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DISCUSSION

DR. EDWIN L. KAPLAN (Chicago, Illinois): I agree with Dr. Hardy completely that in adrenal adenoma and carcinoma, diseases in which the treatment is clearcut—one should remove the tumor. On the other hand, the treatment of hyperplasia is still very perplexing.

One of the other modalities that he did not mention is radiation to the pituitary. Dr. Ed Paloyan has recently presented data where two individuals who were apparently cured—in quotation marks—by irradiation therapy later had recurrences. In one of them it took eight years before the recurrence of Cushing's occurred, so I think we must be wary when we use irradiation to the pituitary, and follow these patients carefully.

We have experience at the University of Chicago with one adrenal transplant. We minced the adrenal cortex, as one would do for a parathyroid transplant, and transplanted this to the muscles of the arm. This patient still requires steroid therapy. However, there is a very nice gradient of both cortisol and aldosterone, which is higher in the arm of the transplant.

I think the technique that Dr. Hardy has proposed today warrants our further investigation.

DR. FRANK GLENN (New York, New York): This report by Dr. Hardy is a great contribution to the matter of the patient who requires a total adrenalectomy. Furthermore it re-enunciates a principle of replacement for an injured or deficient part, specifically for the glands of internal secretion. These 18 cases are of significance

to all of us here because Dr. Hardy has, by study of his management derived a great deal of adequate information from each one detailed that will be of value to those who pursue this type of endeavor in the future.

My interest in this disease goes back to the twelfth case in Dr. Cushing's series, when I was an assistant resident at the Brigham hospital. I have had a great deal of interest in it since.

Our total experience, in close cooperation with the endocrine group at The New York Hospital includes 113 patients with Cushing's disease who have been treated surgically. Sixty of these have had hyperplasia of the adrenals. Fifty-two have been subjected to attempted total adrenalectomy. Those in which total adrenalectomy was accomplished as determined by postoperative studies have been well supported and maintained by replacement therapy. Our longest follow-up is now 28 years.

However, replacement therapy leaves much to be desired from the patient's viewpoint. Dr. Hardy's experience will have an impact on the future management of the patient with Cushing's disease. I would suggest that for those with hyperplasia the posterior approach affords a better opportunity to look for aberrant adrenal tissue. Such tissue and any remaining adrenal tend to become exuberant when subtotal adrenalectomy is done.

Dr. Hardy has mentioned the pigmentation of the skin following total adrenalectomy. Here are two slides that further emphasize this phenomenon that I feel we lack an explanation for. Actually this is but one of many changes that follow total resection. I think it is the tip of the iceberg of many significant changes, particularly as it relates to the pituitary and hypothalamus. I have long believed that the adrenals are only one but an important link in the complex

physiology of the glands of internal secretion. Perhaps adrenal rests or fragments of adrenal tissue may have been left in the operative area.

(Slide) Here is the pigmentation that Dr. Hardy has mentioned in his paper.

(Slide) Here is the pigmentation in the hands.

The complications resulting from the altered physiology here are fantastic. It is the link with the glands of internal secretion, and as Dr. Hardy has pointed out, we are coming back to the pituitary, Cushing's original conception.

This report of Dr. Hardy's is a model for surgeons who seek to advance surgical therapy by observation and trial innovations to meet the needs of depleted or diseased parts. The excellent documentation of 18 patients with adrenal tissue reimplantation is a historical landmark in surgery, and does a lot to clear up some of our misadventures and poor reasoning in the past.

DR. WILLIAM H. REMINE (Rochester, Minnesota): I'll confine my remarks entirely to adrenal hyperplasia, which I think is the important factor in this discussion. I don't know that we've ever really gotten away from Cushing's original premise that these problems were caused by pituitary tumors, but because of frustration in making the diagnosis of the tumor there, we have treated the end product of the disease, and I think we're now getting back to what was originally described. This is the result of more sophisticated means of diagnosis at the present time, with spiral tomography and carotid arteriography.

Around 1950, partial adrenalectomy was performed because we had no method of supporting the patient after removal of all the adrenal tissue. With the advent of steroids, we then went to total adrenalectomy for Cushing's disease. At that time, our experience with the long-term followup of over 300 cases, showed a 15% incidence of development of pituitary tumors that eventually needed some type of treatment.

In the last 4-½ years, my colleagues have been interested in transphenoidal removal of microadenomas of a great variety of types, not just Cushing's. All together, they have performed over 250 such procedures, with an operative mortality of 1.1%.

Since 1974 we have been conducting a prospective study for Cushing's disease, using spiral tomography and carotid angiography. In this group we have 18 patients that have been treated with transphenoidal removal of microadenomas. Of these that were operated upon, 16 have had complete remission. Of the two who did not have remissions, one had no tumor (this was found at autopsy when the patient died two years later of perforated diverticulitis) and one had a tumor which was removed, but the disease persisted and later responded to irradiation.

Now, why don't we treat them with irradiation? Because it's perfectly obvious that with the techniques used now, the danger of damage to the optic chiasm is great. Therefore, an operation such as this, with removal of microadenomas of the pituitary with a minimum of morbidity and mortality is probably the best form of treatment.

One other comment might be made about the use of o,p'-DDD in the management of this disease. In our experience, this is totally useless. It makes patients terribly sick and in the end they die of their disease anyway.

I would like to ask Dr. Hardy why he is so sure that the recurrence in that one patient is coming from possibly a transplant and not from a recurrence of the tumor in the region of the original operation in the adrenal. In our experience, this has been the place to find it. It's often possible to leave a tiny remnant of adrenal tissue behind when you clamp the adrenal vein, particularly on the right side where it's very short and enters in on the posterior wall of the vena cava. The remnant can remain there and subsequently will enlarge and cause recurrence of the disease.

I compliment Dr. Hardy on the technique that he has developed. It will be interesting to follow and see the outcome.

DR. J. HARTWELL HARRISON (Boston, Massachusetts): It's significant and appropriate that Dr. James Hardy should bring to us

this first description of autotransplantation of the adrenal. To my knowledge, he was the first person to carry out successfully autotransplantation of the kidney.

(Slide) Here is a review of 95 patients having hyperadrenocorticism due to hyperplasia of the adrenal cortex; one sees that 61 of the patients underwent bilateral total adrenalectomy, which has been the accepted operation for this procedure for a long time. Recently, the pituitary has regained its importance in the surgical management of Cushing's syndrome.

I wish to call your attention to subtotal adrenalectomy here; there were 13 of these. In these patients a small remnant of gland was left at the lower pole of the left adrenal, where it would be easily accessible for subsequent removal if necessary. You will note that in seven of these, the lesion became hyperplastic, necessitating removal. This has been emphasized by Dr. Hardy today. Like Dr. Glenn, we have not been successful in our attempts at transplantation by putting slices of adrenal in the muscles of the thorax as we close the wound.

(Slide) Here are the results of a two-to-20-year follow-up. There were 61 patients with normal blood pressure and 12 with hypertension, alive and well.

Two weeks ago there was a Harvey Cushing Memorial Symposium, at which William Sweet and others spoke; at this meeting, William Harvey Cushing, the grandson of Harvey Cushing, presented a sterling silver Revere bowl to the Harvard Medical School, which Elliott Carr Cutler, John Cutler, Roger Cutler and Robert Cutler had presented to Dr. Cushing more than 60 years ago. At this same occasion, Dr. Ray Kjellberg of the Massachusetts General Hospital, presented me with a personal communication as follows:

I have treated 106 patients with Cushing's disease and 18 patients with Nelson's syndrome by stereotactic Bragg peak proton hypophysectomy. In patients with pituitary-dependent Cushing's disease, clinical remission occurs in 65%, but another 20% are improved to the point that no further therapy is invoked.

He shows an 85% overall improvement with this technique to be compared with 73%, which we attained with bilateral total adrenalectomy. The morbidity is less in Kjellberg's series.

There were no deaths or disabling complications. Replacement therapy was necessary in only 13% of these patients, and transient oculomotor disturbances occurred in two to three per cent.

PROFESSOR PHILIP SANDBLOM (Lausanne, Switzerland): May I first express the tremendous pleasure we have who come from far away to attend this summit and culmination of the surgical year. James Hardy's excellent presentation of Cushing's disease exemplifies this.

I have a little comment about the relationship between the Cushing's disease and the wound healing process. A few years ago, we examined the wound healing in different patient groups by the tensile strength of small incisions in the elbow fold. We didn't find many series where the wound healing really was depressed. Even in high ages, the wound healing was close to being normal.

The greatest differences were in the Cushing's group, where the wound healing was often reduced to less than half of normal. In one patient, where we excised an adrenal tumor, the wound healing returned to normal within months after the operation.

With the abdominal incision, there might be some reason for dehiscence, and I would like to ask Dr. Hardy whether he takes special precautions in preventing wound dehiscence when operating on Cushing's disease.

DR. JOHN RAAF, JR. (Houston, Texas): In 1958 Drs. Paul Russell and Sir Peter Medawar reported that adrenalectomized mice could be sustained with implanted corticoadrenal shavings, which were placed into muscle. This provides excellent experimental support for your clinical studies. In these mice, of course, there were no vascular anastomoses, confirming your findings that the anastomosis is not required.

(Slide) At M. D. Anderson more recently, Dr. Robert Hickey

and I have been studying the implantation of parathyroid tissue into muscle and been impressed that, using this implantation site, there is very rapid function of the graft. In rat studies, for example, if you implant parathyroid into muscle of parathyroidectomized animals, function occurs within one week, and you get a normocalcemic animal.

(Slide) In the human, however, it may take a bit longer for normocalcemia to take place. This 37-year-old female had a total thyroidectomy and parathyroidectomy for papillary carcinoma. Two normal parathyroids were placed into the right arm. It took about three weeks for her to return to normocalcemia, and during this time she was kept asymptomatic on oral calcium. Nonetheless, within the first week we were able to demonstrate that the antecubital venous blood in the right arm draining her graft site contained substantially greater amounts of parathyroid hormone than the control left arm. This was also true about three weeks later.

(Slide) We have also observed hyperplasia and hyperfunction of parathyroid tissue which was implanted in a patient. This 67-year-old female had an adenoma, and she underwent total parathyroidectomy. The adenoma was saved, and one half of it was reimplanted. This tissue was roughly divided between the right pectoral muscle and left forearm.

(Slide) As you can see, preoperatively she was hypercalcemic. With the parathyroidectomy and implantation she became normocalcemic. The implanted arm contained greater parathyroid hormone in the antecubital vein than the control arm.

Two years later she became hypercalcemic again, and it was found that in the implanted arm the parathyroid level was quite high. It was a simple matter to excise the arm implant, and she has subsequently remained normocalcemic, and her parathyroid hormone has returned to normal in that arm.

(Slide) The arm site was exposed, as you see, and we had placed silver clips around the implant site, so that it was easy to excise this bloc of tissue.

(Slide) The excised tissue shows viable parathyroid in the muscle site.

This case demonstrates that implanted endocrine tissue can hyperfunction, even in the absence of a pituitary influence, but one can correct for this by partial reexcision of the tissue.

I would recommend to Dr. Hardy that the arm rather than the leg be used for adrenal implantation, because of the availability of draining venous blood for subsequent studies such as cortisol levels.

DR. JAMES D. HARDY (Closing discussion):

Dr. Kaplan, we have not often chosen to employ pituitary radiation. First, most of these patients are women, and we don't want to diminish prolactin secretion, or to diminish growth hormone secretion in teen-agers. Moreover, the literature suggests that only about one fourth to one half of the patients treated with pituitary irradiation have achieved even temporary not to mention permanent remission.

Dr. Glenn certainly has had a large experience with Cushing's disease. Total adrenalectomy has now, I think, replaced subtotal in almost all surgical clinics. The possibility of residual adrenal tissue in the abdomen has to be considered, and we don't completely discount it. However, Franksson excised one of his adrenal autotransplants to the thigh, producing prompt adrenal insufficiency.

One fact has to be borne in mind. It is often literally years—nine in one patient, seven in another—before the plasma levels of 17-hydroxycorticosteroids are normal in these adrenal autotransplant patients. And that's not really too surprising, when one realizes that it often takes years for Cushing's disease to develop; certainly, to the full-blown state. Cushing's disease is a very complex disorder. For example, even though the physical findings may have been returned to normal by adrenalectomy, one can show years later that the response of growth hormone secretion or of 17-hydroxycorticosteroid secretion to induced hypoglycemia is still abnormal in these patients.

Dr. ReMine asked if we thought that we might have adrenal tissue in the abdomen of the patient who developed recurrent Cushing's disease. Well, that, of course, is not discounted, but when we took those eight so-called "adenomas" out of the thigh, the plasma 17-hydroxycorticoid level dropped from 23 mcg/% down to 10 mcg/%. We believe that additional "adenomas" remain in the thigh. Furthermore, data published in the world literature fully support function of the transplants.

Dr. Sandblom asked whether we took special precautions with the abdominal wound closure. No, not particularly, and we haven't had any dehiscences thus far.

As for Dr. Raaf's comment that we might put the transplant tissue in the forearm, I might say that our former splendid Secretary of the Association, Dr. Shires, and his associate used the leg in their patient. Later, they introduced a catheter above the level of the transplant in the thigh and got an elevated plasma hydroxycorticosteroid level there, as compared. I believe, with that in the antecubital vein. So, venous sampling can be done in the leg satisfactorily.

Announcement

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