CASE 1:
A man, age 19, noticed an ill-defined swelling of his right neck for five months. At this time a lymph node was biopsied and reported as nodular hyperplasia. The swelling slowly increased over the next two months. A surgical exploration revealed a large soft tan colored invasive tumor in the right paraspinal muscles. There was bone involvement.

CASE 2:
A man, age 70, had noticed an asymptomatic mass in his right axilla for one year. Four months ago it began to enlarge and he developed clinical evidence of brachial plexus involvement. During this period he had temperature elevation up to 102 degrees Fahrenheit. His W.B.C. was 8,400 with 13.5% eosinophils. A 6 x 5 x 4 cm invasive tumor was excised.

CASE 3:
A man, age 63, had experienced episodes of pain and swelling of his right foot for 15 years. A diagnosis of gout had been suspected but not established by his home physician. When examined at the Mayo Clinic there was a firm mass on the lateral aspect of his foot. An amputation through the mid-leg was done.

CASE 4:
A man, age 53, was found to have a mass on his right shoulder when he presented himself for a routine examination. The lesion was asymptomatic, has been present for 3-4 years but had enlarged during the past three months. A circumscribed tumor 5 x 5 x 4 cm was excised from the subcutaneous tissue.

CASE 5:
A woman, age 51, was seen because of an enlarging mass deep in the left buttock. In 1969 a chordoma had been excised from her sacrum. The chordoma recurred in 1971 and it was treated by surgical excision and radiation (5250 rads). In June of 1975 the patient was seen at the Mayo Clinic because of a large recurrence of the sacral mass and two pulmonary nodules. The patient was given chemotherapy (vincristine, Cytoxan, dactinomycin, Cis-Platinum). By January 1976 there was complete remission of the sacral and pulmonary masses. In October of 1979 a mass in the left buttock was found and excised. The slides are from this tumor.
CASE 6:  
This 66-year-old woman noted a sudden throbbing pain in the anterior neck associated with a feeling of obstruction in her throat. Her physician noted a mass in the left lobe of the thyroid. RMR was reported as +2 and the P.B.I. 5 μg%. At the time of thyroid surgery, a 2 cm circumscribed nodule was noted in the left lobe, represented by this section.

CASE 7:  
This 54-year-old asymptomatic woman during a routine examination was noted to have an enlarged thyroid gland and a firm nodule in the left lobe, 2 cm in diameter. Sections are from the nodule.

CASE 8:  
Male, 55, developed asymptomatic lump in right mid neck 1½ to 2 years prior to admission. The mass grew very slowly during this period of time. Two weeks prior to admission, right cervical lymph node was removed and the patient referred to the Mayo Clinic with a diagnosis of metastatic carcinoma. There were no symptoms referable to chest or urinary tract. 

Admission chest x-ray: Pathologic process in right base, probably bronchiectasis. 
Examination: Mass in right neck which does not move with swallowing. Thyroid primary versus metastatic cancer to neck. 
Surgery: Total right thyroid lobectomy with removal of isthmus. 
Sections are of right thyroid mass.

CASE 8:  
Male, 70, came to the Mayo Clinic in October, 1954, because of a lump in the left side of the neck said to have been present for 40 years. Patient otherwise asymptomatic. 
Surgery: Total right thyroid lobectomy with removal of isthmus. Sections are of left thyroid mass.

CASE 9:  
Female, age 69, admitted on April 3, 1957, with long history of renal calculi, multiple fractures, tumor of ulna and mass in neck. 
Prior surgery: 1936 - Right total lobectomy of thyroid; 1954 - Resection proximal third of ulna. 
Physical examination: Large nodular mass, left neck, extending beneath sternum. Tumorous enlargement of right lower ribs. 
Laboratory data: Serum calcium, 12.0 mgms; phosphorus, 3.3 mgms per 100cc serum; alkaline phosphorus, 247 units. 
Surgery: February 25, 1957: subtotal resection of the left lobe of the thyroid (right lobe resected prior). Hugh cystic mass on the left displacing trachea markedly to the right extending beneath sternum. Mass resected weighed 132 grams. Sections are from mass adjacent to thyroid.

CASE 10:  
Female, age 24, presented with asymptomatic nodule in thyroid gland. Sections are from thyroid nodule.
DIAGNOSES

CASE 1: Extra-osseous Ewing's sarcoma.

CASE 2: Angioblastic lymphoid hyperplasia with blood eosinophilia (Kimura's disease).

CASE 3: Synovial sarcoma.

CASE 4: Pleomorphic lipoma.

CASE 5: Malignant fibrous histiocytoma, inflammatory variant.


CASE 7: Medullary carcinoma vs. spindled trabecular adenoma. Patient is 13 years postoperative with no recurrence.

CASE 8: Clear cell follicular carcinoma: primary in thyroid.
   (a)

CASE 8: Metastatic renal cell carcinoma (hypernephroma).
   (b)

CASE 9: Primary waterclear hyperplasia of parathyroid glands.

CASE 10: Chemodectoma (cellular with mitoses) in thyroid gland. Patient is well 4 years later.
would not be devastating; this proved to be correct. Although the "blowout" on the artery suggested that the subacute infection remained confined to a smaller area of the wall inspection of these aneurysms showed that the necks had a broad origin from at least half the circumference. A clip or ligature would surely have occluded the vessel.

The urgency of craniotomy depends on the site of the aneurysm and whether a significant clot is present. In 3 cases a large intracerebral clot prompted immediate operation. These patients fared poorly; Case 2 died, and Cases 1 and 3 were left with permanent severe deficits. It is unfortunate that the nature of the first aneurysm in Case 3 was not recognized, for treatment might have prevented the severe hemorrhage from the second three months later.

In the absence of significant clot or repeated hemorrhages the location of the aneurysm will determine the priority of medical or surgical treatment. The more peripheral aneurysms should be excised or obliterated promptly since the ensuing neurologic deficit is likely to be negligible. If the aneurysm arises from a major vessel a delay of operation must be considered. Massive appropriate antibiotic therapy should destroy the organism and allow some reparative fibrosis to take place in the wall of the aneurysm and parent artery. A clip or ligature can then more safely be applied, and the unfortunate consequences of an operation on a fragile, acutely inflamed aneurysm, as in Case 2, thus avoided. Such a delay is undoubtedly dangerous because of the possibility of repeated bleeding. In addition the aneurysm may enlarge, as shown angiographically in Case 4 during the four-week period of antibiotic treatment. The decision for delay should be applied only to aneurysms on major vessels and should be based on the improbability of safe surgical treatment at an earlier stage. In cases in which ligation or excision is not possible, or would produce a serious infarct, it might be wise to wrap the lesion in a plastic jacket and rely on antibiotics to destroy the infection within.

**SUMMARY AND CONCLUSIONS**

Rupture of a cerebral aneurysm caused by myotic organisms is a rare cause of spontaneous intracranial bleeding. Of 191 cases (2.6 per cent) were of infectious origin (1 patient had 2 such aneurysms).

These cerebral aneurysms should be suspected if there is an obvious infection, murmur, splenomegaly, petechiae, microscopic hematuria, fever or elevated sedimentation rate, an aneurysm in a peculiar site or a second aneurysm.

Each aneurysm was treated surgically. Two patients are well, 1 is dead, and 2 have serious neurologic deficit. None have clinically significant heart disease.

Peripheral aneurysms should be excised or ligated immediately. Aneurysms involving major vessels should probably be treated with antibiotics initially unless a significant clot is present. Although this delay carries the risk of recurrent bleeding, the resolution of the arterial infection should make the aneurysm less fragile for surgical treatment.

**REFERENCES**


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**MALIGNANT CARCINOID SYNDROME** ASSOCIATED WITH NONCARCINOID TUMORS*

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DURING the past decade the "malignant carcinoid syndrome" has been a favored subject in the medical literature because of the dramatic nature of its acute and chronic clinical manifestations and of its as yet unresolved challenges to the physiol-


drone" coexistent with and presumably produced a primary solid thyroid carcinoma with metastasis.

**Case Report**

A 66-year-old woman was first admitted to the Mayo Clinic on April 13, 1962, because of a mass in the neck that had noted accidentally 2 months previously. She had no significant symptoms, and physical examination revealed only a solitary, firm, 2-cm. nodule in the left lobe of the thyroid gland. Results of basic laboratory studies and assessment of thyroid function were within normal limits. April 20 a total lobectomy on the left and subtotal on the right, with removal of the thyroid isthmus, was performed. At operation the left inferior parathyroid was noted to be enlarged and was also excised, as was the tracheoesophageal lymph nodes. Adenopathy was noted along the jugular vein. Pathological examination revealed a circumscribed, infiltrative carcinoma, 2 cm. in lesser, in the left lobe of the thyroid gland. In addition, there was a single Hurthle-cell adenoma, 1.5 cm. in diameter, within the lobe. The right lobe showed normal thyroid architecture, with slight focal fibrosis. Histologically, the carcinoma was moderately active (Grade according to Broders' classification) and had a solid pattern (Fig. 1a).

Some central hyaline fibrosis was present. Although solid (nonglandular), the tumor appeared somewhat more active than the subtype of thyroid carcinoma that recently referred to as "solid (medullary) carcinoma with solid stroma." Mitotic activity seemed somewhat less than that seen in the anaplastic form of thyroid cancer. Locally, the parathyroid adenoma was 8 mm. in diameter and weighed 350 mg. Microscopically, it consisted of mixed epithelial and transitional water-clear cells.

Because of the parathyroid adenoma the serum calcium was determined at the time of operation and was found to be 2.3 mg. per 100 ml. (normal, 8.9 to 10.1 mg.). Twenty-four hours after the operation the value was 8.7 mg.; at 6 days, to 8.9 mg., and on the 17th postoperative day, it had risen to 9.6 mg. Although data were incomplete, it was as if that this patient had had primary hyperparathyroidism.

February, 1963, she noted enlarged lymph nodes in the side of the neck. She returned to the Clinic on May 3, at which time a radical neck dissection was performed. Pathological examination showed metastatic, Grade 3, solid carcinoma involving multiple lymph nodes of the middle and lower jugular regions. The histologic architecture was identical with that of the tumor in the corresponding lobe previously resected (Fig. 1b).

The patient remained asymptomatic during 1963 and early 1964. She returned again on August 25, 1964, when she stated that for 6 months she had had recurrent attacks of intense flushing involving the face and chest. The attacks occasionally came on after the ingestion of a large meal but were invariably precipitated by the use of alcohol. Very small quantities of alcohol were required to precipitate an attack, and she became flushed after taking a sip of her husband's beer or a single teaspoonful of elixir of terpin hydrate and codeine, which she took for a cold. Two and a half months before this admission, she had noted the sudden onset of diarrhea, which had persisted. She had from 15 to 20 watery stools daily, 5 or 6 of them awakening her from sleep at night. Because profuse diarrhea occurred after meals, she was afraid to eat, with a resultant 13.6-kg. (30-pound) loss in weight. She had had no respiratory symptoms or skin rash. For the previous 5 months she had noted a progressively enlarging nodule in the skin of the left-temple area. Physical examination revealed a hard node, deep in the left side of the neck, and a raised, tender cutaneous lesion of the left temple, 1 by 1.2 cm. She had no heart murmurs. A typical carcinoid flush was reproduced by the ingestion of alcohol. Normal results were obtained from routine hematologic studies and tests of blood sugar and serum electrolytes. The carcinoid syndrome, including alkaline phosphatase, prothrombin time and bromsulfalein retention, and from tests of thyroid function, including basal metabolism and protein-bound iodine. Chemical analyses of fecal fat showed that daily excretion was 3.2 gm. and that fat constituted 16 per cent of the total fecal solids. A urinalysis for catechol amines was negative. A liver scan with 131-iodinated rose bengal was within normal limits. A proctoscopic examination showed sacculation of the sigmoid and several diverticula. A roentgenogram of the colon demonstrated diverticulosis; roentgenograms of the stomach and small bowel were normal. X-ray study of the chest disclosed fibrosis and calcification in both apexes that had been present and unchanged for at least 17 years, which was consistent with a previously known tuberculous infection in 1920. Studies pertinent to the patient's carcinoid syndrome are listed in Table 2. On September 9, 1964, the skin lesion was excised, and histologic sections revealed metastatic, Grade 3, solid carcinoma identical in structure with the thyroid tumor (Fig. 1c). Seven days later, abdominal exploration revealed multiple metastatic nodules, measuring up to 1 cm. in diameter, in the right and left lobes of the liver. There was a superficial, solitary 2-cm. nodule in the body of the pancreas. Both liver (Fig. 1d) and pancreatic nodules were similar in histologic structure to that seen in the thyroid gland. A careful search of the entire gastrointestinal tract gave no evidence of carcinoid tumor,
and there was no involvement of the mesenteric lymph nodes. The appendix had been removed for acute appendicitis in 1923. The concentrations of 5-hydroxytryptamine (serotonin, 5-HT) in the metastatic lesions of the skin and liver are given in Table 2. Serotonin was not detected in a specimen of normal skin. After operation, the diarrhea and flushing continued, and the patient complained of pain in the right hip. A roentgenogram of the pelvis showed a metastatic lytic lesion involving the right innominate bone.

**DISCUSSION**

The "malignant carcinoid syndrome" in this pa-
Asympt of 5-Hydroxyindoles and Histamine in a "Malignant Carcinoid Syndrome" Associated with Noncarcinoid Tumors.

<table>
<thead>
<tr>
<th>URINE*</th>
<th>SOURCE</th>
<th>CUTANEOUS METASTASES</th>
<th>HEPATIC METASTASES</th>
<th>UNINVOLVED SKIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>per 24 hr.</td>
<td>per ml.</td>
<td>per gm.</td>
<td>per gm.</td>
<td>per gm.</td>
</tr>
<tr>
<td>55.2, 41.2, 45.7, 56.7 mg. (normal, &lt;9 mg.)</td>
<td>None detectable</td>
<td>0.6, 0.4 microgm. (normal, &lt;0.3 microgm.)</td>
<td>31.1 microgm.</td>
<td>63.5 microgm.</td>
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5-HIAA measured by method of McFarlane et al.; paper chromatographic studies of 5-hydroxyindoles in urine, according to Smith, revealed presence or absence of 5-HT & 5-HTP.

Determination of 5-HT in whole blood measured by method of Udenfriend.

Determination of 5-HT in tissue homogenates determined after preincubation as described by Weissbach et al., followed by reaction. 12

as definitely established. The attacks of diarrhea and the diarrhea were both typical. Lab results were likewise diagnostic, with high levels of 5-hydroxyindoleacetic acid (A) in the urine and high levels of blood 5-HT. The onset of the carcinoid syndrome had been delayed until there were hepatic metastases.

Once that this syndrome was not produced by primary carcinoid tumor is also strong for observations, including abdominal explorations of such tumors. The most convincing, however, was the very high serotonin of tumor regions that, histologically, were carcinoid type.

Exact pathological classification of the tumor itself. Intestinal or bronchial carcinoid was ruled out because the cells were considerably larger than usual carcinoid figures were more numerous than would be expected in a carcinoid. The time sequence in a primary thyroidal neoplasm, with metastatic regional lymph nodes one year later and spread to the liver, pancreas, skin of the abdominal bone, sixteen months after the original tumor. As a primary thyroidal lesion, the tumor resembled the subtype designated as "solid with amyloid stroma." Although zones of fibrosis were present, classic amyloid change was minimal, and the degree of mitotic activity was at greater than in the usual carcinoma of the thyroid gland. Metastasis to the thyroid gland from a small primary lesion in the liver must be considered a strong alternative possibility, especially in view of the fact that 2 of the other previously cited cases had a primary pancreatic adenocarcinoma. In our opinion, however, the histology, the time sequence and the pattern of metastatic spread tip the scales in favor of a primary lesion in the thyroid gland.

Some common denominator among the cases of carcinoid tumors associated with the "malignant carcinoid syndrome" may be present. All the cases reported with known primary sources have originated in tissues derived from the entoderm of pouches of the primitive foregut — that is, pancreas, lung and thyroid gland. The possibility of a stem cell common to all these tumors, therefore, can be considered.

Of interest is the fact that 3 of the 8 patients had no other evidence of endocrine hyperfunction. The patient of Harrison and his associates had Cushings syndrome, apparently related to an oat-cell carcinoma of the lung since the adrenal glands were normal at autopsy; the same tumor presumably was responsible for the patient's "malignant carcinoid syndrome." The patient of van der Veer and his co-workers had an insulin-producing, malignant islet-cell tumor and had well documented hypoglycemic attacks, the same tumor seemingly producing a carcinoid syndrome. The patient described above had a parathyroid adenoma with hypercalcemia and was assumed to have hyperparathyroidism. Although the possibility of coincidence cannot be denied, the odds against 3 such examples of endocrine hyperfunction occurring by chance among 8 patients chosen at random seem to be astronomically high. Furthermore, a similar association of hyperfunctioning endocrine tumors has been noted with bronchial carcinoid tumors, 13 also derived from the primitive foregut.

As more cases of this kind are studied, these problems may be clarified.

SUMMARY

A case involving a metastatic solid carcinoma that was assumed to have its origin in the thyroid gland and was associated with high tumor serotonin content, hyperserotonemia and a "malignant carcinoid syndrome" is reported. In this case a parathyroid adenoma and hyperparathyroidism were also noted.

Of the 8 cases (including the present case) of "malignant carcinoid syndrome" associated with noncarcinoid tumors now reported, 7 in which the primary tumor was known to have arisen in tissues with a common embryologic anlage. Three of these 8 patients also had other conditions of endocrine hyperfunction.

REFERENCES

VASCULAR LESIONS CAUSING HYPERTENSION IN NEUROFIBROMATOSIS

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NEUROFIBROMATOSIS is a congenital and hereditary disorder involving ectodermal, neuroectodermal and mesodermal tissue. Café-au-lait spots, cutaneous neurofibromas, tumors of the central and peripheral nervous systems, skeletal changes of scoliosis, orbital-wall defects, pseudarthrosis and gigantism are well known manifestations. The occurrence of vascular lesions is less well known but has been described by a number of authors.1-4 These vascular changes are said to predominate in the kidneys, adrenal glands, heart and gastrointestinal tract, and may lead to arterial stenosis or obliteration of the arterial lumen. When these vascular lesions of neurofibromatosis involve the abdominal aorta or the renal arteries systemic arterial hypertension may result.

Two recent cases of neurofibromatosis, hypertension and renal-artery stenosis have been studied at the New York Hospital. We have also obtained additional information by reviewing the case reported from this institution by Glenn et al.5 in 1952. We have been able to find only 7 similar cases in the literature, the details of which are given in Table 1.

CASE REPORTS

CASE 1.‡ A 19-year-old woman presented generalized neurofibromatosis manifested by café-au-lait spots, multiple neurofibromas and moderate scoliosis. Multiple facial hemangiomas present an at birth later coalesced to create disfigurement requiring repetitive facial surgery. Severe systemic hypertension in the range of 230/120 in the upper extremities and 150/120 in the lower extremities had been recognized for 10 years. Intravenous and retrograde arteriography revealed a fusiform narrowing of the lower thoracic and proximal abdominal aortic involving the celiac axis, with extension down to the renal arteries. A large aneurysm of the proximal portion of the right renal artery was present. Operation consisted of a bypass of the coiled segment of the aorta utilizing the splenic artery. A tuft of densely adherent fibrotic tissue surrounded and constricted the aorta at the level of the 11th and 12th thoracic segments. Histologically, this was composed of fibrous and muscular layers of age revealed a pleural fibroma. Numerous café-au-lait spots were present over the body. The patient's mother also had neurofibromatosis. Hypertension was first noted at the age of 3½ years, and in recent years the blood pressure had ranged from 145/36 to 193/130. The systemic arterial hypertension had been relatively unaffected by antihypertensive therapy during the last 5 years.

Pertinent studies performed during the repeated hospital admissions revealed normal excretory urograms at the age of 4 and at the age of 12. Fractional intravenous and retrograde pyelograms at 13 and 14 years of age were normal. At that time a radioisotope renogram was interpreted as giving no evidence of unilateral renovascular dysfunction. Differential renal-function studies were normal at the age of 14 and 18. All biochemical and laboratory studies, including an angioensin assay, were within normal limits.

On percutaneous transfemoral renal arteriography and selective renal arteriography performed in 1963 (Fig. 1) the proximal half of the right main renal artery was absent. Renal blood flow on this side was provided by collateral channels from the 12th intercostal artery, the inter- and suprarenal arterial and the hypogastric arteries. Stenosis of the left main renal artery, with 3 aneurysms distal to the stenotic segment, was observed. Operation was contraindicated by the complexity of the arterial lesions.

CASE 2. An 18-year-old boy had had 19 admissions to the New York Hospital for correction of disfiguring facial neurofibromas. Facial hemangiomas‡ presumed at birth later coalesced to create disfigurement requiring repetitive facial surgery. Severe systemic hypertension in the range of 230/120 in the upper extremities and 150/120 in the lower extremities had been recognized for 10 years. Intravenous and retrograde arteriography revealed a fusiform narrowing of the lower thoracic and proximal abdominal aortic involving the celiac axis, with extension down to the renal arteries. A large aneurysm of the proximal portion of the right renal artery was present. Operation consisted of a bypass of the coiled segment of the aorta utilizing the splenic artery. A tuft of densely adherent fibrotic tissue surrounded and constricted the aorta at the level of the 11th and 12th thoracic segments. Histologically, this was composed of fibrous and muscular layers of age revealed a pleural fibroma. Numerous café-au-lait spots were present over the body. The patient's mother also had neurofibromatosis. Hypertension was first noted at the age of 3½ years, and in recent years the blood pressure had ranged from 145/36 to 193/130. The systemic arterial hypertension had been relatively unaffected by antihypertensive therapy during the last 5 years.

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CASE 3. A 3¾-year-old girl was admitted to the New York Hospital in 1954, when systemic arterial hypertension (blood pressure of 150/110) was detected during the course of routine follow-up observation of a known cystic meningioma of the third ventricle. Blood pressure had been normal. Café-au-lait spots were present over the trunk and extremities, without associated skin nodules. A complex radiographic skeletal examination revealed mild scalloping of the anterior margins of the 4th through 9th thoracic segments. The patient's father also showed café-au-lait spots but no other manifestation of neurofibromatosis.

Routine laboratory studies, blood chemical findings and catecholamine determinations were within normal limits. Fractional intravenous pyelography showed normal and

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†Aided by a grant from the Whitehall Foundation.
‡Associate professor of radiology, Cornell University Medical College.
§Previously reported by Glenn et al.5