Catecholamines in the Localization of Pheochromocytoma

By J. Richard Crouth, M.D., and Albert Sjoerdsma, M.D., Ph.D.

THE MEASUREMENT of norepinephrine and epinephrine in urine and plasma provides a reliable basis for the diagnosis of pheochromocytoma.1,2 Previous work1,3 has suggested that these assays may also be helpful in defining the location of the tumor in the body, thereby facilitating successful surgical treatment. In 6 cases of pheochromocytoma von Euler3 noted a correlation between the type of amine excreted in the urine and the location of the tumor: 3 patients excreted increased amounts of epinephrine as well as norepinephrine and had tumors of the adrenal regions, while the other 3 excreted norepinephrine alone and had tumors in extra-adrenal sites. In a later review of 35 cases of pheochromocytoma, however, von Euler and Ström1 noted several exceptions to this general correlation between the type of amine excreted and the location of the tumor. They concluded that the differential catecholamine assay in urine provided only suggestive evidence of tumor location. More precise information concerning the tumor site was obtained by catheterizing the venae cavae and demonstrating an increase in plasma catecholamine concentration at the level of venous drainage from the tumor.1,4

To evaluate the practical usefulness of these approaches for localizing pheochromocytomas, we have reviewed our own and other data on urinary catecholamine excretion. In addition, we have performed 6 venous catheterizations in 5 patients with pheochromocytoma to determine the plasma catecholamine concentration at various locations within the great veins. The results indicate that both procedures may be distinctly helpful under selected circumstances in the preoperative localization of the tumor.

Materials and Methods

Twenty-four-hour urine specimens obtained from 18 patients with pheochromocytoma were assayed for free norepinephrine and epinephrine by a modification5 of the fluorimetric method of von Euler and Floding.6 The catecholamine content of pheochromocytoma tissue was determined by homogenizing a portion of tumor in trichloroacetic acid and assaying the supernatant colorimetrically or fluorimetrically.7 Epinephrine values were considered to lack quantitative significance when they were less than 10 per cent of the norepinephrine figure.

Vena caval catheterization was performed in 5 cases through either an antecubital or saphenous vein. Blood samples were obtained at various sites within the venae cavae as the catheter was withdrawn and repositioned under fluoroscopic control. The specimens were drawn approximately at 3-minute intervals on any single passage up or down the venae cavae. The blood samples (20 to 30 ml.) were collected in heparinized syringes and stored in ice until the procedure was completed. Plasma obtained after centrifugation was assayed fluorimetrically for catecholamines (as norepinephrine equivalents) by the ethylenediamine condensation procedure of Weil-Malherbe and Bone.8

Results

The results are given in two sections: the first presenting data on urinary catecholamine excretion and tumor location in the entire series of patients, and the second describing in detail the case histories of 5 patients upon whom vena caval catheterizations were performed.

Urinary Catecholamines and Tumor Location

The values for free urinary norepinephrine and epinephrine in 18 cases of pheochromocytoma are shown in table 1. In cases 1 to 14 norepinephrine was the predominant catecholamine in the urine; the epinephrine value in each case was less than 10 per cent of the norepinephrine excretion. Eleven of these patients had tumors of the adrenal gland and the remaining 3 had tumors in nonadrenal sites. Cases 15 to 18 showed a significant elevation of epinephrine as well as of norepi-
Table 1
Urinary Excretion of Free Catecholamines and Location of the Tumor in Eighteen Patients with Pheochromocytoma

<table>
<thead>
<tr>
<th>Case no.*</th>
<th>Norepinephrine (μg./day)</th>
<th>Epinephrine (μg./day)</th>
<th>Location of tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>310</td>
<td>I</td>
<td>Right adrenal</td>
</tr>
<tr>
<td>2</td>
<td>320</td>
<td>I</td>
<td>Right adrenal</td>
</tr>
<tr>
<td>3</td>
<td>97;‡</td>
<td>I</td>
<td>Right adrenal</td>
</tr>
<tr>
<td>4</td>
<td>1510</td>
<td>I</td>
<td>Right adrenal</td>
</tr>
<tr>
<td>5</td>
<td>930</td>
<td>I</td>
<td>Left adrenal</td>
</tr>
<tr>
<td>6</td>
<td>1590</td>
<td>I</td>
<td>Left adrenal</td>
</tr>
<tr>
<td>7</td>
<td>3800</td>
<td>I</td>
<td>Right adrenal</td>
</tr>
<tr>
<td>8</td>
<td>620</td>
<td>I</td>
<td>Bilateral adrenal tumors</td>
</tr>
<tr>
<td>9</td>
<td>820</td>
<td>I</td>
<td>Right adrenal</td>
</tr>
<tr>
<td>10</td>
<td>260</td>
<td>I</td>
<td>Left adrenal</td>
</tr>
<tr>
<td>11</td>
<td>740</td>
<td>I</td>
<td>Generalized metastases, presumably from adrenal tumor removed 2 years previously.</td>
</tr>
<tr>
<td>12</td>
<td>3000</td>
<td>I</td>
<td>Right adrenal</td>
</tr>
<tr>
<td>13</td>
<td>880</td>
<td>I</td>
<td>Behind inferior vena cava, medial to right adrenal.</td>
</tr>
<tr>
<td>14</td>
<td>2700</td>
<td>I</td>
<td>Right side of neck</td>
</tr>
<tr>
<td>15</td>
<td>690 280</td>
<td></td>
<td>Right adrenal</td>
</tr>
<tr>
<td>16</td>
<td>42 36</td>
<td></td>
<td>Left adrenal</td>
</tr>
<tr>
<td>17</td>
<td>1030 510</td>
<td></td>
<td>Right adrenal</td>
</tr>
<tr>
<td>18</td>
<td>690 110</td>
<td></td>
<td>Surrounding aorta at origin of inferior mesenteric artery (organs of Zuckerkandl)</td>
</tr>
</tbody>
</table>

Normal 10-70 0-15

*Cases 1, 3, and 12 have been reported independently by Sunderman and Sunderman,\textsuperscript{1} cases 8 and 14 by Cone and associates,\textsuperscript{10,11} and case 6 by Greenberg and Gardner.\textsuperscript{2}

‡I-insignificant; i.e., less than 10 per cent of the norepinephrine value.

nephrine in the urine. Three of these patients had tumors of the adrenal glands and the fourth had a tumor of the organs of Zuckerkandl.

A review of the literature covering the period from 1950 through June 1959 revealed 61 additional cases of pheochromocytoma with sufficient data to correlate urinary norepinephrine and epinephrine excretion with the tumor site. Thirty-two of these cases were from the series of von Euler and Ström,\textsuperscript{1} and 29 were from individual case reports.\textsuperscript{13-33} The 79 cases were divided into 2 groups: (1) those in which the excretion of both norepinephrine and epinephrine was significantly elevated and (2) those in which only norepinephrine was increased, epinephrine accounting for less than 10 per cent of the catecholamine excretion (table 2). Thirty-three patients had tumors producing significant amounts of epinephrine, and 31 of these had tumors located in the adrenal areas. Only 2 cases of a nonadrenal tumor producing significant amounts of epinephrine have been reported (case 18, table 1),\textsuperscript{18} and in both of these the tumor originated from the organs of Zuckerkandl. Forty-six patients had tumors that secreted only norepinephrine in significant amounts. Thirty-one of these had tumors of the adrenal area, the remainder having extra-adrenal tumors varying in location from the lower abdomen to the neck.
Table 2

Urinary Catecholamines and Tumor Location in Seventy-nine Cases of Pheochromocytoma*

<table>
<thead>
<tr>
<th>Location of Tumor</th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal Areas:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Left</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Side not specified</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Non-adrenal Areas:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organs of Zuckerkandl†</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Organ aorta (other than in organs of Zuckerkandl.)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Paravertebral lumbar</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Thorax</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neck</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Generalized spread</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Total tumors</td>
<td>33</td>
<td>46</td>
</tr>
</tbody>
</table>

*References 1, 13-35, and present series (table 1).
†The organs of Zuckerkandl are located on either side of the aorta near the base of the inferior mesenteric artery. All tumors described as located “along the aorta at the level of the duodenum” or “between the lower poles of the kidneys” are also included in this category.

Case Reports and Catheterization Studies

Descriptions of each of the 5 cases in which vena caval catheterizations were performed are presented individually, and the results of the catheterization procedures are summarized in table 3.

Case A

C. R., (case 14, table 1), an 8-year-old white boy was admitted to the National Naval Medical Center, Bethesda, Maryland, in August 1957 because of hypertension and a mass in the right side of the neck. Two years previously a pheochromocytoma had been removed from the right adrenal area. Following this operation he was normotensive and in good health until 5 months prior to admission, when the cervical mass was first noted. Recurrence of hypertension was discovered 3 weeks before admission.

The patient's maternal aunt and her son had both had pheochromocytomas, and the patient's mother (case E) was later found to have a pheochromocytoma.

The physical examination revealed a blood pressure of 155/120 mm. Hg, Horner's syndrome on the right, and a 4 by 4 cm. firm, nontender mass in the right submandibular region. The catecholamine excretion after acid hydrolysis of the urine was on 2 occasions 1,750 and 2,680 μg. per day of norepinephrine. The free catecholamine excretion in a third specimen was 2,700 μg. per day of norepinephrine. No significant amount of epinephrine was found in the urine.

Since no instance of a cervical pheochromocytoma had been reported prior to this case, the question arose as to whether the submandibular mass was a pheochromocytoma or whether it was an unrelated tumor associated with a pheochromocytoma in the abdomen. Massage of the mass produced a slight increase in the blood pressure, which was difficult to interpret. The vena cava was catheterized through a right antecubital vein, and blood samples were drawn at 4 levels within the vena cavae (table 3). The catecholamine concentration was markedly elevated in each sample, but the highest values were found in samples obtained from the superior vena cava, suggestive of a cervical pheochromocytoma. The highest single plasma level was found not high in the superior vena cava as anticipated but low in the superior vena cava, near the right atrium. Possible explanations for this finding included a higher secretion rate by the tumor at the time the low superior vena cava sample was drawn, poor sampling high in the superior vena cava due to a “streaming effect,” or the presence of a second pheochromocytoma in the thorax draining via the azygous vein. However, no tumor could be visualized by roentgenography of the chest. The cervical tumor was subsequently removed and found to be a 15-Gm. pheochromocytoma containing 5.0 mg. per Gm. of norepinephrine but no detectable epinephrine.

The catheterization was of value in indicating that the cervical mass was indeed a pheochromocytoma, in spite of the unusual location. Definitive surgical therapy could thus be undertaken without subjecting the patient to further diagnostic procedures in search of a pheochromocytoma in the abdomen.

Case B

H. F., (case 13, table 1), a 40-year-old Negro man was admitted to the National Heart Institute in July 1958 because of hypertension. In 1949 a pheochromocytoma was suspected because of hypertension. During an exploration of the right adrenal area the patient developed acute pulmonary edema and the operation was terminated im-

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mediately. Later in 1949 bilateral exploration of the adrenal regions did not reveal a tumor. Because of continuing hypertension a bilateral thoracolumbar sympathectomy was performed in 1950 and again a tumor was not found along either sympathetic chain. For the following 8 years he was treated with various antihypertensive drugs, of which phenoxybenzamine (Dibenzyline) was the most effective. He was asymptomatic except for occasional headaches and excessive perspiration.

Physical examination revealed blood pressures of 170/110 in the supine position and 140/90 mm. Hg in the standing position. Funduscopic examination showed moderate arteriolar narrowing without hemorrhages or exudates. The heart was slightly enlarged and a grade-III systolic murmur was audible at the apex. Deep palpation of the abdomen revealed no masses and failed to alter the blood pressure. A urinary catecholamine determination was diagnostic of pheochromocytoma—880 µg. per day of free norepinephrine with no detectable epinephrine. An intravenous urogram was normal.

The major problem was thus to localize the tumor in this patient who had already undergone abdominal and thoracic explorations for pheochromocytoma. Since no significant amount of epinephrine was present in the urine, all possible sites had to be considered. The superior vena cava was catheterized by way of the right saphenous vein and blood samples were drawn as indicated in table 3. All the plasma values were elevated above normal. Only one plasma specimen showed a marked step-up in catecholamine concentration—the one obtained from high in the inferior vena cava in series 3. Since the patient's blood pressure was elevated rather uniformly during most of the procedure, the failure to demonstrate a consistent step-up in plasma catecholamine level in all of the high inferior vena caval samples was puzzling. Therefore the study was repeated 3 days later through the left saphenous vein. In only one of 3 trials was a marked step-up high in the inferior vena cava demonstrated. Thus, of 6 samples drawn from high in the inferior vena cava in 2 catheterizations only 2 showed a marked elevation in plasma catecholamine concentration above samples drawn from other sites. The findings were interpreted as being compatible with a pheochromocytoma in the upper abdomen. The failure to demonstrate a constant step-up high in the inferior vena cava was believed to be due to intermittent secr-

### Table 3

<table>
<thead>
<tr>
<th>Case</th>
<th>Sampling series</th>
<th>Plasma norepinephrine-equivalent (µg./L.)</th>
<th>Average blood pressure (mm. Hg)</th>
<th>Location of tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>49</td>
<td>23</td>
<td>140/100</td>
</tr>
<tr>
<td>B (first cath.)</td>
<td>1</td>
<td>23</td>
<td>21</td>
<td>200/120</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>21</td>
<td>14</td>
<td>200/120</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>41</td>
<td>15</td>
<td>190/120</td>
</tr>
<tr>
<td></td>
<td>(second cath.)</td>
<td>1</td>
<td>9</td>
<td>168/116</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>14</td>
<td>13</td>
<td>174/124</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>70</td>
<td>18</td>
<td>170/110</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>31</td>
<td>12</td>
<td>164/98</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16</td>
<td>18</td>
<td>180/106</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>45,46</td>
<td>16,16</td>
<td>140/104</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31 (left flank massage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 (right flank massage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>160/100</td>
</tr>
<tr>
<td></td>
<td>2‡</td>
<td>4</td>
<td>7</td>
<td>160/100</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>140/90</td>
</tr>
</tbody>
</table>

*Underlined values considered to represent significant 'step-ups' in plasma catecholamine concentration.

†High SVC, superior vena cava near the junction of the innominate veins; low SVC, superior vena cava near the right atrial junction; high IVC, inferior vena cava near the right atrial junction; low IVC, inferior vena cava near the iliac bifurcation.

‡Following the intravenous injection of 0.025 mg. of histamine.
tion by the tumor or to poor sampling from a "streaming effect" in the inferior vena cava.

In October 1958 the patient underwent another abdominal exploration and a small tumor was finally located behind the inferior vena cava medial to the right adrenal gland. The excised tumor weighed 26 Gm. and contained 0.68 mg. per Gm. of norepinephrine and insignificant amounts of epinephrine.

The catheterization was of value in this case in localizing the tumor to the upper abdomen, thus permitting a fourth operation to be performed with some assurance that the proper area was being explored.

Case C

M. S., (case 17, table 1), a 63-year-old white woman, was admitted to George Washington University Hospital in July 1959 because of diabetes and hypertension of 2 years' duration and mental confusion during the previous week. The blood pressure varied from 260/155 to 160/100 mm. Hg and the patient was lethargic and confused. There was a diffuse macular rash over the trunk. The general physical examination was otherwise negative. The fasting blood glucose was 370 mg. per cent. An intravenous injection of 5 mg. of phentolamine (Regitine) produced a decrease in the blood pressure from 184/118 to 100/48 mm. Hg. A urinary catecholamine determination revealed 1,030 \( \mu g \) per day of free norepinephrine and 510 \( \mu g \) per day of epinephrine. An intravenous urogram was normal.

The high excretion of epinephrine suggested a tumor localized in one of the adrenal glands. Two series of blood samples were obtained along the vena cava by catheterization (table 3). Only 1 of the 2 samples drawn from high in the inferior vena cava, the level of the tumor, showed a marked step-up in plasma catecholamine concentration. In September 1958 a 47-Gm. pheochromocytoma was removed from the right adrenal region; the tumor contained 5.8 mg. per Gm. of norepinephrine and 2.4 mg. per Gm. of epinephrine.

Though the catheterization was an elective procedure in this case, the findings confirmed the presence of a tumor in one of the adrenal areas.

Case D

D. M., (case 7, table 1), a 28-year-old white man, was admitted to the National Heart Institute in May 1959 because of hypertension, excessive perspiration, tachycardia, and progressive loss of weight for 1 year. Two months prior to admission he had suffered an acute myocardial infarction. The patient was thin and perspired continuously. The blood pressure was 150/100 mm. Hg in the supine position and 90/70 mm. Hg in the standing position. The pulse rate ranged from 100 to 160 beats per minute. There was slight cardiac enlargement. Palpation of the abdomen revealed no masses, and massage of both flanks failed to alter the blood pressure consistently. The fasting blood glucose was 137 mg. per cent and the basal metabolic rate was +23 per cent. An intravenous urogram combined with laminography of the adrenal regions failed to reveal any abnormal masses. A 24-hour urine specimen contained 3,800 \( \mu g. \) of free norepinephrine but no detectable epinephrine.

The patient's activity was seriously limited by postural hypotension and tachycardia, occasional attacks of angina pectoris, and severe fatigue and anxiety. Blood samples were drawn during a single passage of a catheter down the vena cavae with duplicate specimens being obtained from high and low in the inferior vena cava (table 3). The catecholamine content of all the plasma samples was elevated, and a marked increase was found in the samples from high in the inferior vena cava. An attempt was made to lateralize the tumor by drawing samples during massage of each flank but no marked difference was found. The data were interpreted as demonstrating a tumor of the upper abdomen. At operation a pheochromocytoma was found in the right adrenal region. The excised tumor weighed 124 Gm. and contained 0.34 mg. per Gm. of norepinephrine but no detectable epinephrine.

In this case the catheterization provided unequivocal evidence of a tumor in the upper abdomen but gave no information concerning the involved side.

Case E

B. R., (case 10, table 1), a 33-year-old white woman (mother of C. R., case A) was admitted to the National Naval Medical Center, Bethesda, Maryland, in October 1958 because of hypertension. A sister, a niece, and a son all had documented pheochromocytomas. The blood pressure was 160/100 mm. Hg. The general physical examination was otherwise negative. The free catecholamine excretion on two separate occasions was 170 and 260 \( \mu g. \) per day of norepinephrine. After acid hydrolysis of the urine the value was 460 \( \mu g. \) per day of norepinephrine (normal after hydrolysis: 50 to 250 \( \mu g. \) per day). One year earlier the urinary catecholamines after acid hydrolysis had been 230 \( \mu g. \) per day of norepinephrine. No significant amount of epinephrine was found in any of the specimens.

The vena cavae were catheterized through the right saphenous vein (table 3). The samples drawn in series 1 were obtained during a single passage down the vena cavae with the patient at rest. Series 2 shows the values obtained after the intra-
venous injection of 0.025 mg. of histamine base. One minute after the injection the blood pressure fell from the control level of 160/100 to 100/50 mm. Hg and the patient developed pounding headache and a facial flush. The blood pressure returned to control levels in 3 minutes. The sample from low in the superior vena cava was drawn 3 minutes after, and that from high in the inferior vena cava 5 minutes after the injection of histamine. Neither a prominent increase in blood pressure nor a rise in plasma catecholamine level occurred after the histamine injection. Ten minutes after the histamine test a third set of samples (series 3) was drawn across the abdominal area. The plasma catecholamine values showed a general downward trend during the procedure, and most of the values in series 2 and 3 were in the normal range. None of the specimens showed a step-up in catecholamine concentration convincing enough to suggest a tumor site. In July 1959 a 12-Gm. pheochromocytoma of the left adrenal gland was removed. The tumor contained 6.3 mg. per Gm. of norepinephrine but no significant amount of epinephrine.

In this case the blood pressure was sufficiently elevated during the catheterization to suggest that the tumor was secreting continuously. Nonetheless, the secretion rate was not high enough to produce a distinct increase in plasma catecholamine concentration in most of the blood samples drawn. In the presence of such a minimally secreting tumor and a negative histamine test, the catheterization was of no assistance in localizing the neoplasm.

Discussion

In the collected series of 79 cases of pheochromocytoma 78 per cent of all patients had tumors of the adrenal glands, and 95 per cent had tumors localized within the abdomen. These percentages are comparable to those reported previously by other authors.\(^1\)\(^{37}\) Thus, on a statistical basis alone, exploration of the abdomen through an upper transverse incision should provide a successful surgical approach in most cases of the disease.\(^38\)\(^{39}\) If a thoracic or cervical site can be excluded, nearly all pheochromocytomas should be accessible through this incision. A careful x-ray examination of the chest to exclude an extra-abdominal tumor is thus a very important procedure. Since both adrenal areas and the periaortic region must be examined in each case to rule out bilateral or multiple tumors,\(^37\)\(^{38}\) extensive efforts to localize abdominl chromaffin tumors preoperatively do not seem warranted in most patients with this disease. Deaths have occurred in patients with pheochromocytoma from procedures such as retroperitoneal gas insufflation and aortography.\(^40\)\(^{42}\)

The differential assay of epinephrine and norepinephrine in the urine may be of value in suggesting an adrenal versus a nonadrenal tumor site. If the urine contains increased amounts of epinephrine as well as norepinephrine, the neoplasm is almost always in one of the adrenal areas. The 2 nonadrenal tumors of this type have been found in the organs of Zuckerkandl. No similar positive correlation exists, however, between a nonadrenal tumor site and a failure to produce epinephrine. If the increased excretion of catecholamines in the urine is limited to norepinephrine alone, the tumor may still be expected to lie in or near one of the adrenal glands in two thirds of the cases. In the remaining third in this group, however, the tumor will be extra-adrenal in location, and all possible sites must be considered.

The reason why epinephrine-producing tumors are localized almost entirely to the adrenal glands is not clear. Certain cells of the normal adrenal medulla have been shown to contain only norepinephrine, while others have the ability to N-methylate norepinephrine and thus form epinephrine.\(^43\) The epinephrine-producing cells are therefore presumed to synthesize both amines. A histochemical study of one epinephrine-producing pheochromocytoma of the adrenal has been reported.\(^35\) A few clusters of cells containing large amounts of norepinephrine were found among a background of cells containing small amounts of norepinephrine and considerable quantities of epinephrine; the authors were not convinced, however, that they had shown two distinct cell types comparable to those occurring in the normal adrenal medulla. It thus remains uncertain whether tumors that produce significant quantities of both amines are derived only from epinephrine-producing cells or whether they represent "mixed" tumors composed of both parent cell types. The
predominance of epinephrine-producing cells in the adrenal medulla probably accounts for the high incidence of epinephrine-producing tumors in this area. The almost negligible occurrence of epinephrine-producing pheochromocytomas elsewhere in the body remains unexplained, however, for epinephrine-producing cells are believed to be scattered throughout the course of the sympathetic chains and plexuses.\textsuperscript{44} There is no evidence that nonadrenal epinephrine-producing chromaffin cells lack the capacity for tumor formation, as 2 tumors of these cells have been reported in the organs of Zuckerkandl. The infrequent occurrence of such tumors may reflect only the low incidence of epinephrine-producing cells relative to norepinephrine-producing ones in nonadrenal chromaffin tissue. If this is true, there is no fundamental biochemical or anatomic reason why an epinephrine-producing tumor cannot occur anywhere along the sympathetic system, and in the future such a case may be reported.

In certain unusual cases of pheochromocytoma accurate preoperative localization of the tumor may be necessary and catheterization of the vena cava has proved useful in such instances. This procedure may be indicated (1) when previous surgical exploration has been negative (case B\textsuperscript{45}), (2) when an extraabdominal tumor is known to be present, which may or may not be the pheochromocytoma (case A), or (3) when the clinical situation of the patient is so desperate as to suggest that he may not survive a negative exploration (case E). It is indicated only when the tumor is a "pure" norepinephrine-producer and when the catecholamine secretion by the tumor appears to be continuous. Even in continuously secreting tumors, however, a consistent elevation of the plasma catecholamine level near the tumor site is not always found. This suggests that some of these tumors may be "paroxysmal" when considered on a minute-by-minute basis. Catheterization in our experience has been both a safe and accurate means of demonstrating the general level of the tumor in the body but not in lateralizing the neoplasm to one side or the other. However, using a spectrophotofluorimetric method of assay,\textsuperscript{46} Vendsalu\textsuperscript{47} found that "by careful sampling at various levels with the tip of the catheter directed against the walls of the vena cava, it was possible to localize and lateralize the tumor in three cases."

Finally, the relative value of plasma versus urinary catecholamine determination in the diagnosis of pheochromocytoma is well demonstrated by the values obtained in the 5 case reports. In patients A through D the plasma catecholamine concentration low in the inferior vena cava (representative of a peripheral venous sample) ranged from 12 to 23 $\mu$g. per liter. This is 2 to 4 times the upper limit of normal in our laboratory (6 $\mu$g./L.). In these same patients the free urinary catecholamines ranged from 800 to 3,800 $\mu$g. per day, an 8- to 38-fold increase over normal (<100 $\mu$g./day). In case E many of the plasma samples were clearly in the normal range, even though the patient was mildly hypertensive and had a catecholamine excretion at least twice normal. These findings illustrate that infusion rates of catecholamines sufficient to produce only modest elevations in plasma levels may result in large accumulations of these compounds in the urine over a period of time. Furthermore, while plasma catecholamine levels in patients with paroxysmal hypertension are increased only during the period of blood pressure elevation,\textsuperscript{2,48} the 24-hour urinary excretion in such cases is usually increased rather constantly.\textsuperscript{3} For these reasons the determination of urinary catecholamines provides in most cases a more distinct and reproducible separation of normal persons from patients with pheochromocytoma than does the assay of plasma. More specific methods for the determination of plasma catecholamines than the one used in these studies are available.\textsuperscript{46,48,49} These methods give normal values of less than 1 $\mu$g. per liter and may allow a clearer separation of normal from abnormal subjects than was found here. However, their application to a large number of patients in the diagnosis of pheochromocytoma has not been reported.
CATECHOLAMINES AND PHEOCHROMOCYTOMA

Summary

Data on urinary catecholamines in a collected series of 75 cases of pheochromocytoma, including 18 of our own cases, indicate that the differential assay of urinary norepinephrine and epinephrine may be of value in predicting the location of the tumor preoperatively. If there is a significant elevation of urinary epinephrine (42 per cent of all cases), the tumor may be expected to lie in or adjacent to one of the adrenal glands in about 95 per cent of cases. Other tumors of this type have been found only in the organs of Zuckerkandl. If the urine contains norepinephrine alone (58 per cent of all cases), the tumor will be found in one of the adrenal areas in about two thirds of the cases and in an extra-adrenal location in the remainder. In a few patients (6 per cent) of this type, the tumor may be extra-abdominal.

In some unusual cases more precise information on the location of the tumor must be obtained preoperatively. The demonstration of a marked step-up in plasma catecholamine concentration at the level of the tumor, the sampling being done by venous catheterization, is a useful and safe means of localizing the tumor. Five cases are presented illustrating the use of this procedure.

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Urine specimens in cases 1, 3 and 12 (table 1) were kindly supplied by Dr. F. William Sunderman, Jr., National Naval Medical Center, Bethesda, Maryland.

Summario in Interlingua

Datos concernente con le catecholaminas urinari in un serie de 75 casos de pheochromocytoma—colligite ab varie reportos sed includente 18 casos de observation personal—indica che le essayo differential de norepinephrina e epinephrina urinari es possibilemente de valor in predicer le sito del tumor ante le operation. Si le epinephrina urinari es significative mente elevate (42 pro cento de omne le casos), on potte expectar que le tumor jace in un del glandulas adrenal o in adjacentia de illo. Iste expectacion se provara correcte in 95 pro cento del casos. Altere tumores de iste typo ha essele trovate solmente in le organos de Zuckerkandl. Si le urina contine solmente norepinephrina (38 pro cento del casos), le tumor va essever trovate in un del areas adrenal in circa duo tertios del casos e in un area extra-adrenal in le remanente tertio. In alieune inter iste patientes (6 pro cento), le tumor es extra-abdominal.

In certe casos inusual, plus precise informaciones relative al sito del tumor debe esser obtenite ante le operation. Le demonstration de un marcare augmento del concentration de catecholamina in le plasma al nivello del tumor—determinare super le base de specimens obtenite per catheterismo venose—es un medio utile e salve pro localizar le tumor. Es presentate cinque casos que illustra le uso de iste procedimento.

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Circulation, Volume XXII, October 1960
Neuroses of the Heart
Angina Pectoris

Etiology and Pathology: The following views have been entertained.

(1) That it is a neuralgia of the cardiac nerves. In the true form the agonizing cramp-like character of the pain, the suddenness of the onset, and the associated features, are unlike any neuralgic affection. The pain, however, is undoubtedly in the cardiac plexus and radiates to adjacent nerves. It is interesting to note in connection with the almost constant sclerosis of the coronary arteries in angina that Thoma has found marked sclerosis of the temporal artery in migraine and Dana has met with local thickening of the arteries in some cases of neuralgia. (2) Heberden believed that it was a cramp of the heart-muscle itself. This would explain the agonizing character of the pain and the suddenness of the onset as well as the frequency of the fatal termination; but if the cramps were general in the heart-muscle and similar to those which occur in the voluntary muscles, death would invariably ensue with great rapidity. Cramp of certain muscular territories would explain the attack. (3) That it is due to the extreme tension of the ventricular walls, in consequence of an acute dilatation associated, in the majority of cases, with affection of the coronary arteries. Traube, who supported this view, held that the agonizing pain resulted from the great stretching and tension of the nerves in the muscular substance. A modified form of this view is that there is a spasm of the coronary arteries with great increase of the intracardiac pressure.—William Osler, M.D. The Principles and Practice of Medicine. New York, D. Appleton & Company, 1893, p. 655.
Catecholamines in the Localization of Pheochromocytoma

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