Current Management of Pheochromocytoma

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A study of 138 cases of pheochromocytoma encountered at the Mayo Clinic in the years 1926 to 1970 is presented. Of the 138 patients, 63 were males and 75 were females. Their ages ranged from 3 to 78 years with a peak incidence in the fifth decade of life. Hypertension was present in 91% of patients. Symptoms and signs were reported but did not correlate with size, distribution, and location of tumor. The incidence of bilaterality was 4.8%, of extra-adrenal tumors 10%, and of malignancy 13.1%. The diagnostic method used was the determination of metanephrine in 24-hour collections of urine. Nephrotomography was extremely helpful in diagnosis with an accuracy rate of 67.4% for adrenal tumors. The surgical mortality in this series was 2.9%; the recurrence rate after surgical treatment was 9.8% and the 5-year survival subsequent to treatment for the benign tumors was 96% and for malignant tumors, 44%. The actuarial survival curve for patients with benign tumors was similar to that of the normal population, while the curve for malignant tumors showed a significant decrease in survivalship when compared to that of the normal population.

OUR KNOWLEDGE OF PHEOCHROMOCYTOMA has undergone considerable expansion since Dr. Charles Mayo performed the first resection of such a tumor in 1926.[14] Today these functional chromaffin-tissue tumors are best diagnosed by biochemical methods that quantitate catecholamine production and its degradation products such as vanillylmandelic acid (VMA), metanephrine, and normetanephrine.

In the present study, further observations were made on the accuracy of various diagnostic methods [1,2,6,9,20,24,25] in current use, the pathologic behavior of these tumors, and the long-term survival of patients after treatment for localized or benign and metastatic or malignant pheochromocytomas.

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Method

All cases of patients with pheochromocytoma diagnosed and treated at the Mayo Clinic during the years 1926 through 1970 were reviewed. Only those cases in which patients had undergone operation were included. A detailed analysis was made of each patient's age, sex, family history, and presenting symptoms. Results of biochemical tests (24-hour urinary vanillylmandelic acid, metanephrine, normetanephrine, and catecholamines) were tabulated both before and after operation. Followup was on an annual basis. Patients who were operated on more than 3 years prior to the study, who were asymptomatic and doing well, and who were unable to return for followup examination were requested to mail a 24-hour specimen of urine for biochemical analyses.

The pathologic sections were reviewed by one of us (E.G.H.), and criteria used to separate malignant from benign tumors were based on proved metastasis to nonchromaffin tissues since cytologic features could not separate those neoplasms that were more aggressive. Data from the entire group of 138 patients, 18 of whom had malignant disease, form the basis of this report.

Patients were traced by interviews or by letters. Six patients were lost to followup 1, 1, 1, 4, 6, and 10 years after treatment. The shortest followup was 1 year and the longest was 24 years.

Age and Sex

Over the 44-year period, 138 patients with pheochromocytoma were operated upon at this clinic, 63 (45.6%) of whom were male and 75 (54.4%) female. They ranged in age from 3 to 78 years with a median distribution of

46.5 years. About three-fourths of the 138 patients were between 30 and 60 years of age. The peak incidence was in the fifth decade of life (Fig. 1).

There were 18 patients with malignant pheochromocytomas, giving an incidence of malignancy of 13.1%. The sex distribution of this group of patients showed an even higher female preponderance than the total group (72.3% females: 27.7% males). The ages of those patients with malignant disease ranged from 16 to 67 years with a median age of 44 years.

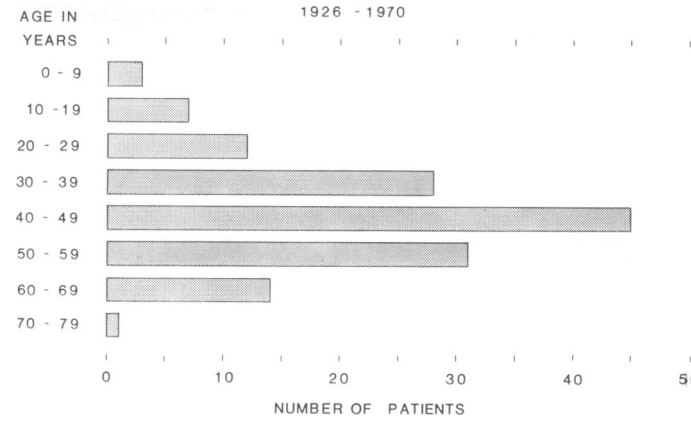


FIG. 1. Pheochromocytoma. Age distribution of 138 patients (1926–1970).

Clinical Presentation

Clinical findings for these patients with pheochromocytoma were similar to those documented in previous publications from this institution.[4,11,17,19,25] The symptoms and signs did not correlate with the size, distribution, location, or histopathologic nature of the tumors.

Hypertension was present in 91% of patients in the series. Although paroxysmal hypertension, with sudden rise of both systolic and diastolic blood pressure, associated with attacks was more dramatic than sustained hypertension for the patient and his physician, it only occurred in 42% of the 138 patients. Sustained hypertension[27] was slightly more common, being present in 49%.

Patients with malignant pheochromocytoma had signs and symptoms similar to those of the group as a whole. Twelve of the 18 patients with malignant tumors presented with hypertension, 2 with definite increase in perspiration, and 4 with abdominal pain due to large, easily palpable abdominal masses.

Associated Diseases

Thirty-two (23.2%) of the patients had cholelithiasis proved radiologically or at operation. Four patients had the Sipple syndrome (positive family history, hyperparathyroidism, medullary carcinoma of the thyroid gland, and bilateral pheochromocytoma). Three of these 4 patients were from one family; the other patient had siblings treated elsewhere. Of 138 patients, only 3 exhibited neurofibromatosis (von Recklinghausen's disease).

Pathologic Aspects

Site

Ninety per cent of the tumors were situated in the adrenal gland and 10% in an extra-adrenal location within the abdomen. No primary tumor was found in the thorax and none in this series involved the urinary bladder wall. Since 1970, two patients with primary functioning paraganglioma in the mediastinum and one with primary pheochromocytoma of the bladder have been seen.

Of 124 intra-adrenal tumors, 70 (56.5%) were in the right gland and 48 (38.7%) in the left. In six patients, tumors were present in both adrenal glands, giving an incidence of bilaterality of 4.8%. Three of the 6 patients with bilateral tumors had a positive family history for pheochromocytoma.

Ninety-three per cent of these tumors were single and 7% were multiple. The distribution of extra-adrenal tumors is shown in Fig. 2. The commonest extra-adrenal[3] tumors were those involving the organs of Zuckerkandl[13] followed by those situated in para-aortic locations.

In the group of patients with malignant tumors, 6 tumors were extra-adrenal and three were bilateral.

Gross Features

The tumors varied considerably in size, measuring 1–16 cm in diameter. The larger growths tended to be associated with cystic necrosis and hemorrhage into the central portion of the tumor. Malignant tumors were among the largest tumors in this series. The average weight of the benign tumors in 88 patients was about 113 gm and of the malignant tumors in 10 patients was 176 gm.

The tumors generally were rounded and encapsulated by a compressed rim of cortical tissue and a thin layer of vascularized fibrous tissue. On the cut surface, they varied from gray to dusky red, and after formalin fixation they appeared yellowish to brown, some showing cystic changes, hemorrhage, and necrosis, which at times had almost destroyed the neoplasm. The formalin solution in which tumor tissue had been stored usually was

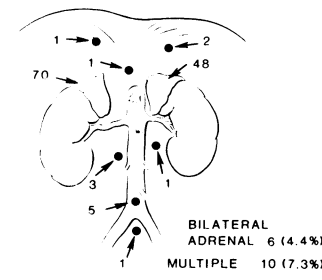
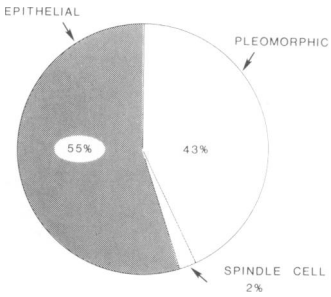


FIG. 2. Tumor locations in 138 patients.

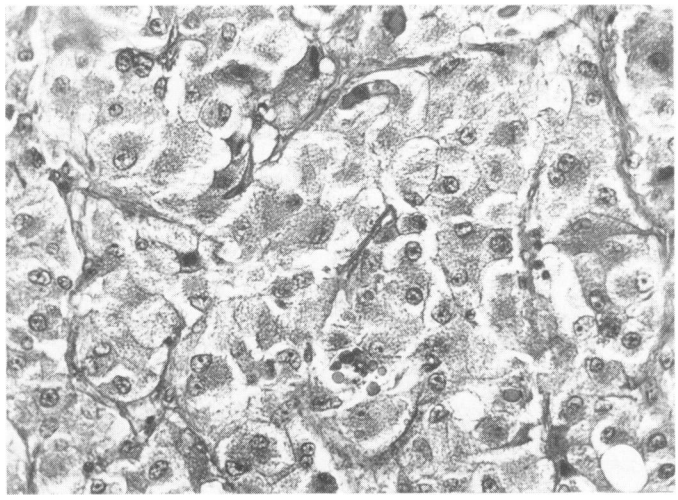
a light brown, ciderlike color that became light green under fluorescent light due to solubilized catecholamine compounds.

Histopathologic Findings

Microscopically, three patterns were seen:[12,15,26] epithelial in 55%, pleomorphic in 43%, and spindel cell in 2% (Fig. 3). In the more common epithelial variety, clusters and cords of cells with abundant granular eosinophilic cytoplasm were scattered uniformly throughout the tumor. These were separated by thin bands of connective tissue with plentiful thin-walled blood vessels in close proximity to tumor cells. Their nuclei were ovoid with moderate-sized nucleoli and occasional hyperchromatic, degenerating forms. In the pleomorphic variety, cells were somewhat similar to the epithelial type but were more varied in shape and size and had more irregular and hyperchromatic nuclei; giant cells were frequent. Irregular hyperchromatic, degenerating nuclei were so common that on first observation a poorly differentiated neoplasm was suggested. The spindle cell variety was uncommon and comprised zones of plump spindle cell forms that often blended into zones similar to the epithelial type. Mitotic figures rarely were identified, and invasion of the adrenal veins was uncommon. No correlation was seen between the histopathologic category of the growth and its behavior in regard to malignancy.



3a.



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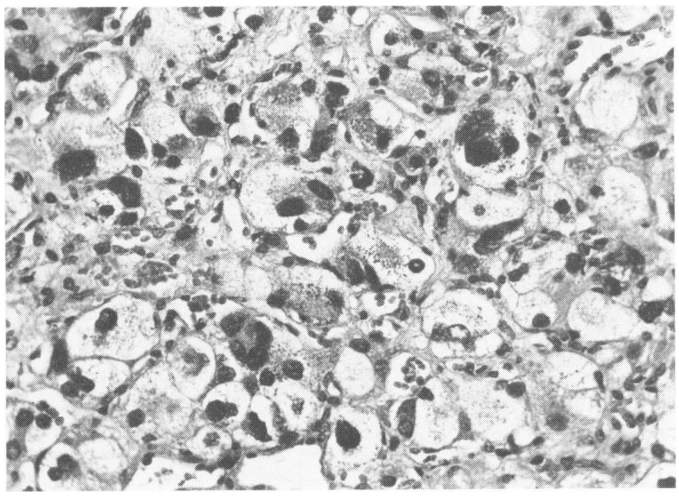

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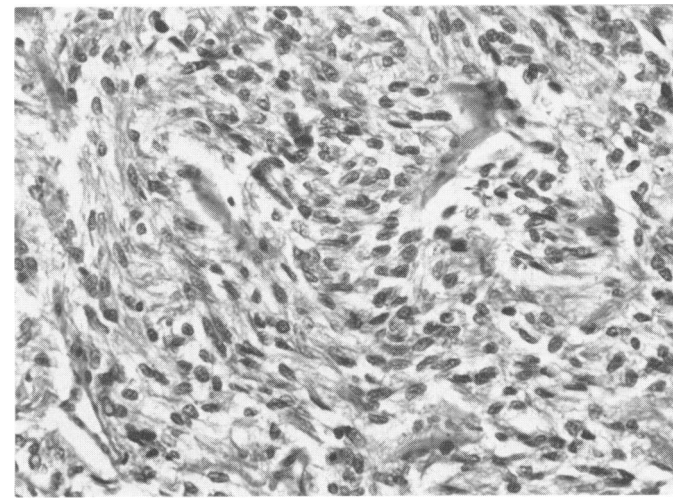

3d.

FIGS. 3a-d. Pathologic variations of 138 tumors. 3a. Distribution of types. 3b. Epithelial. 3c. Pleomorphic. 3d. Spindle cell. (Hematoxylin and eosin stain; ×300.)

Metastasis of tumor to bone occurred in 10 patients, to regional lymph nodes in 9, to the liver in 8, the lungs in 5, the brain and spinal cord in 3, and the pancreas in 1. Several tumors were multiple. Fresh tumor tissues fixed in dichromate solution had a characteristic appearance in that tumor blocks became dark brown due to fine intracytoplasmic granules resulting from the polymerization of catecholamines into colored compounds. A positive chromaffin reaction could not be developed if tissues were previously fixed in formalin, apparently due to previous loss of catecholamine in the formalin solution.

Biochemical Evaluations

Vanillylmandelic Acid Versus Urinary Catecholamines

The 24-hour urinary excretion of catecholamines (UCA) and vanillylmandelic acid (VMA) in 51 pa-

tients with pheochromocytoma is shown in Fig. 4A. In 10 patients (20%), both VMA and UCA were normal; in 4 patients (8%), the VMA levels were elevated while the UCA levels were normal. In six patients (12%), the VMA levels were normal while those for UCA were elevated. Only 31 of 51 patients (60%) had both VMA and UCA levels elevated in the 24-hour specimens of urine.

Metanephrine Versus Vanillylmandelic Acid

The relationship of metanephrine and VMA in the 24-hour output of urine is shown in Fig. 4B. Of 47 patients tested, 2 had normal levels of both metanephrine and VMA; in 12, metanephrine was elevated while VMA was normal. In 33 patients (70%), both metanephrine and VMA were elevated.

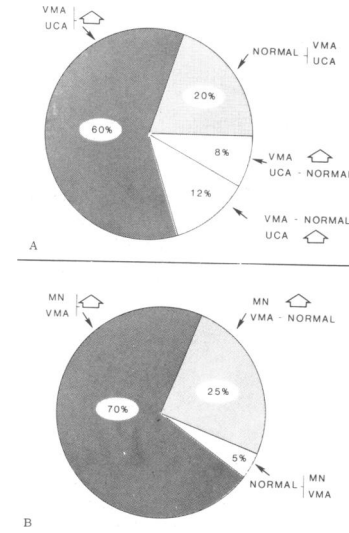

FIG. 4. A. Results of biochemical studies of VMA and UCA in 51 patients (1961–1970). B Results of biochemical studies of metanephrines (MN) and VMA in 47 patients (1961–1970).

Metanephrine Versus Urinary Catecholamines

The relationship between metanephrine and UCA is shown in Fig. 5. Forty-seven patients were examined. Both metanephrine and UCA levels were normal in 2 patients, while metanephrine levels were elevated with normal UCA in 11 patients. In 34 patients (75%), both metanephrine and urinary catecholamine levels were increased in the 24-hour specimens of urine.

Our results showed that the most accurate biochemical test, that is, the one with the least false-negative findings (Fig. 6), was the measurement of the 24-hour urinary excretion of metanephrine. Both UCA and VMA levels gave a rather high percentage of false-negative results (21% and 29%, respectively), while false-negative results were obtained in only 4% with metanephrine. Furthermore, in these patients the increase above normal in excretion of metanephrine was far greater than that for either VMA or UCA.

Radiologic Tests

Radiologic tests included roentgenograms of the chest and abdomen, intravenous pyelography, nephrotomography, and arteriography. When metastatic tumors were suspected, skeletal roentgenograms were helpful. Metastatic bony lesions were observed in the pelvis, vertebral column, femur, ribs, skull, and sternum. These bony lesions were either solitary or multiple, oval or circular, variable in size but averaging about 3.3 cm, and predominantly osteolytic in type.[7] In five patients roentgenograms of the chest revealed multiple small nodular metastatic lesions situated in the peripheral lung fields.

Nephrotomography,[8] used in localization of pheochromocytoma, is most helpful. In the first 5-year period of our study (1961 through 1965) of 27 patients with pheochromocytoma, 12 (44.5%) had nephrotomograms, 6, or 50%, of which were reported to be positive for tumors. In the latter 5-year period (1966 through 1970), 34 of 37 patients with pheochromocytoma had nephrotomograms (92%) and 25 of the 34 were positive for tumors, giving a percentage of 73.5. In the 10-year period, 31 of 46 nephrotomograms were positive, giving diagnostic accuracy of 67.4%.

The size of the tumors was an important factor that determined whether the nephrotomogram was positive or negative, as no tumor smaller than 2.5 cm in diameter was demonstrated in this series. The nephrotomogram confirmed the presence of the tumors and further lateralized their position.

Selective arteriography and venography were of great assistance in localizing extra-adrenal tumors in a few cases, particularly when venography was combined with plasma catecholamine assays as in the "inferior vena cava search."

Diagnosis

In our earlier series, pheochromocytoma was not diagnosed before operation in 10 patients. With the increased awareness of this disease and with improved biochemical methods of measuring metanephrine, VMA, and catecholamines, the condition has been correctly diagnosed before operation in almost all patients seen since 1960.

Determination of metanephrine is the most accurate method available and it is thus ideally suited for screen-

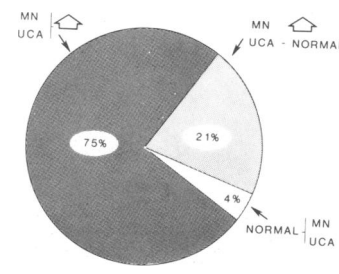

FIG. 5. Results of biochemical studies of MN and UCA in 47 patients (1961–1970).

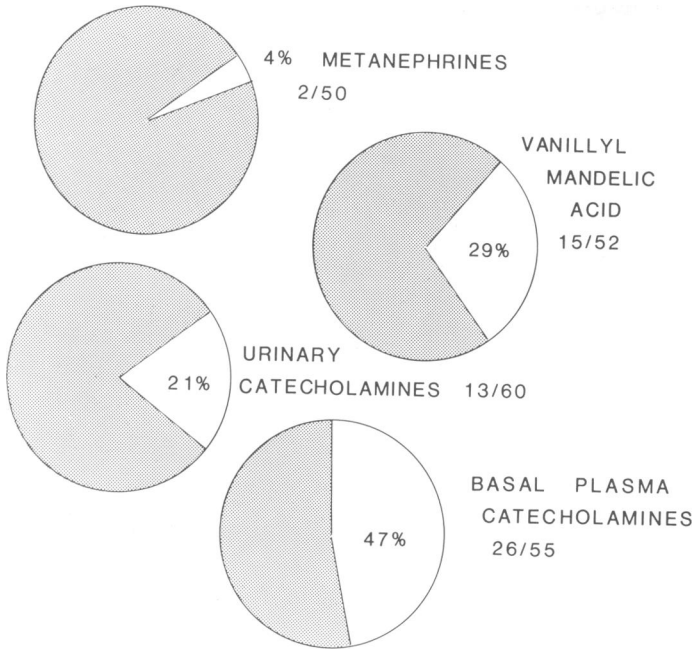

FIG. 6. Comparison of false-negative biochemical studies for MN, VMA, UCA, and basal plasma catecholamines.

ing patients for pheochromocytoma. False-negative results occurred in only 4% of cases in this series. When pheochromocytoma is suspected because of elevated metanephrine and the diagnosis is confirmed by elevated UCA, VMA, plasma catecholamines, and repeat collections, then simple roentgenograms of the chest and abdomen as well as nephrotomograms should be obtained. Nephrotomography is an excellent, noninvasive radiologic tool for diagnosing adrenal tumors greater than 2.5 cm in diameter. We have come to rely more and more on nephrotomography (92% performed in the latter 5 years compared to 44.5% in the earlier 5 years) to localize adrenal tumors before operation. The rate of accuracy of 73.5% in the last 34 nephrotomograms performed in 1965 through 1970 is high enough to justify using this test in all patients suspected to have pheochromocytoma. It carries no mortality and its morbidity is extremely low when compared to arteriography, the use of which had been associated with sudden death[18] and hypertensive crises[1] due to tumor infarction and release of catecholamines. Retrograde venography, when combined with plasma catecholamine assays, is an appealing approach in the localization of extra-adrenal tumors. It was used successfully in only one case in this series.

Since our biochemical methods provide safe, reliable, and accurate means of making a diagnosis, the need for provocative pharmacologic testing with histamine, phentolamine, tyramine, or glucagon has been greatly reduced. Apart from its relative nonspecificity, pharmacologic testing also carries some definite risks of hypertensive crises, cardiac arrhythmias, and sudden death. For those reasons, pharmacologic testing should be reserved for the uncommon selected cases in which biochemical results are equivocal. In these situations, urine and blood should be collected for catecholamines, and urine for VMA and metanephrine estimations; in addition, changes in blood pressure should be observed when histamine is used to stress the tumor.

Preoperative and Anesthetic Management

Prior to 1965, preoperative management of patients with pheochromocytoma consisted of correcting preexisting hypovolemia as well as pulmonary and cardiac risk factors.[23] From 1965 to 1969, a phenoxybenzamine regimen was used in 20 patients (30 to 60 mg orally per day) for 7 to 14 days before operation. Since 1969, patients also received propranolol (30 mg orally per day) for 3 days before operation. Our experience showed that preoperative use of α-adrenergic blocking agent was of considerable help in stabilizing the blood pressure, and we believe that adding propranolol to the preoperative regimen decreased the incidence of cardiac arrhythmias during the surgical procedure.

Effective preoperative preparation—correction of hypovolemia and electrolyte disturbance and a receptor blockade regimen—has decreased the former frightening and "nightmarish" hazards of surgical procedures for this tumor.

Various anesthetic agents have been used, including methoxyflurane, halothane, diethyl ether, and Innovar. Halothane produced ventricular arrhythmias.[7,16,21] Diethyl ether was an excellent agent but because of its explosive property, it was replaced by Innovar.

At the time of operation, the patient's blood pressure, central venous pressure, pulse, blood loss, and ECG should all be monitored continuously. The anesthesiologist should have norepinephrine and blocking agents such as propranolol and phentolamine readily available.

Operative Management

Several surgical approaches have been used, including transabdominal, thoracoabdominal, posterior, and flank incisions. Two reasons persuaded us that the transabdominal approach was mandatory. First, as these tumors were multiple in about 7% of our patients and extra-adrenal in about 10%, thorough exploration of all chromaffin tissue in the abdomen was imperative. Second, associated intra-abdominal diseases, such as cholelithiasis, could be corrected at the same time.

Since the transabdominal approach is sufficient for all the surgical procedures, we do not think it is necessary, or even wise, to transgress the integrity of the pleural cavity. Our preference is for a bilateral subcostal incision. After a general examination of all viscera, particular

attention should be focused on all chromaffin tissues and, finally, on the adrenal glands. The site under suspicion for tumor should be examined last in order to avoid wide fluctuations in blood pressure during palpation, which would make further examination difficult or hazardous. The treatment of choice for single adrenal tumors is adrenalectomy with removal of surrounding fatty tissue. The contralateral gland is examined carefully to exclude bilateral tumors. When bilateral tumors are present, a small portion of hormonal adrenal tissue can be left behind in the gland with the smaller tumor. The results in these studies show that the operative mortality can be kept below 3%.

Malignancy

An incidence of malignant lesions of 13.1% in this series is higher than that reported in series from other institutions. Our criterion for diagnosing malignancy is based on proved spread of tumor to involve the nonchromaffin tissues such as lymph nodes, liver, and bone. Histologic features such as mitosis, giant cells, and nuclear pleomorphism are not reliable factors in making a diagnosis of malignancy, as no correlation exists between the presence of these cellular characteristics and the likelihood of metastasis. Difficulties, however, can arise in diagnosing malignancy when multiple tumors in the periaortic areas are too large for resection and only small specimens are taken for biopsies to establish that the tumor type is a pheochromocytoma. The onus on the surgeon and the pathologist is to prove that there is indeed metastasis before the tumor is labeled as malignant rather than multicentric.

Metastatic tumors are generally functional and when disease recurs, symptoms reappear and hypertension becomes difficult to manage; the biochemical indices of excess production of catecholamines often presage tumor recurrence. The time interval between surgical treatment and recurrence varies and disease can recur many years after the primary lesion has been removed. Our studies showed that in 11 of 13 patients with malignant tumor resected for cure, recurrences developed with a median distribution of 5.6 years after operation. Our policy is to follow the condition of our patients indefinitely, if feasible. A determination of urinary metanephrine is made annually at first and then less often; when findings are abnormal, a search is made for recurrence. When recurrent tumors are proved to exist, an endeavor is always made to remove all the anatomically accessible metastases, unless major medical contraindications dictate against surgical procedures, so as to ameliorate symptoms and allow better control of hypertension, in view of the long survivorship with this tumor. If complete surgical resection of metastatic tumors is not possible, then effort should be made to reduce the size of the tumor. Recurrent disease should be viewed with optimism as it is compatible with long survival, even up to 20 years.

Chemotherapy is of little help in the management of widespread malignant disease as the tumor is not sensitive to most chemotherapeutic agents. In contrast, radiation therapy may be of benefit in palliation.[10]

Followup

Survivalship

All 138 patients were treated surgically, the operative procedures consisting of partial or total adrenalectomy in 124 (118 unilateral and 6 bilateral), excision of tumors in 9, and palliative procedures in 5.

The operative mortality was 2.9%. Four deaths occurred prior to 1965. Two deaths were due to massive uncontrollable bleeding as a consequence of trauma to the inferior vena cava and the common iliac veins. In the other two deaths, cardiac arrests complicated hypotension at the time of operation. The recurrence rate after surgical treatment was 9.8% and the 5-year survival subsequent to treatment was 96% for benign tumors and 44% for malignant tumors.

The 18 patients with malignant pheochromocytoma were treated as follows: 5 patients had palliative procedures, because the tumors had already metastasized when the patients were first seen, and 13 had curative resections. Of these 18 patients, 12 died of the disease 1 month to 17 years after the primary operation, the median interval being 5.6 years; 2 were alive without disease at last followup, and 4 were alive with disease 5, 20, 20, and 21 years after primary surgical treatment. Two factors influenced prognosis. First, significant differences were noted in mortality between the patient with adrenal tumors and those with extra-adrenal tumors. Of 14 patients with extra-adrenal tumors, 4 had metastasis and all 4 died of the disease within 2 years after surgical treatment, a mortality of 28.6%. In contrast, of 124 patients with adrenal tumors, metastasis developed in 14 patients, but at the time of this report only 8 had died of the disease, a mortality of 6.5%. Of the six other patients still alive at last followup, four have active disease and two do not. Secondly, patients with pulmonary metastasis had a poorer prognosis than other patients.[4,5,10,22]

The results of surgical treatment of the patients with nonmalignant pheochromocytomas and those with malignant pheochromocytomas were compared with each other and with a group of normal population (Fig. 7). The actuarial survival curve for the group of patients with benign pheochromocytoma was comparable to the expected survival curve for a group of the same age and sex distribution under the death rates for whites, 1960 (Northwest Central States).

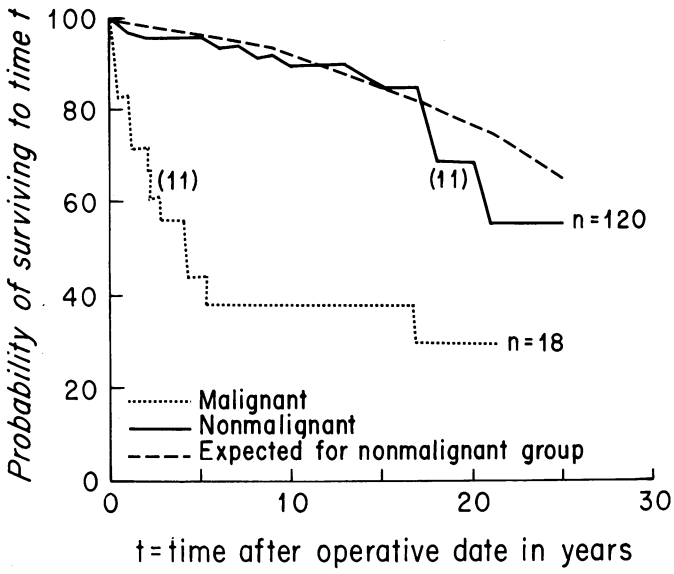

FIG. 7. Actuarial survival curve for patients with benign and malignant tumors compared to that of the normal population.

However, the actuarial survival curve for patients with malignant pheochromocytomas showed a significant decrease in survivorship when compared with the curve for patients with benign tumors or the curve of a normal population of similar age and sex distribution.

Postoperative Blood Pressure Status

The 1-year postoperative blood pressure status of 108 patients with benign pheochromocytoma operated on in 1950 through 1970 was determined. Five patients were lost to followup. Of the other 103 patients, 75 had normal blood pressure while 28 had persistent hypertension 1 year after surgical treatment. Of those with persistent postoperative hypertension, the preoperative clinical setting was as follows: 18 had sustained hypertension, 9 had episodic hypertension, and 1 patient, with Sipple syndrome, was normotensive.

Comment

Pheochromocytomas are functional tumors of chromaffin tissue. The commonest sites of occurrence in order of decreasing frequency are the adrenal glands and extra-adrenal chromaffin tissue in the abdomen, bladder, thorax, and mediastinum. Some chemodectomas of the glomus jugulare and carotid body occurring in the neck may produce catecholamines (functioning paragangliomas) and are difficult to distinguish from pheochromocytomas.[12]

The incidence of pheochromocytoma at the Mayo Clinic as shown at autopsy was 0.1% or 15 of 15,934 autopsies.[15] Kvale *et al.*[11] reported 51 cases in 7,993 patients who were screened with pharmacologic tests and blood catecholamines for hypertension, giving an incidence of 0.63% of patients with pheochromocytoma among hypertensive patients. Four to six new cases of this tumor per year have been encountered in this clinic in the last decade. Two new cases of pheochromocytoma were found in Rochester, Minnesota residents over the past 45 years; thus the yearly incidence of new cases is 0.14 (0.2 to 0.52)/100,000 per annual population. The peak incidence for both benign and malignant pheochromocytoma is in the fourth to fifth decades of life. An interesting finding was the higher preponderance of females in the group with malignant pheochromocytoma, the significance of which remains obscure.

Observations that the right adrenal gland is involved more frequently than the left and that intra-adrenal tumors are about nine times more common than extra-adrenal tumors again confirm studies from other institutions. However, the incidence of bilaterality (4.8%) is lower than most series.

The incidence of Sipple's syndrome is about 3%. Since 1970, several new families of patients with this syndrome have been seen in this institution. Serum calcium and calcitonin levels should be assayed as well as urinary metanephrine in first order relatives of any patient with this syndrome. It is still debatable whether patients presenting with pheochromocytoma as part of this syndrome should have routine cervical exploration for medullary carcinoma of the thyroid gland, even when no thyroid enlargement is noted. Hopefully, the development of a reliable calcitonin assay may resolve this question.

References

1. Amery, A. and Conway, J.: A Critical Review of Diagnostic Tests for Pheochromocytoma. Am. Heart J., **73**:129, 1967.
2. Flint, L. D. and Bartels, C. C.: Ten Years' Experience With 15 Operated Cases of Pheochromocytoma. Surg. Clin. North Am., **42**:721, 1962.
3. Fries, J. G. and Chamberlin, J. A.: Extra-Adrenal Pheochromocytoma: Literature Review and Report of a Cervical Pheochromocytoma. Surgery, **63**:268, 1968.
4. Gifford, R. W., Jr., Kvale, W. F., Maher, F. T., Roth, G. M. and Priestley, J. T.: Clinical Features, Diagnosis and Treatment of Pheochromocytoma: A Review of 76 Cases. Mayo Clin. Proc., **39**:281, 1964.
5. Glenn, F. and Mannix, H., Jr.: The Surgical Management of Chromaffin Tumors. Ann. Surg., **167**:619, 1968.
6. Goldfien, A.: Pheochromocytoma: Diagnosis and Anesthetic and Surgical Management. Anesthesiology, **24**:462, 1963.
7. Gould, A. B., Jr. and Perry, L. B.: The Anesthetic Management of Pheochromocytoma: Cases Involving Nonexplosive Techniques, Metastatic Tumors, and Multiple Procedures. Anesth. Analg. (Cleve.), **51**:173, 1972.
8. Hartman, G. W., Witten, D. M. and Weeks, R. E.: The Role of Nephrotomography in the Diagnosis of Adrenal Tumors. Radiology, **86**:1030, 1966.
9. Hume, D. M.: Pheochromocytoma in the Adult and in the Child. Am. J. Surg., **99**:458, 1960.
10. James, R. E., Baker, H. L., Jr. and Scanlon, P. W.: The Roentgenologic Aspects of Metastatic Pheochromocytoma.

Am. J. Roentgenol. Radium Ther. Nucl. Med., **115**:783, 1972.

11. Kvale, W. F., Roth, G. M., Manger, W. M. and Priestley, J. T.: Present-Day Diagnosis and Treatment of Pheochromocytoma: A Review of Fifty-one Cases. JAMA, **164**:854, 1957.
12. Levit, S. A., Sheps, S. G., Espinosa, R. E., ReMine, W. H. and Harrison, E. G., Jr.: Catecholamine-Secreting Paraganglioma of Glomus-Jugulare Region Resembling Pheochromocytoma. N. Engl. J. Med., **281**:805, 1969.
13. Lulu, D. J.: Pheochromocytoma of the Organs of Zuckerkandl. Arch. Surg., **99**:641, 1969.
14. Mayo, C. H.: Paroxysmal Hypertension With Tumor or Retroperitoneal Nerve: Report of Case. JAMA, **89**:1047, 1927.
15. Minno, A. M., Bennett, W. A. and Kvale, W. F.: Pheochromocytoma: A Study of 15 Cases Diagnosed at Autopsy. N. Engl. J. Med. **251**:959, 1954.
16. Perry, L. B. and Gould, A. B., Jr.: The Anesthetic Management of Pheochromocytoma: Effect of Preoperative Adrenergic Blocking Drugs. Anesth. Analg. (Cleve.), **51**:36, 1972.
17. Priestley, J. T., Kvale, W. F. and Gifford, R. W., Jr.: Pheochromocytoma: Clinical Aspects and Surgical Treatment. Arch. Surg., **86**:778, 1963.
18. Rossi, P. Young, I. S. and Panke, W. F.: Techniques, Usefulness, and Hazards of Arteriography of Pheochromocytoma: Review of 99 Cases. JAMA, **205**:547, 1968.
19. Roth, G. M., Flock, E. V., Kvale, W. F., Waugh, J. H. and Ogg, J.: Pharmacologic and Chemical Tests as an Aid in the Diagnosis of Pheochromocytoma. Circulation, **21**:769, 1960.
20. Roth, G. M. and Kvale, W. F.: A Tentative Test for Pheochromocytoma. Am. J. Med. Sci., **210**:653, 1945.
21. Schnelle, N., Carney, F. M. T., Didier, E. P. and Faulconer, A., Jr.: Anesthesia for Surgical Treatment of Pheochromocytoma. Surg. Clin. North Am., **45**:991, 1965.
22. Scott, H. W., Jr., Riddell, D. H. and Brockman, S. K.: Surgical Management of Pheochromocytoma. Surg. Gynecol. Obstet., **120**:707, 1965.
23. Sheps, S. G.: Pheochromocytoma. *In* Cardiovascular Disorders. A. N. Brest and J. H. Moyer, editors. Philadelphia, F. A. Davis Company, 979, 1968.
24. Sheps, S. G. and Maher, F. T.: Comparison of the Histamine and Tyramine Hydrochloride Tests in the Diagnosis of Pheochromocytoma. JAMA, **195**:265, 1966.
25. Sheps, S. G., Tyce, G. M., Flock, E. V. and Maher, F. T.: Current Experience in the Diagnosis of Pheochromocytoma. Circulation, **34**:473, 1966.
26. Sjoerdsma, A., Engelman, K., Waldmann, T. A., Cooperman, L. H. and Hammond, W. G.: Pheochromocytoma: Current Concepts of Diagnosis and Treatment. Ann. Intern. Med., **65**:1302, 1966.
27. Thomas, J. E., Rooke, E. D. and Kvale, W. F.: The Neurologist's Experience With Pheochromocytoma: A Review of 100 Cases. JAMA, **197**:754, 1966.

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.