thyroid carcinoma. Each of these 3 patients is normotensive.

Among the 22 other patients who had a single benign pheochromocytoma removed was one woman who had a renal hilar tumor and coexisting renal artery stenosis which was repaired when the tumor was excised. Both she and 12 others in this group who have been followed from 18 months to 20 years have remained normotensive and asymptomatic with no evidence of recurrence of pheochromocytoma. However, in the 9 other patients hypertension has persisted or developed in the period of followup after excision of the tumor. One of these patients had malignant hypertension with diffusely severe renal arteriolosclerosis and nitrogen retention at the time her small para-aortic pheochromocytoma was excised. She sustained no improvement from removal of the tumor and died in uremia 3 months later. Catecholamines were normal after operation in this patient and have been within the normal range in each of the other 8 patients who have developed hypertension during the followup period. In each instance the hypertension has been controlled satisfactorily with antihypertensive drugs. Three of these patients are on Digitalis preparations and one also has an enlarged heart which has been attributed to catecholamine myocardiopathy.

Diabetic glucose tolerance tests which existed before operation in 9 patients have reverted to normal in 7 after removal of the pheochromocytoma.

Comment

We have reviewed the clinical experience with pheochromocytoma at Vanderbilt University Affiliated Hospitals over the last 25 years. Between 1950–1975, 44 patients were observed in whom this diagnosis was histologically confirmed. Bilateral adrenal tumors occurred in 3 patients (6.8%), extra-adrenal tumors occurred in 7 others (16%), 33 patients (75%) had single tumors arising in one of the adrenal glands; in one of these a malignant tumor developed 5 years later in the ipsilateral renal fossa. Five of the 44 patients (11.3%) proved to have malignant pheochromocytomas and died with metastases. In 11 patients in the early years of this study the clinical diagnosis was not made and the tumor was identified by the pathologist at autopsy. There was a single postoperative fatality among the 33 patients in whom the clinical diagnosis was established. Four of these clinically recognized patients died during followup 9 months to 11 years with metastatic disease. Seventy per cent of all survivors with benign tumors have remained normotensive; hypertension has persisted or developed in 30% including one patient with pre-existing malignant hypertension who died in renal failure 3 months after excision of a small pheochromocytoma. All others have normal catecholamines and have been controlled with anti-hypertensive medication.

Pheochromocytoma can simulate any hypertensive syndrome. Although it is an uncommon cause of high blood pressure, all hypertensives should be screened for the tumor. Followup for life is mandatory in all patients with surgically treated pheochromocytoma.

References

1. Christenson, R. H., Smith, C. W. and Burko, H.: Arteriographic Manifestations of Pheochromocytoma. Am J. Roentgenol. Radium Ther. Nucl. Med., In Press.
2. Glushien, A. S., Mansuy, M. M. and Littman, D. S.: Pheochromocytoma: Its Relationship to the Neurocutaneous Syndromes. Am. J. Med., 14:318, 1953.
3. Harrison, T. S. and Thompson, N. W.: Multiple Endocrine Adenomatosis—I and II. Current Problems in Surgery, Chicago, Year Book Medical Publishers, Inc. 1975.
4. Pearse, A. G. E.: Common Cytochemical and Ultrastructural Characteristics of Cells Producing Polypeptide Hormones (the APUD Series) and Their Relevance to Thyroid and Ultimobranchial C Cells and Calcitonin. Proc. R. Soc. Lond. (Biol.), 170:71, 1968.
5. Pearse, A. G. E.: The Cytochemistry and Ultrastructure of Polypeptide Hormone-producing Cells of the APUD Series and the Embryologic, Physiologic and Pathologic Implications of the Concept. J. Histochem. Cytochem., 17:303, 1969.
6. ReMine, W. H., Chong, G. C., Van Heerden, J. A., et al.: Current Management of Pheochromocytoma. Ann. Surg., 179: 740, 1974.
7. Scott, H. W., Jr., Riddell, D. H. and Brockman, S. K.: Surgical Management of Pheochromocytoma. Surg. Gynecol. Obstet., 120:707, 1965.
8. Steiner, A. L., Goodman, A. D. and Powers, S. R.: Study of a Kindred with Pheochromocytoma, Medullary Thyroid Carcinoma, Hyperparathyroidism and Cushing's Disease: Multiple Endocrine Neoplasia, Type 2. Medicine, 47:371, 1968.
9. Van Way, C. W., III, Scott, H. W., Jr., Page, D. L. and Rhamy, R. K.: Pheochromocytoma. Current Problems in Surgery. June, 1974. Chicago, Year Book Medical Publishers, Inc. 1974.

Discussion

(Note: Some of the discussants' remarks refer to both this paper and to the preceding one by Dr. Frank Glenn.)

Dr. Robert M. Miles (Memphis): We are indeed indebted to Drs. Glenn and Scott for calling attention to these unusual tumors and newer methods of diagnosis and treatment. The hospital incidence in our area is about 1.3 per 100,000 admissions—certainly a rare tumor.

With angiography and the laboratory determinations referred to, it's a far cry from the situation twenty-five years ago, when we had to depend upon a high index of suspicion and sometimes misleading pharmacological tests. But even the new methods of diagnosis and localization are not perfect, and despite preoperative identification of what is thought to be a pheo, at surgery, which is preferably done through the transabdominal approach, a careful search should be made for additional tumors. We have been surprised on more than one occasion to find extra-adrenal tumors.

(Slide) In this patient we found one on the right side; and this is it,

bisected. In addition, we found another in the left adrenal, and an extra-adrenal tumor just above it. That is, three in all. This patient also had a medullary carcinoma of the thyroid, qualifying him for diagnosis of Sipple's syndrome.

(Slide) In another patient, this is the pheo in the organ of Zuckerkandl, between the aorta and vena cava.

Although the alpha and beta blocking agents have simplified management, and have made surgery safer, they are not foolproof. It should be remembered that with propanolol one can titrate the heart rate to zero, if enough is given. One should not take refuge in these agents to the point of delaying surgery unnecessarily. All should be considered urgent. We have seen one patient die the night before surgery was scheduled, and another necessitated emergency surgery at 2:00 a.m. because of rapidly progressing hemiplegia.

As far as location of these tumors is concerned, Dr. Scott mentioned that they may be found anywhere from the base of the brain to the bladder.

(Slide) Actually, they may be found lower than that—in the scrotum. This area should be carefully examined in these patients. If what's thought to be three testicles are found, one should be suspicious of one of them being a pheo.

DR. JOHN VAN HEERDEN (Rochester, Minnesota): As Dr. Scott stated, two years ago, before this very society, Dr. ReMine and I presented our experience with 130 patients with pheochromocytoma. We are certainly pleased that Dr. Scott and his colleagues have so accurately corroborated our results.

I rise for two reasons: Firstly, to ask Dr. Scott whether any of these patients formed part of the multiple endocrine neoplasia type II syndrome; and perhaps he would like to elaborate on the two patients that he mentioned. And secondly, we would like to emphasize the association of pheochromocytoma in this M.E.N. Type II syndrome.

In 1972, Dr. Jackson, *et al.* postulated that C-cell hyperplasia of the thyroid was a precursor, or a premalignant phase, to medullary carcinoma of the thyroid gland in this familial syndrome. Dr. Aiden Carney, one of our surgical pathologists, has similarly postulated that adrenal medullary hyperplasia might indeed be a precursor to pheochromocytoma in the familial syndrome.

This has been substantiated recently by our opportunity to review the adrenal glands in 19 patients with the M.E.N. Type II syndrome. In these 19 patients, we have found synchronous bilateral pheochromocytomas in nine patients, almost 50% of this group, asynchronous pheochromocytoma in one patient, unilateral pheochromocytoma with contralateral medullary hyperplasia in four patients, bilateral adrenal medullary hyperplasia in two patients, no abnormality in two patients, and unilateral pheo in one more.

The clinical importance of both this association of pheochromocytoma in the Sipple syndrome and the premalignant phase could be summarized as follows. Firstly, as Dr. Scott has pointed out, I believe, undiagnosed pheochromocytoma is responsible for significant mortality in this syndrome. The literature reports up to about 22% of causes of death due to hypertensive crises.

Secondly, we all know that advanced adrenal medullary pathology might be present without clinical manifestations.

Thirdly, as we have stressed before, the biochemical tests, and in particular the provocative tests, for pheochromocytoma might be negative in this familial syndrome.

Fourthly, medullary carcinoma can be now readily identified and diagnosed by serum calcitonin assay.

Fifthly, if adrenal medullary hyperplasia is diagnosed, a bilateral total adrenalectomy should be performed. The first such patient that underwent total adrenalectomy at our institution was operated on by our colleague, Dr. Hugh B. Lynn.

Sixthly, (slide) although we all recognize the patient with the typical familial neuroma phenotype we should remember that the non-neuroma phenotype is also encountered quite commonly in the M.E.N. II syndrome.

DR. PAUL T. DECAMP (New Orleans): There is one item in Dr. Scott's presentation that struck my fancy, and that is he was not distressed by the significant number of patients in whom a diagnosis had been made and adequate surgery had been performed, and nevertheless had persistent hypertension. This did not lead him to a guilt syndrome, that he had misdiagnosed and mistreated these patients.

The application of this to another type of surgical hypertension is, perhaps, in order. Years ago, when we first ran into renovascular hypertension, nobody really knew how to make a definition and to some extent that still exists. This has led to a guilt syndrome, because to this day, in spite of adequate diagnostic techniques demonstrating anatomical changes that are appropriate, and then either pharmacologic or hemodynamic findings which are consistent with the disease, and then appropriate and effective treatment, we still find a residual group of hypertensives.

I would simply urge that we should not feel guilty under these circumstances. Some patients who have had hypertension, for some reason, even though that reason has been removed, may still have hypertension. I feel we can go to bed at night with a clear conscience under those circumstances.

DR. H. WILLIAM SCOTT, JR. (Closing discussion): I'm concerned, Dr. Glenn, about the terminology, the use of the term "organ of Zuckerkandl" as a specific item today, as it was used when Zuckerkandl described it in 1901. The question I would like to have you answer is whether it is appropriate to restrict the term "organ of Zuckerkandl" to the paraganglia immediately adjacent to the inferior mesenteric artery, as he described, or, indeed, to all the extra-adrenal paraganglia from the base of the skull to the testicle, or the scrotum.

The pathologists at the Armed Forces Institute of Pathology have come forward with a monograph in which they describe a new concept of the paraganglion system; and they, of course, include the adrenal medulla as the largest collection of paraganglionic tissue in the body. It is today, I believe, most appropriate to think of these specialized cells in relation to their hormonal output, the polypeptide hormones that they secrete, and perhaps leave to the past the old terms of the chromaffin and nonchromaffin responses, and not to dwell too much on differences based on histologic staining characteristics.

I congratulate Dr. Van Heerden and Dr. ReMine on their excellent results. We had two patients only who had the multiple endocrine neoplasia Type II syndrome with bilateral pheochromocytomas. Each of these patients had medullary carcinomas of the thyroid—unfortunately, with liver metastases—and each patient has been studied extensively with great interest in their familial relationships.

The comments by Dr. Myers are very well taken. The problem of pheochromocytoma in pregnancy has been catastrophic, and I congratulate him on his handling of this difficult problem.

Dr. Miles made some very sound points about localization and management of the tumors.

And finally, Dr. DeCamp, I am beset by guilt complexes of all types, specifically those related to pheochromocytoma. Thirty per cent of our patients did indeed have persistent hypertension. None of them had elevated catecholamines. Each has been followed and has been managed satisfactorily, with one exception, on antihypertensive medication. To our knowledge, there are no correctable renovascular hypertensive problems in the group.

One patient who did have a pre-existing arteriolonephrosclerosis, with nitrogen retention, had no response to removal of an extra-adrenal pheochromocytoma, and died in uremia about four or five months after removal of this tumor, which accomplished very little for her advanced status.