Discussion

Dr. Melvin A. Block (La Jolla, California): We question that total parathyroidectomy with autotransplantation will significantly improve results if used for all patients with primary parathyroid hyperplasia. This concern is based on two observations. First, our experience with subtotal parathyroidectomy for primary parathyroid hyperplasia indicates reasonably favorable results. Second, although total parathyroidectomy and autotransplantation should be applicable particularly for patients in whom all parathyroid glands are greatly enlarged, there is a wide spectrum of varied enlargement of parathyroid glands in patients with primary parathyroid hyperplasia, making subtotal parathyroidectomy technically attractive as well as, in our experience, usually corrective.

Our experience at Henry Ford Hospital and supported by more recent evidence at the Scripps Clinic indicates a 14% recurrence or persistence after subtotal parathyroidectomy for 44 patients with primary parathyroid hyperplasia caused by gross enlargement of at least three parathyroid glands. The follow-up period extended from one to 19 years with an average of nearly five years. The subtotal parathyroidectomy consisted in the removal of all except for an estimated 30–100 mg of viable parathyroid tissue. Evidence of the multiple endocrine neoplasia 1(MEN-1) syndrome was present in three of six patients showing recurrent or persistent hyperparathyroidism. Subtotal parathyroidectomy has controlled the primary hyperparathyroidism in four additional patients with evidence of familial hyperparathyroidism not associated with features of the MEN-1 syndrome.

We agree that the greatest problem in the control of primary parathyroid hyperplasia occurs in patients with the MEN-1 syndrome. Three of the six patients with the MEN-1 syndrome we have operated on have had recurrence or persistent hypercalcemia, recurrence in a patient being recognized 18 years after operation. The other problems in the control of hyperparathyroidism in primary parathyroid hyperplasia relate to identification and removal of hyperplastic supernumerary parathyroid glands and the presence of complicating chronic renal insufficiency. If patients with MEN-1 are eliminated from our series of patients treated with subtotal parathyroidectomy, the recurrence or persistence rate would be approximately only 8%.

It should also be emphasized that primary parathyroid hyperplasia is associated with a wide spectrum of the degree of enlargement of parathyroid glands. Enlargement of all parathyroid glands is not present in all patients, but it is this group that does present technical difficulty in preserving the proper amount of viable parathyroid tissue if subtotal parathyroidectomy is performed. Twenty-five of our 44 patients had diffuse enlargement of all parathyroid glands, with the fourth parathyroid gland being normal in size or only slightly enlarged in 19 patients.

Currently we follow a policy of selective total parathyroidectomy with autotransplantation for primary parathyroid hyperplasia. Total parathyroidectomy with autotransplantation is advocated for three groups of patients, including those with evidence of the MEN-1 syndrome, those with severe enlargement of all parathyroid glands making preservation of a viable properly sized remnant technically difficult and those requiring reoperation for persistence or recurrence not caused by a large supernumerary parathyroid gland. Freezing of parathyroid tissue is advocated for use if needed later to correct permanent hypoparathyroidism.

Do Dr. Wells and his associates advocate total parathyroidectomy and autotransplantation for patients with enlargement of less than four glands as a manifestation of primary parathyroid hyperplasia? Have they had experiences with the use of cimetidine in controlling the release of parathyroid hormone and hypercalcemia for those problem cases, especially if hypercalcemia is mild?

Dr. Arnold G. Diethelm (Birmingham, Alabama): I would like to direct my comments toward using a similar procedure, but for a different disease, that disease being secondary hyperparathyroidism as a result of chronic renal failure. At the University of Alabama from 1975 until 1980, we operated on 62 consecutive patients with chronic renal failure and renal osteodystrophy with secondary hyperparathyroidism. We have used a modification of Dr. Wells' procedure, described earlier by Dr. Starzl and colleagues wherein instead of placing the autografted implant in the forearm, we place it in the sternocleidomastoid muscle.

We have studied and followed all of these patients, ten of whom had the operation and subsequently had renal allografts, and then had normal serum calcium levels. That was a true test of whether or not the implant was functioning.

The second group that was of interest to us was five patients that had this procedure after successful renal transplantation; in other words, the operation was for tertiary hyperparathyroidism. In that particular group we also had normal serum calcium levels after the operation.

Would Dr. Wells elaborate a bit more on the size of the autograft in the forearm? Recognizing that we use the operation for a different disease, we have used an implant of 10–20 mg, and I believe he said 50–100 mg. That might play a role in the recurrence of the disease or the graft-dependent hyperparathyroidism.

Does Dr. Wells have any information as to the activity of the parathyroid hormone levels at days seven, 14 and 21 after the implantation? In patients with secondary hyperparathyroidism in many instances it takes several weeks to replace serum calcium, recognizing that this is undoubtedly caused by a large calcium deficit in the skeletal system.

Dr. Donald S. Gann (Providence, Rhode Island): Our experience has been very much like that of Dr. Block, in that we have had a low incidence of recurrence with three and one-half gland resection. Our only exceptions to that experience thus far have been in patients with familial disease. I wonder if Dr. Wells and his colleagues have any clue as to what is different about the patients with familial disease that makes them likely to have a recurrence.

Aurbach and his colleagues have described over the past several years neural control of parathyroid secretion, probably under beta-adrenergic control. It seems to me that because of the autotransplantation, Dr. Wells has an unusual opportunity to study the control of parathyroid hormone secretion in what might be a denervated gland.

I wonder, first, if you know from the specimens that you have removed whether, in fact, there is regrowth of nervous tissue into these transplanted segments; and second, is there anything peculiar about the control of PTH secretion in the transplanted gland?

Dr. Samuel A. Wells, Jr. (Closing discussion): Regarding Dr. Block's statements, one fairly clear difference ought to be made when one speaks of parathyroid hyperplasia. There are patients who have two or three large glands and their management is confusing, primarily because there are few published reports of postoperative evaluation of such patients. All of the patients presented in this study have four large parathyroid glands. These are not patients who were found at operation to have either two or three glands enlarged.

Also, I have appreciated the fact that there has been a high incidence of recurrent hypercalcemia after subtotal resection in patients with familial hyperparathyroidism, as mentioned by Dr. Block and Dr. Gann. I would concede that there are patients with nonfamilial hyperplasia who might not need to have total parathyroidectomy and autotransplantation. If you recall from the presented slides, there was absence of recurrent hypercalcemia in patients with nonfamilial hyperplasia who were undergoing operation for the first time. It is bothersome, however, that in patients having three and one-half gland resection for generalized parathyroid enlargement there is a rather substantial incidence of hypocalcemia. Edis recently reported 55 patients at the Mayo Clinic who were treated for parathyroid hyperplasia by three and one-half gland resection. The incidence of permanent hypoparathyroidism was 5%; however, transient hypoparathyroidism occurred in 27% of the group. The average length

of replacement therapy required was ten months, and up to two years in some patients.

Castleman's group recently reported the experience at the Massachusetts General Hospital of patients undergoing operation for chief cell parathyroid hyperplasia. The incidence of permanent hypoparathyroidism in patients followed beyond one year was 15%.

None of the patients with nonfamilial disease reported in this study had hypoparathyroidism.

We have not had any experience with cimetidine, so I cannot comment on its use in patients with either markedly elevated or minimally increased serum calcium concentrations.

Dr. Diethelm presents an extensive experience of managing secondary hyperparathyroidism in patients with renal osteodystrophy. His results have been excellent, and I would only argue for implanting the parathyroid tissue in the forearm rather than the sternocleidomastoid muscle. If graft-dependent hyperparathyroidism develops, the tissue is easily accessible and can be removed under local anesthesia. General anesthesia would be required for excising parathyroid tissue grafted to the sternocleidomastoid muscle.

The graft size of each parathyroid piece is $1 \times 1 \times 3$ mm and the total weight of the entire amount of 15–20 pieces ranges between 75 and 90 mg. The amount of parathyroid tissue grafted is similar to that described as remaining after three and one-half gland parathyroidectomy.

We have not studied parathyroid autografts soon after implantation. We have detected gradients of parathyroid hormone between the grafted and nongrafted arms as early as seven days. If one follows these patients beyond seven days to two weeks, almost all of them have parathyroid graft function sufficient to allow termination of oral calcium and vitamin D replacement therapy. A substantial number of patients in our group did not require replacement therapy after total parathyroidectomy and grafting.

Regarding Dr. Gann's comments, we have not looked closely at all aspects of parathyroid graft function. This is a nice model to study PTH secretion, because one samples venous blood just 2 or 3 cm from the grafted tissue.

This technique of total parathyroidectomy and autotransplantation is useful. I am not sure of its place in patients with nonfamilial parathyroid hyperplasia. It is often difficult, however, to make this categorization preoperatively or intraoperatively. A distinct advantage seems to be that patients with parathyroid disease are spared a seemingly high incidence of hypocalcemia and, of course, if graft-dependent hypercalcemia develops, it is more easily corrected with the tissue in the forearm.