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Discussion

Dr. Charles Eckert (Albany): I arise to emphasize two points, both of which were covered in his paper. The first is that if you have a patient you are going to operate upon with thyroid disease who is hypertensive, by all means screen the patient for the presence of a pheochromocytoma, because of the possibility of Sipple's syndrome.

Next, I think adequate preoperative preparation of the patient has eliminated for the most part the terrifying swings in blood pressure that were experienced before we used adrenolytic therapy, and we seldom use propranolol. All our patients are treated with Dibenzyline. We consider this, for the most part, adequate, and only in those patients who have arrhythmias, or who are not properly controlled, do we add propranolol to their management.

I think the other important feature is restoring the plasma volume deficits that are always present in these patients. While we continue to have norepinephrine in the operating room and adrenolytic drugs, we seldom have to use them today, since we now have such good methods of preoperative preparation.

Dr. H. William Scott, Jr. (Nashville): Pheochromocytoma, as you can see, is not a very common tumor, even at the Mayo Clinic. Not too long ago we heard a report by Dr. ReMine on 25,000 cases of gastric cancer which have been submitted to exploration at the Mayo Clinic; this tumor certainly has quite a different incidence.

In the last 20 years in the hospitals affiliated with Vanderbilt, the pathologic diagnosis of pheochromocytoma has been made in about 40 patients. In nine of these patients during this time, the clinical diagnosis was not made, the patient was not operated on for pheo, and every one of those nine patients died, the diagnosis being made at autopsy by the pathologist. This is indicative of the hazards of this dangerous tumor.

In the remainder, the clinical diagnosis was made. Three of these were patients referred to our chemotherapy clinic with metastatic pheo. There were two other patients in the group who had malignant tumors, one of which was successfully removed and cured. The other one, unfortunately, recurred five years after initial removal and died subsequently with metastases. In the remainder the tumor was benign and was removed with survival in all except one patient, unfortunately, who succumbed in the postoperative period from renal shutdown, which we believe was due to Penthrane anesthesia, which has since been abandoned in this particular use.

The screening tests for pheochromocytoma, we think, should be used in all hypertensive patients, since the tumor can simulate any hypertensive syndrome. We are very much interested in Dr. ReMine's use of the blocking agents, and the success he has obviously had. We, like Dr. Eckert, have tended to use phenoxybenzamine in the last several years, believing that alpha blockade enhances the safety of operation and is not very hazardous as far as its side effects are concerned, whereas we have been concerned about the use of propranolol, and have reserved it, as he has, for only the patients with arrhythmias.

I wish Dr. ReMine would say a word about what his anesthesiologists do in the operating room. Ours tell us that pre-op alpha blockade with phenoxybenzamine is only a small part of the handling of these patients. Unlike the anesthesiologists at the Mayo Clinic, Dr. Bradley Smith likes to use large doses of halothane taking the patient down deeply before the patient is intubated. He also uses a lidocaine drip to control arrhythmias during operation, and our patients usually have a very smooth course during the operative removal of the tumor. I wonder what Dr. ReMine's anesthesiologists use in this regard.

I have one slide which I might show. Dr. Oates in our Department of Medicine has been interested for many years in the use of alpha methyl tyrosine as a metabolic inhibitor of the biosynthesis of the catecholamines. This inhibitor fits into this area, (indicating) blocking tyrosine's conversion to dopa in the biosynthesis of epinephrine and norepinephrine. I wonder if Dr. ReMine has had any experience with the use of this agent. It has been controversial and our experience is limited.

Finally, I'd like to ask Dr. ReMine if he knows of any chemotherapeutic agent that has value in treating a malignant pheochromocytoma. Dr. Vernon Reynolds in our institution has tried the combination of vincristine and Cytoxan with some success temporarily in a few patients.

I wonder if Dr. ReMine has had any experience with these or other chemotherapeutic agents; and if so, what value do they have?

DR. WILLIAM P. LONGMIRE, JR. (Los Angeles): I would like to compliment Dr. ReMine and his co-authors for presenting to us a review of the experiences of the surgeons at the Mayo Clinic in the treatment of pheochromocytomas since the time that Dr. Mayo performed the first resection in 1926. Certainly, this large, well-evaluated study gives us great specific knowledge about the diagnosis, the treatment, and the results of this fascinating but relatively rare tumor.

The surgeons are to be commended for the very excellent operative mortality of 2.9%, with all of the deaths occurring prior to 1965. They have stressed in their manuscript the importance of preoperative management of patients with pheochromocytoma with correction of hypovolemia and electrolyte disturbances and the institution of a receptor blockade regime to lower and to stabilize the blood pressure and pulse rate, thereby diminishing the critical swings of blood pressure and cardiac action during operation and during the immediate postoperative period. The ages of their patients ranged from 3 to 78 years, with the peak incidence in the fifth decade of life.

Our interest in pheochromocytoma in children was stimulated by the case of a 15-year-old girl who was operated upon for a bilateral pheochromocytoma with complete relief of her symptoms for over a year. In reviewing the literature concerning pheochromocytomas in children at the time of this operation, we found that the most persistent symptom was a sustained hypertension occurring in about 80% of patients, as contrasted to 49% in Dr. ReMine's series. Extra-adrenal pheochromocytomas were reported in 31%, and multiple tumors such as occurred in our case were present in 32% of pheochromocytomas in children. Of some concern was the fact that there had been five instances reported of a second pheochromocytoma appearing following the removal of an earlier tumor, one as long as four years after the original operation. Contrary to the occurrence in adults, such as was reported in the present paper, where females show a great preponderance, in children, males seem to predominate. Sixty-two per cent of the cases occurring in girls have been concentrated during the premenarchal period.

DR. LESLIE P. LEQUESNE (London): I need hardly say that neither I nor my colleagues at The Middlesex Hospital have an experience which in any way compares with his, but we have seen a number of these tumors, and we have been very interested in one aspect of them which he only briefly touched upon, and that is the hypovolemia that some of these patients have. We believe that the correction of this is exceedingly important in the management of these patients, and I would like to suggest to you that it's important in respect to another manifestation of the tumor, which is comparatively rare.

A few years ago we had a visit at The Middlesex Hospital from Dr. Robert Zollinger, and we asked him to do a CPC for us, and we sent him the protocol of the case, which I thought was, for practical purposes, undiagnosable. One of the manifestations of this very complicated illness was that the patient had a persistent hypokalemia. And after 45 minutes of, as you can imagine, extremely lively dissertation on this patient, Dr. Zollinger finally ended up by saying: Well, of course this patient had a pheochromocytoma. And of course he was right, and at the time none of us understood this.

A few years later we had the opportunity to study a patient who had got an established pheochromocytoma, and also had a persistently low serum potassium. We measured this patient's blood volume, and it was significantly reduced. We then measured the patient's aldosterone, and we found that this patient had a persistent secondary hyperaldosteronism. I would like to suggest to you that this rare manifestation of pheochromocytoma is a very interesting expression of secondary hyperaldosteronism.

There's one question I would like to ask Dr. ReMine. He mentioned briefly the use in the diagnosis of these patients of adrenal venography. We're rather chary of this, because we have seen serious complications from this investigation, and I know that throughout Great Britain there have also been a number of complications. I would be loath to accept the fact that our radiologist are more heavy-handed than yours, and I wondered if Dr. ReMine had had any problems with this investigation.

DR. JONATHAN A. VAN HEERDEN (Closing discussion): Since we have been using propranolol, our anesthesiologists like us a little bit better than they did in the past. It seems to control the incidence of arrhythmias during surgery, which we seldom see these days. The anesthesia of choice has been Innovar, with Regitine as a standby.

As far as chemotherapy is concerned, Dr. Scott, we don't know of anything specifically valuable for malignant pheochromocytomas. The use of long-term Dibenzyline has tended to control the symptoms, but it certainly had no influence on the malignant course of the disease.

Perhaps our radiologists do have smaller hands. We have not had any trouble with selective venography. We have had minor trouble with selective venography for aldosterone secreting tumors, in that some of them have had some small hemorrhages.

In the past number of years we have become quite fascinated with the entity of Sipple's syndrome, which you all know well. This syndrome is transmitted as an autosomal dominant trait with a high degree of penetrance. Accurate diagnosis is possible by the assay of serum thyrocalcitonin, with or without the aid of calcium infusion. The treatment is total thyroidectomy.

We bring this up only to point out that the pheochromocytomas found in people with Sipple's syndrome differ from the common garden variety of pheochromocytoma. It differs in that it is more often bilateral, it is more often multicentric, and, most interestingly and completely unexplained, it is often unresponsive to provocative diagnostic tests.