 20% of the cases of hyperplasia.5

Thus, there are potential dangers for those who use this technique, especially for the inexperienced surgeon. We tell our residents that when they are as experienced as Professors Wang and Tibblin, they may use a unilateral approach. Until then, they and we should look at both sides of the neck.

Bilateral Operations

In a recent survey, 83% of major centers performing parathyroidectomies for primary HPT reported that they use a bilateral neck exploration.42 This, they believe, permits a better assessment of the pathologic process that is present.

Initial Neck Exploration—The Authors’ Approach

All surgeons agree that a parathyroidectomy should be performed in an unhurried, careful, delicate way. The operative field should be kept as blood free as possible. At the University of Chicago Medical Center, a bilateral operation has been the rule. If one gland is enlarged and the others are normal, this is an adenoma. In the last 10 years, our operative approach for adenoma has changed. In the late 1970s, our aim was to search for all normal glands when an adenoma was present and to carefully perform biopsies on each of them. This technique was modified in the early 1980s, when we demonstrated that a lesser degree of transient postoperative hypocalcemia occurred when all normal glands were visualized but when biopsies were done on only one or two of them.9 We continue to be very pleased with this “middle ground approach,” which was favored by two thirds of North American parathyroid centers in a recent survey.42 In recent years we have performed biopsies on fewer normal glands.

If four glands are found to be enlarged, this is hyperplasia. In such cases, at least a subtotal parathyroidectomy is necessary. Three glands and part of the fourth are excised, leaving a well-vascularized remnant of about 50 mg tissue. Each thymic tongue also should be excised routinely as part of this procedure, to be certain that supernumerary parathyroid glands are not present. The partial resection of the parathyroid gland that is to be left always should be performed first, so that one can see that the remnant remains well vascularized before removing the other three glands. In cases of familial hyperparathyroidism or the MEN-I syndrome, one should strongly consider doing a total parathyroidectomy with an autotransplant of parathyroid tissue to the arm, as recommended by Wells et al.44 This technique is advantageous because it is known that recurrent hyperparathyroidism occurs with some frequency, especially in patients with these familial, genetically induced syndromes.23,24 If graft-dependent hyperparathyroidism recurs in the arm, this area can be explored under local anesthesia without the risk of a recurrent nerve injury, as would occur if the neck were re-explored. Wells et al.44 recommend this approach for all cases of hyperplasia, familial and otherwise.

So-called double adenomas occur in a nonfamilial setting when two glands are enlarged and two others appear perfectly normal, grossly and histologically. This multi-glandular disease is curable by removal of both enlarged parathyroid glands and biopsy of the two normal ones.

Search for Ectopic Parathyroid Glands

If an adenoma cannot be found in the usual locations at exploration, each normal parathyroid gland should be explored by biopsy and marked, and after positive identification as parathyroid tissue on frozen section, a diagram should be made of its location for later reference. Do not remove normal parathyroid glands; this complicates the situation when the adenoma is ultimately found. If three normal parathyroid glands are found and the
fourth cannot be located, the surgeon should assess whether an upper or a lower parathyroid gland on that side is missing.

Very frequently, it is an adenoma of the upper parathyroid gland that is overlooked. This may be found posterior to the esophagus, or it often falls down along the esophagus into the posterior-superior mediastinum. The mistake in this situation is that the dissection was not carried out deeply enough, back to the prevertebral fascia of the neck. When this is done near the upper pole of the thyroid, a finger can be inserted safely behind the inferior thyroid artery and posterior to the recurrent laryngeal nerve. In many instances, an adenoma is palpable beside or behind the esophagus, and this gland can be pulled up and easily removed.

If the missing gland is the lower parathyroid gland, as much of the thymus as possible should be pulled up into the neck and resected, because the inferior adenoma often is found within the thymus. If the adenoma still cannot be found, the dissection should be carried up in a cephalad direction to the hyoid bone, where occasionally an “undescended” lower parathyroid adenoma is found anterior to the carotid artery bifurcation. If this is still nonrewarding, the carotid sheath should be opened from the level of the clavicle upward. Occasionally, a parathyroid adenoma will be found, which cannot be palpated, because it is flattened out like a pancake. The area of the neck lateral to the jugular vein also should be explored, for we have identified two patients who had a parathyroid adenoma in this unusual location. Finally, the thyroid lobe on the side of the missing gland should be carefully palpated. Any lump within the thyroid should be excised, for this might represent an intrathyroidal parathyroid adenoma. Even if no lump is present, a “blind” subtotal resection of the thyroid lobe on the side of the missing gland should be performed. Sometimes a nonpalpable parathyroid adenoma will emerge. Others use a thyroidotomy and incise the lower pole of the thyroid rather than resecting it.

Remember that even if four normal glands are found in the neck, the surgeon should search all of these ectopic sites for a fifth gland that is adenomatous. Similarly, if four hyperplastic glands are found, these same sites should be explored because supernumerary glands may be present.

Only rarely should a sternotomy and formal mediastinal dissection be done as part of the first exploration. This procedure is probably indicated only if the patient is extremely ill from hypercalcemia that cannot be adequately managed medically. The reasons for this approach are several. First of all, rarely the diagnosis of hyperparathyroidism might be in error. Second, occasionally hypercalcemia regresses or is eliminated by the first neck exploration, despite the fact that no abnormal parathyroid tissue has been removed. This probably occurs when an adenoma is infarcted by accidental ligation of its arterial supply. Finally, it is well known that in almost all cases of persistent hyperparathyroidism, the offending gland or glands can later be removed through a neck incision, particularly if the first surgeon is not very experienced in this area. This approach is clearly illustrated in the Mayo Clinic series in which, until 1970, 1000 parathyroid explorations were performed and only 12 required a sternotomy, an incidence of 1.2%. At the Massachusetts General Hospital, 21% of cases of primary hyperparathyroidism involved ectopically placed parathyroid adenomas. Almost all of these, however, could be removed through a neck incision. Thus, do not rush to do a sternotomy as part of the first operation.

Reoperation for Persistent or Recurrent Hyperparathyroidism

Before reoperating, a number of factors that should be considered:

1. Be certain that the patient has primary hyperparathyroidism and not some other hypercalcemic state.
2. Be certain that the severity of the hyperparathyroid state warrants the risk of reoperative surgery.
3. Be certain that the patient does not have familial hypertopic hypercalcemia. If so, do not reoperate. Such patients are cured of hypercalcemia only by total parathyroidectomy and they usually have few complications of their disease state.
4. Carefully read the previous operative note and pathology report and understand how many normal or abnormal parathyroid glands on each side were identified histologically and how many of them were removed. Review the pathologic slides if at all possible. Is this a case of a missing adenoma, incompletely treated hyperplasia, or even a recurrence of a carcinoma?
5. Use localization studies extensively.

Strategy and Technique

Reoperations of the neck are more difficult because of the scarring, changes in anatomy, and loss of tissue planes that occur as a result of the first exploration, whether it was for a thyroid or a parathyroid disorder. Frequently, for example, the strap muscles will be densely adherent to the anterior surface of the thyroid lobes, making entry into the usual anatomic planes more difficult. Furthermore, the recurrent laryngeal nerve is in greater jeopardy because it may be encased in scar tissue, but especially because it might lie immediately beneath the strap muscles if the thyroid lobe was previously removed. Always evaluate vocal cord function preoperatively in such cases. Finally, because one’s knowledge of how many
viable parathyroid glands remain in the neck after the first exploration is often limited, the chance of creating permanent hypoparathyroidism after removal of one or more abnormal parathyroid glands found at re-exploration is increased.

Usually there is not a rush to reoperate, and it is better to allow some time to pass to permit the wound to heal, to re-evaluate the diagnosis, to perform localization testing, and to assess the findings of the previous operation. The location of parathyroid adenomas that were removed by Wang at reoperation are shown in Figure 11.

When reoperating, we almost always explore the neck again first, unless an adenoma is localized to the mediastinum or to another ectopic site preoperatively. When an experienced parathyroid surgeon did the initial operation and was "certain" that the lesion was not in the neck, it is much more likely to be found in an unusual location.

The prior transverse neck incision is used and subplatysmal flaps are elevated. The strap muscles are often adherent to the thyroid lobes; hence, instead of separating them in the midline, it is often easier to use a "lateral approach, as described by Fiend," and to dissect the vertical plane between the sternocleidomastoid muscle and the strap muscles (Fig. 12). Not infrequently, this plane is totally unscarred, and by retracting the carotid sheath laterally and the thyroid gland medially, a "fresh" area containing the recurrent laryngeal nerve and parathyroid glands sometimes will be entered. If this area is scarred, the dissection should be started as low in the neck as possible, because this region is often untouched. Once the recurrent nerve is identified, it can be safely followed in a cephalad direction. If the adenoma was not localized beforehand, a bilateral neck exploration may be necessary if it can be done safely. In the case of either positive localization or retrospective determination of the side of the neck of the missing gland, the cervical dissection might be started there initially and might be unilateral if an adenoma is found or if the dissection is technically very difficult.

One of the most rewarding maneuvers, one that should be done early, is to look for an upper parathyroid gland that has fallen down into the posterior superior mediastinum. Introduce one's finger downward behind the inferior thyroid artery along the esophagus into the posterior mediastinum as far as one can reach. Often the missing adenoma can be palpated here before it can be seen. This is the area in which many missing adenomas are found because the initial dissection was not carried out deep enough.

If this is unsuccessful, all of the sites already described under the heading The Search for Ectopic Parathyroid Glands should be explored. This involves pulling up and removing the thymus on each side into the neck,
dissecting as high in the neck as the hyoid bone, removing a part of one or both thyroid lobes, and opening and exploring the carotid sheath areas and even lateral to the carotid sheath. A careful neck re-exploration done in this manner will almost always yield the missing adenoma or the elusive hyperplastic gland or glands that remain.

Before the operation, consent should be obtained for a possible sternotomy, if that is your plan. Either a partial sternotomy to the third intercostal space or a complete sternotomy can be performed. First, the thymus and surrounding fat pads should be palpated. On several occasions, we were able to feel a mass, which proved to be the missing adenoma, and only a partial thymectomy was necessary. Otherwise, the entire thymus should be removed. If the parathyroid gland is not found therein, a posterior dissection then should be performed. Lesions have been found between the aorta and pulmonary artery, in the middle mediastinum, and even, very rarely, in an intrapericardial location. Needless to say, these dissections can be very long and tedious.

When an adenoma is found in the neck or chest, it should be totally removed. If at least one additional normal gland remains viable after the first operation, the patient will be normocalcemic with normal postoperative parathyroid function. This fact stresses the importance of not removing normal parathyroid glands during an unsuccessful initial operation.

If hyperplastic glands are identified at reoperation, a subtotal parathyroidectomy can be performed. Others prefer a total parathyroidectomy, arguing that if recurrence were to occur in a remnant that is left, this would necessitate a third neck operation. If total parathyroidectomy is used, or after removal of an adenoma when one thinks that no other parathyroid tissue remains, one has the option of either immediately autotransplanting some of the abnormal parathyroid to the arm after confirming that it is not a carcinoma, or else cryopreserving the tissue and waiting to see whether or not hypocalcemia occurs postoperatively. If permanent hypoparathyroidism occurs, a subsequent autotransplant to the arm would be employed.

Either of these approaches has advantages and disadvantages. In our hands, cryopreservation has not been developed to the extent described by Wells et al. and Brennan et al. Furthermore, reimplantation of tissue that has been cryopreserved is not always successful. Hence we would be more likely to use immediate autotransplantation if it were thought to be necessary, but only if we believed strongly that all other parathyroid tissue had been removed from the patient. The long-term prevalence of recurrent hyperparathyroidism when part of an adenoma or of a hyperplastic gland is used as an autotransplant to the arm remains a fruitful area for study.

Surgery for Parathyroid Cancer

Parathyroid cancer accounts for less than 1% of cases of primary HPT at the University of Chicago Medical Center and elsewhere, but has been reported to occur in up to 6% of cases in other series. A carcinoma often presents as a "sticky," adherent gland at operation. Often a thick, dense, fibrotic, whitish capsule is present.

If recognized or suspected intraoperatively, one should not enter its capsule, for local seeding of tumor is a common occurrence. The gland should be removed widely, taking the ipsilateral thyroid lobe with it. Ipsilateral lymph nodes should be dissected in the central compartment and perhaps in the lateral neck as well, for nodal spread can occur. Distant spread occurs to the lungs, bone, brain, and elsewhere. If hypercalcemia recurs after any parathyroidectomy for parathyroid carcinoma, metastases should be aggressively localized and resected, because there is no good therapy other than surgical excision. In general, death occurs from unrelenting hyperparathyroidism with all of the complications of this disorder, rather than from tumor spread itself.

Results of Parathyroidectomy for Primary Hyperparathyroidism

There is no question that the results of parathyroidectomy for primary hyperparathyroidism relate to the experience of the operator. In a recent report from Scandinavia, this is clearly shown. In centers that specialize in endocrine surgery, 90% of patients were normocalcemic, with mean follow-up of 4.4 years after their initial parathyroidectomy—6% were hypercalcemic and 4% were hypocalcemic. In contrast, in a general Scandinavian survey of all hospitals done at roughly the same time and with similar follow-up, 76% of patients were normocalcemic. In hospitals in which less than 10 operations for primary hyperparathyroidism were done each year, only 70% were normocalcemic at follow-up—15% had persistent or recurrent hyperparathyroidism and 14% had permanent hypoparathyroidism.

In a number of other studies from centers that have considerable experience in parathyroid surgery, approximately 95% of patients or more can be rendered normocalcemic by the initial operation. At the University of Chicago, for example, over 97% of the last 300 patients who had their initial exploration at our Institution were normocalcemic, 1 month or longer after operation. Recurrent hyperparathyroidism occurs infrequently in nonfamilial cases, but remains a problem in familial hyperparathyroidism and in others with the MEN-1 syndrome. In experienced hands, the complication rate is low in these initial operations. Permanent recurrent laryngeal nerve injuries occurred in less than 1%.
manent hypoparathyroidism has been reported to be 2% or less in a number of series, but is higher in others. Finally, the operative mortality rate is consistently far less than 1%. Reoperations for persistent or recurrent hyperparathyroidism are more difficult and have a greater potential for hypoparathyroidism, for recurrent nerve injuries, and for failure. Using advanced localization studies, however, up to 90% of these tumors may be found and corrected, in the best of series. Thus, the results of parathyroid surgery for primary hyperparathyroidism in the 1990s are excellent when done by experienced surgeons. As stated by Malmaeus and coworkers, "These findings strongly advocate special training and interest in parathyroid surgery in order to ensure success."

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