Presidential Address

Location, Location, Location

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THANK YOU, RICH, for your "kind" introduction. The Midwest Surgical Association is my favorite organization, and for you all to have elected me your President is an honor indeed. I first heard of the Midwest Surgical Association in 1980 when John Glover returned from Lincolnshire, having been the Harridge Lecturer, to describe this wonderful organization with an applicable clinical scientific program, but which also included the families of the members and offered a relaxed atmosphere for the members to get to know one another as something beyond "talking heads." I signed up immediately and have enjoyed immensely my association ever since. The Organization has grown with the times. Our membership has grown, and the definition of the Midwest has expanded from Michigan and Illinois such that we now have sizable contingents from Iowa, Minnesota, and Kansas, with our membership roles listing members from Pennsylvania to California. We continue to have a nice mix of "town and gown." Our scientific program has grown in sophistication but retains its strong clinical flavor and applicability to our practices. We each should be proud of his/her part in making the Midwest Surgical Association grow from a group that gathered in Champaign, Illinois to watch University of Illinois football games and talk about surgery, to a significant regional surgical society.

That said, I am then burdened as your President to discharge my one significant duty: the Presidential Address. Until this experience, I had always wondered why others in this circumstance always began their talks with explanations of what a daunting responsibility this was. Now I know. One is tempted to wax philosophical, addressing the weighty issues of our time. I considered this. A series of titles that came to mind included:

1. Managed Care: A New Paradigm for Excellence in Surgical Care and Education.
2. Operation Restore Trust: Bringing Honesty Back to Academic Practice.
3. The Nationalization of Health Care: Restoring Health to Our Country.

While I am told by the institutions with which I am associated that all of these statements are true and the way of the future, and that I should embrace them enthusiastically, my skepticism keeps me from doing so. In fact, the restructuring of our profession as a pawn for the political or economic advantage of others is an issue that I find almost terminally depressing. This hardly seems something that I should share with you in this venue. My own association with a large city public hospital brings to mind another issue: that of the importance of the public hospital in our health care system and its indispensability in a rounded surgical education. Yet I find that concept threatened by the current model of our health care system as a business opportunity that pays lip service to, but that disregards the consequences to the disadvantaged of our society and the education of the next generation of physicians. Again, this is a topic that depresses me and one that I am loathe to share with you, despite the fact that my daughter, Francie, initiated a literature search on these issues.

Having rejected philosophical issues, I am left with the subject chosen with great success by the majority of my predecessors in this position, that of my surgical hobby. In my case, this is parathyroid surgery, and the specific area which will occupy the next several minutes is parathyroid localization. My very first experience with the parathyroids as an intern was an unmitigated disaster, a fruitless 10-hour search by a then-inexperienced surgeon for a nonexistent parathyroid adenoma in a hypercalcemic patient, who, at post, was discovered to have myeloma. Although this was an issue of the ultimate localization problem, that of assuring preoperatively that the patient has the disease being sought, the experience left me with a sense of uneasiness with this operation even now, despite the relative frequency with which I perform it. My experiences during the remainder of my residency in Minneapolis, most with this year's Harridge lecturer, Jack Delaney, were fortunately considerably more encouraging. In Minneapolis, I was exposed to two localization techniques: (1) that of Rich Lillehei, "it's always left and inferior," and (2) functional localization with toluidine blue. As I recall, Rich's localization philosophy was the more likely to work. This is no longer

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the case, and I think that currently available localization techniques do, in fact, find the abnormal gland often enough to be helpful, and they are helpful particularly to the less confident parathyroid surgeon. It is my intent to outline the early development of parathyroid surgery, the evolution of techniques intended to help find the parathyroid glands, and to highlight these comments with our own experience in Indianapolis.

Parathyroid Glands: Their Existence and Morbid Anatomy

In 1850, Richard Owen, curator of the Hunterian Museum of the Royal College of Surgeons of London and the Hunterian Professor of Comparative Anatomy, was offered by the London Zoo a dead great Indian rhinoceros for dissection. In a subsequent article published in 1862 in the *Transactions of the Royal Society of London*, he described "a small, compact, yellow glandular body [that] was attached to the thyroid at the point where the veins emerged." Although unconfirmed by microscopic examination, this observation is regarded as the first mention of the structures subsequently to be known as the parathyroid glands. Unfortunately for Owen, his observation was unrecognized by the scientific community until after others had duplicated and expanded upon it. Independently, in 1877, Ivar Sandstrom, a 25-year-old medical student in Uppsala working during the summer as an assistant in the anatomy lab, discovered while dissecting the neck of a dog "a small hemp seed-sized structure which was included in the same capsule as the thyroid, but distinguished itself from it by a brighter color." Similar structures were found by Sandstrom in subsequent dissections of the rabbit, cat, ox, horse, and 50 humans. He noted that in humans, the glands were almost always four in number, and that their location, while usually near the inferior thyroid artery, could be quite variable. He even described glands up to 15 mm in diameter and described morphologic variations that would now be associated with parathyroid adenomata. He also suggested that the name "glandulae parathyreoidiae" be assigned to these structures, and his appellation has endured. Early parathyroid investigators and their patients tended not to fare well, and, following the publication of his findings in 1880, Sandstrom sank into depression and, in 1889, he committed suicide. In 1891, Friedrick von Recklinghausen reported on a series of patients with progressive skeletal degeneration. Among these patients was Herr Bleich, a 40-year-old mason, who died after sustaining multiple pathologic fractures. Described in the autopsy was, "at the left side of the neck below the thyroid gland, a reddish-brown tumor."

Surgical Localization

Perhaps the first surgical parathyroidectomy was memorialized by Wolfer in 1879 in his description of postoperative tetany in Billroth's first successful total thyroidectomy. The relationship of tetany to the parathyroids was determined by Gley, a French physiologist, who induced tetany and death in rabbits and rats by the selective destruction of the parathyroid glands. Recognizing the significance of this finding, and drawing upon careful dissections of the neck, Halsted stressed the importance of preservation of the glands and their blood supply from the inferior thyroid artery during thyroid operations. During the first quarter of the 20th century, pathologists in Europe and physiologists in North American slowly began to recognize the association between abnormalities of calcium metabolism and the parathyroid glands. European pathologists recognized the presence of enlarged parathyroid glands(s) in patients with various bone diseases. Erdheim, who ascertained the relationship of the parathyroid glands to calcium metabolism experimentally in rats, subsequently found evidence of parathyroid enlargement in patients dying with osteomalacia. He surmised that the enlargement of the glands was compensatory, and this principle was applied to other disorders of calcification, notably osteitis fibrosa cystica. Inevitably, this principle was applied therapeutically. The first patient to undergo surgery for osteitis fibrosa cystica was Albert, a streetcar conductor in Vienna. Based on the interpretations of Erdheim's work, the first intervention was to administer an extract of parathyroid glands of animals. When this failed and the surgeons became involved, he underwent, in 1924, the implantation of parathyroid tissue removed from a cadaveric donor. This procedure was performed by Felix Mandl, a surgical grandson of Billroth, again without success. Albert's deteriorating condition prompted Mandl to take the opposite tack and explore the neck and, on July 25, 1925, Mandl undertook the first planned neck exploration finding a parathyroid tumor. Albert's condition soon began to improve, validating the concept that the underlying defect in von Recklinghausen's disease of bone is a tumor of the parathyroid glands. Albert's bad luck unfortunately continued, and he suffered a relapse of his symptoms, ultimately succumbing to his disease. Subsequent review of the autopsy findings strongly suggested that the original tumor was not an adenoma, but rather a carcinoma.

Simultaneously in North America, a diverse group of physiologists were at work on the parathyroids. MacCallum and Voegtlin, in 1909, demonstrated in dogs the association among tetany, hypoparathyroidism, and hypocalcemia. They also demonstrated that the tetany in parathyroidectomized dogs could be relieved by the infusion of calcium. In 1924, Hanson and Collip, each working independently, successfully developed parathyroid extracts which, when injected into hypoparathyroid dogs, reversed the hypocalcemia, and Collip determined that normal dogs given an excess of the parathyroid extract became hypercalcemic. Greenwald subsequently showed that animals given parathyroid extract had increased levels of calcium in their urine, suggesting that the hypercalcemia was not simply the result of impaired renal excretion of calcium. Although the clinical syndrome of hyperparathyroidism was not known to exist in 1925, its characteristics were clear. The European patient Albert's counterpart in America was Charles Martell, an officer in the Merchant Marine, and an unfortunate man with all the stigmata of osteitis fibrosa cystica, who ultimately presented to the medicine service of Bellevue Hospital in New York City coming under the care of Eugene DuBois. Upon finding Captain Martell to be hypercalcemic, DuBois conducted a series of calcium balance experiments, and found results in concert with those of Collip and Greenwald. He concluded that Martell must have an excess of parathyroid hormone, thus making the clinical diagnosis on chemical grounds for the first time. Martell was referred to the Massachusetts General Hospital where, between 1926 and 1931, he underwent six unsuccessful surgical procedures with the removal of three normal parathyroid glands without effect on his hypercalcemia. Oliver Cope, a medical student and surgical house officer at the Massachusetts General Hospital during this time, noted that the surgeons performing the original procedure were unaware of Mandl's experience and were equally unaware of what they were looking for. Cope was taken under the wing of Churchill and sent to the anatomy lab to ascertain the appearance, location, and anatomic relationships of the parathyroid glands. During these dissections, he also noted the variability in the location of these structures, finding them in the "entire theoretic embryological distribution from high in the neck well above the thyroid upper pole, and down into the anterior mediastinum along with the thymus." With this background, he returned to the operating room with Churchill and, in 1932, performed six successful operations for hyperparathyroidism, including one on Martell, finally affirming the curative role of careful and thoughtful surgical exploration for this condition. During this seventh procedure on Captain Martell, Edward Churchill found and removed a mediastinal tumor. True to form, Martell became profoundly hypocalcemic postoperatively, a condition compounded by renal failure, and he died 6 weeks later following an operation to extract a ureteral stone.

While Martell's operative experience underscores the pitfalls in surgical exploration for hyperparathyroidism, the first successful parathyroidectomy based on the chemical diagnosis of hyperparathyroidism was performed by Isaac Olch at the Barnes Hospital in St. Louis on a patient named Elva Dawkins. At this operation performed on August 1, 1928, she was found to have an adenoma in the left inferior position. Although she too fared badly postoperatively, requiring calcium supplementation the rest of her life and ultimately succumbing to renal failure, the procedure was notable in that it was successful in confirming the presence of a parathyroid tumor in a patient expected to have one and in reversing the clinical hypercalcemic syndrome also as expected. It was in the article describing this case that the term "hyperparathyroidism" was introduced and the clinical syndrome of rarefaction of bone, cystic bone tumors, muscular weakness, increased urinary secretion of calcium, renal stones, and hypercalcemia described.

Over the next several decades, the typical and anomalous locations of the glands, the frequency of this variability, and its embryological basis were described. The operation was performed in more and more centers, but still relatively infrequently. With the advent of the multichannel analyzer in the early 1960s and the ready availability of serum calcium and phosphorous levels in everyone on whom it was run, there resulted a sudden large increase in the frequency of the diagnosis of hyperparathyroidism, current estimates of the incidence being 1 in 1000 in the general population. This and further advances in protein chemistry, which led to a reliable assay for parathyroid hormone, allowed the diagnosis to be made in settings other than metabolic units. With the diagnosis and ultimately the surgical treatment now being done in the community, the enthusiasm for help in locating the offending glands grew.

Anatomic Techniques

With the development of ever more exotic and complex radiographic technologies, each one of these has in its turn been used to seek the parathyroid glands, by and large only to be discarded. Although an adenoma may show up on a set of X-rays of the chest or soft tissues of the neck, such experiences are anecdotal and frequently appreciated only in retrospect. A more common approach in the past was the barium swallow or cine-esophagography, which would occasionally show an indentation of the esophagus by the occasional greatly enlarged superior gland lying in the tracheoesophageal groove. Given the size necessary to indent the barium column and the relative frequency of large glands in this position, the sensitivity of the test was accordingly low, and it has largely been abandoned.

Angiographic techniques have been employed, particularly in the case of second explorations. Both conventional and digital subtraction angiography have been used with success. Once the catheters are in place and the arterial and venous anatomy ascertained, blood samples at various points can be collected and assayed for parathyroid hormone levels, so-called parathyroid venous sampling. Catheterization also affords the opportunity for angiographic ablation of the parathyroid adenoma if it is found. Miller, in a group of patients with prior unsuccessful neck explorations, found that the true positive rates for digital subtraction angiography, conventional angiography, and parathyroid venous sampling to be 49, 60, and 80 per cent, respectively, and the false positive rates to be 3, 5, and 0 per cent, respectively. All such techniques are quite operator dependent and obviously invasive. They have been reserved for those with persistent hyperparathyroidism who are candidates for further surgical exploration.

Computerized tomography (CT) is another means of locating the parathyroids. CT scans are sometimes confounded by the presence of silver clips left at prior exploration and the similar appearance of the thyroid gland. They are better at finding lesions in the mediastinum. The sensitivity of CT scanning in the detection of parathyroid adenomas has been reported to be 46 to 76 per cent. Again, because of the expense of the test and its limitations in the neck itself, CT has been relegated to the second exploration group.

Magnetic resonance imaging (MRI) is a more recent and increasingly available modality. It offers several advantages over CT. It is said to yield superior soft tissue differentiation, easy delineation of blood vessels without the use of iodinated contrast materials, lack of ionizing radiation, and avoidance of streak and clip artifacts. The sensitivity of MRI has been reported to be 50 to 78 per cent. In cases of suspected mediastinal lesions, Kang has shown MRI to have sensitivity of 88 per cent. MRI is felt to be more reliable in the neck than CT scanning, and is clearly of use in the detection of mediastinal tumors. MRI is, however, expensive, and its use can be justified only in those in the second exploration group.

Ultrasonography is probably the most frequently used modality, being both widely available and relatively inexpensive. It may be confounded by thyroid lesions and is unlikely to detect lesions behind the esophagus or trachea. Ultrasound cannot be used to detect mediastinal lesions because the bony thorax confounds the transducer. It is an operator-dependent technique, and reports of its sensitivity vary widely. Variations in its application, such as the use of a transesophageal probe allowing visualization of the paratracheal and paraesophageal areas, may increase its sensitivity, although Henry found this particular technique to be successful only 50 per cent of the time. Most experienced institutions, however, report sensitivities in the 70 per cent range. Reporting before this group in 1992, we reported a sensitivity and accuracy of 50 and 53 per cent by site, and 60 and 60 per cent by side, respectively. The positive predictive value was 86 per cent by site and 83 per cent by side, leading us to conclude that it was a very helpful test when positive. Because of its relative inexpensiveness, ease of performance, and noninvasiveness, it is the localization technique most frequently recommended for patients about to undergo either an initial exploration or a reexploration for persistent or recurrent disease.

Functional Studies

An alternate approach to the localization of the parathyroid glands has been to exploit a physiologic characteristic. Such tests have used a radionuclide-tagged tracer and then relied upon scintigraphic assessment of areas of uptake. These tests are more related to the level of function of the glands and conversely are less sensitive to the absolute size of a gland. Agents used have included cobalt 57 vitamin B-12, selenium methionine, radioiodinated toluidine blue, thallium, pertechnetate, and sestamibi. Selenium-methionine and radioiodinated toluidine blue were the first markers to be used but had low sensitivities and have been supplanted by newer techniques.

Thallium-technetium subtraction scanning was the first widely used technique. Thallium is a scintigraphic measure of blood flow and images both the thyroid and the parathyroids. Technetium is taken up by the thyroid gland exclusively. Technetium and thallium images are obtained, digitized, and subtracted one from the other leaving then only the parathyroid image(s) on the film. A collected review reported an overall sensitivity of 67 per cent, 80 per cent for adenoma, and 45 per cent for hyperplasia. Other studies have reported sensitivities of 70 to 90 per cent. Again, in 1992 before this group, we reported a sensitivity of 64 per cent, an accuracy of 58 per cent, and a positive predictive value of 83 per cent for thallium technetium subtraction scanning. Like ultrasound, if thallium-technetium subtraction scan (TTSS) is positive, the lesion is very likely to be where the study says it will be and, except for the expense, it can be very helpful. The combination of the two agents offers the disadvantages of a relatively high dose of radioactivity to the patient and an increased likelihood of motion artifact which, with the superposition of two images, increases the risk of interpretive error.

In 1989, O'Doherty suggested that technetium-99m-sestamibi, which had been introduced as a cardiac imaging agent to replace thallium, might also image the parathyroid glands. It was shown that sestamibi was sequestered in the mitochondria, suggesting that tissues with large cellular concentrations of mitochondria would be most likely to retain the radionuclide and hence be imaged scintigraphically. Parathyroid tissue is such a tissue, and the increased cellularity of an adenomatous or hyperplastic gland would be expected to enhance this property. Indeed, the initial uptake of sestamibi by the parathyroids is greater than that of the thyroid gland, and the washout rate is also lower for the parathyroids than the thyroid. While the original studies were done with a simultaneous iodine 123 image to subtract from the sestamibi image, subsequent studies have utilized the differential clearing phenomenon, to make the subtraction of an early-phase image from a late-phase image. Overall, sensitivity and specificity numbers are somewhat better than those of thallium-technetium subtraction scanning, some studies reporting sensitivities in the 88 to 100 per cent range, but the ease of the study and the reduction of radioactive dosing has made sestamibi scanning the current standard.

Intraoperative Localization

A number of tricks have been introduced over the years to aid in the operative strategy to find the parathyroid glands. To date, none have obviated the need for an understanding of the anatomy and some experience with the pathologic anatomy of the glands themselves. In the 1960s, first methylene blue and then toluidine blue were administered intra-arterially or intravenously once the neck was open. While some articles expressed enthusiasm for the latter, photographs, testimonials, and personal experience were unconvincing, and both have been abandoned. In addition, toluidine blue in a dose adequate to stain the parathyroids was also capable of inducing cardiac arrhythmias.

Intraoperative ultrasound has also been suggested as an adjunct to exploration. Again, while early reports were enthusiastic, the size of the transducers and the difficulty of interpretation have limited the acceptance of this technique.

Most recently, it has been suggested that with a perioperative injection of sestamibi, adenomatous or hyperplastic parathyroid glands might be detected with a sterile, handheld gamma-detecting probe. Martinez, in 1995, reported anecdotally her success in two operations and one reoperation for hyperparathyroidism. Most recently, there has been some enthusiasm for octreotide as an intraoperative localizing agent. Our own experience with the latter has been brief and mixed, although such procedural problems as developing a workable dosing schedule and obtaining probes of an appropriate size have hindered our success. With the development of better agents and smaller, less cumbersome and more precise probes, this may well become a more important part of the surgical exploration.

Indiana University

Since January 1985, at the Indiana University School of Medicine, 168 neck explorations for hyperparathyroidism have been performed. Of these, 120 have been done on the general surgical service for primary hyperparathyroidism, 39 have been done on the transplant service for complications of renal failure, and nine have been performed on the ear, nose, and throat (ENT) service. Of 137 patients with primary hyperparathyroidism, 101 were confirmed to have a single adenoma and 36 were found to have hyperplasia; 25 additional patients with secondary hyperparathyroidism, of course, had multiglandular disease. Six explorations were unsuccessful, two of these on the ENT service. Of the other four, one at post was found to have renal cell carcinoma, but the other three would appear to have persistent, but unfound, disease.

Of these 168 patients, 109 underwent preoperative ultrasound. Sixty-five before 1993 underwent preoperative thallium-pertechnetate subtraction scans, and 40 since 1993 underwent sestamibi scans. Since 1985, 93 have undergone both ultrasonography and scintigraphy. In our series, the sensitivity of ultrasound in predicting exact location is 59 per cent, that of TTSS is 66 per cent, and that of sestamibi is 73 per cent. The sensitivity of ultrasound in predicting the side of the lesion is 61 per cent, that of TTSS is 67 per cent, and that of sestamibi is 74 per cent. In those patients in whom both studies were done, the sensitivity for prediction of exact location is 77 per cent, and that of prediction of side is 73 per cent. In that this group of patients was preselected by biochemical evidence to have hyperparathyroidism, the specificity and negative predictive value of the studies are less meaningful. Positive predictive value, however, is meaningful information, and the positive predictive value of ultrasound in predicting exact location was 85 per cent, that of TTSS was 76 per cent, and that of sestamibi was 90 per cent. The positive predictive value of ultrasound in predicting side was 91 per cent, that of TTSS was 95 per cent, and that of sestamibi was 97 per cent. Clearly, if any one of the studies predicts a location, the lesion is very likely to be there, and sestamibi scanning would appear to be the study with the highest positive predictive value. Likewise, a negative study is basically unhelpful.

Summary

The essence of parathyroid surgery is finding the diseased gland or glands. Even the most experienced parathyroid surgeons have a finite, albeit small, miss rate. The information above shows that there has been, over the years, a significant amount of effort expended to find a way to localize the glands in a reliable fashion. Although current parathormone assays are virtually certain to identify the disease, available localization studies still miss a sizable number of lesions, and the statement, "The best way of localizing the parathyroid glands is to localize an experienced parathyroid surgeon," probably remains valid. Does such a surgeon need an ultrasound or sestamibi scan preoperatively? Probably not. I would note, however, that many such surgeons have written of their experience with these localization studies, suggesting that they usually operate with this information available to them. In the managed care era, with many of these procedures being done by less frequent parathyroid surgeons despite the failure of currently available studies to show any advantage in operative time or success, the high positive predictive value of the sestamibi scan in particular can, I think, be very helpful in focusing the procedure. Certainly, the patient should not be denied this advantage by cost issues, which in this uncommon disease only serve to benefit the balance sheet of the managed care organization.

Well, enough of radiologists and the parathyroid glands. I hope that these comments have been of some interest to you. I have enjoyed greatly my year as your President, and appreciate deeply the honor to have been chosen. Thank you.