Present Status of Diagnosis and Treatment of Pheochromocytoma

By U. S. von Euler and G. Ström

For detection and diagnosis of pheochromocytoma, the method of urine analysis is considered the most convenient, safe, and accurate. Analysis of blood samples obtained by catheterization at different levels in the vena cava aids in localization. Some features of the clinical symptomatology and the pharmacologic and operative treatment of patients with chromaffin-cell tumors are given.

PHEOCHROMOCYTOMA is a neoplasm of the chromaffin cells of the sympathetic nervous system (adrenal medulla, aberrant tissue near the sympathetic chain, paraganglia). Its occurrence in man is known from early reports of autopsies.1 It is now being diagnosed in vivo with increasing frequency, partly because the characteristic clinical syndrome2 that is produced by the secretion of chromaffin cell hormones from the tumor (norepinephrine and epinephrine) has been duly recognized, and partly because valid and relatively precise methods for the laboratory diagnosis have been developed.

The tumor usually develops in adult life, slightly more often in women than in men, but may occur in children;3 it is usually situated in or near the adrenal glands but may be found at other places along the sympathetic chain;4 it may be multiple and may also be malignant in a minority of cases;6 it may show familial occurrence8 and is sometimes associated with neurofibromatosis.10, 11

The untreated tumor usually leads to a fatal outcome within a relatively short number of years with a clinical course resembling that of malignant hypertension. An increasing number of cases is being reported where surgical complete removal of the tumor12 has led to partial or complete reversal of the structural and functional changes in the circulatory system that had developed before operation.

SYMPTOMATOLOGY

A pheochromocytoma may give local symptoms due to its increasing size; these are not considered here. The tumor with rare exceptions retains the secreting function of the chromaffin-cell system, as evidenced by an augmented urinary excretion of norepinephrine and sometimes also of epinephrine. Malignant metastases may also be actively secreting.13 The exaggerated secretion of catechol amines into the circulation leads to systemic changes14 that can be predicted from the present knowledge of the physiologic effects of norepinephrine and epinephrine (table 1).

In accordance with expectations, an actively secreting pheochromocytoma produces several or all of the following main changes: arterial hypertension with increase of systolic as well as diastolic blood pressure; no consistent change of resting pulse rate; increased sweating; cutaneous vasoconstriction; increase of basal metabolism; increase of fasting blood sugar concentration and sometimes glucosuria; central nervous excitation.2, 15-17 In some cases the augmented secretion of catechol amines occurs intermittently with “paroxysms” of effector reactions, but in the majority of patients it is continuous. The subjective experience of the patient is usually dominated by headache, sweating, nervousness, and loss of weight. When these symptoms occur in paroxysmal attacks the case history may be immediately suggestive of pheochromocytoma but it is more difficult to evaluate when the symptoms are continuously present. In the latter case, the usual sequence of vascular changes in the retinal, coronary, cerebral, and renal areas secondary to prolonged arterial hypertension will appear. At this stage the clinical picture may simulate essential hypertension.18 Although pharmacologic tests (pro- vocative or blocking) may still be helpful in establishing the correct diagnosis, this ultimately has to rely on the estimation of the urinary excretion (or blood concentration) of
catechol amines. The electrocardiographic changes that often appear do not seem to be specific.

**Physiologic Diagnostic Methods**

*Urinary Excretion of Catechol Amines.* Holtz and associates gave the first evidence that the adrenal medulla of the cat produces norepinephrine as well as epinephrine. The occurrence of norepinephrine in chromaffin-cell tumors was demonstrated by Holton and soon confirmed by several workers. In 1950 Engel and Euler showed that large amounts of norepinephrine were secreted in the urine in 2 cases of hypertension in which subsequently pheochromocytomas were found and removed. In 1 of these cases also epinephrine was secreted in large amounts in the urine. The diagnostic value of this finding was pointed out and the method of urine analysis has since been used extensively for the diagnosis of pheochromocytoma. This method has several advantages over other methods used for the diagnosis. It incurs no risk or inconvenience to the patient and can be repeated frequently. Since the method is based on quantitative estimation of the pathogenic factor, there is hardly any risk of false positive or false negative results, which not infrequently occur with other methods. Moreover, the test gives quantitative information on the activity of the tumor, which is not obtained with other tests.

Several technics for the estimation of the urinary catechol amines have been described. A relatively simple method suitable for routine determinations in clinical laboratories has recently been elaborated by Euler and Floding. This technic is based on the adsorption of the catechol amines on aluminium oxide, elution with acid, and fluorimetric estimation of the stabilized fluorescent products obtained by oxidation with ferricyanide at different pH.

The urinary output of catechol amines in cases of pheochromocytoma varies according to the conditions, but in the presence of an actively secreting tumor it is invariably increased. This increase is based on the fact that circulating catechol amines are excreted in the urine in a fairly constant proportion of approximately 1 to 5 per cent of the adminis-
tered amount. When urine from a case with tumor is collected over a period of 24 hours, variations in the output during the day will be smoothed out and a representative figure is obtained. This is evidenced by the relative constancy of the output during a series of subsequent days (table 2). A continuous release of catechol amines from the tumor is also borne out by the production of a permanently high blood pressure level. Even in cases characterized by paroxysmal attacks and with approximately normal blood pressure between the attacks, the 24-hour catechol-amine values were found elevated in our cases. Removal of the tumor is usually followed by a return of blood pressure to normal levels and a precipitous fall in the catechol-amine excretion. The urinary output of norepinephrine is sometimes slightly elevated even after the operation; this persistence may be due to a compensatory increase in vasomotor activity. Normal figures are usually found after a lapse of 1 to 2 weeks.

Table 3 gives the available data from 35 cases of pheochromocytoma that have been subjected to urine analysis in our laboratory and in which the location and nature of the tumor have been verified at operation and in most cases also by microscopic examination.

The results may be summarized as follows: 1. In all cases showing clinical signs of a secreting tumor the catechol-amine excretion in the urine is increased. 2. There is good agreement between the proportion of norepinephrine and epinephrine in the tumor and in urine. 3. While norepinephrine is increased in the urine in all cases of secreting tumors, epinephrine is increased only in certain cases. 4. In no instance of pheochromocytoma was increased content of epinephrine alone found in the urine or in the tumor.

Since norepinephrine is normally excreted in urine in amounts of about 20 to 40 $\mu g./24$ hours and may be considerably increased in various clinical conditions (trauma, surgical stress, fever, burns, myocardial infarction), there is no exact way of deciding the lower limit of excretion that indicates a tumor. The lowest 24-hour values of urinary catechol amines accompanying verified tumors have been 104 and 109 $\mu g.$ (case 10 and 17 in table 3). In 32 of our 35 cases the urinary excretion exceeded 300 $\mu g./24$ hours. For practical purposes a daily excretion of 100 to 200 $\mu g.$ of norepinephrine may be regarded as the lower limit for the diagnosis of a clinically active tumor. It is also of value to establish such a limit, since lower excretions may be due to tumors that are not big enough to allow surgical detection.

**Blood Content of Catechol Amines.** While the urine analyses permit integration of the tumor secretion over an arbitrary length of time, the blood estimations give information about the catechol-amine concentration at any given moment. This may be of value for instance during an attack, and may allow a differentiation of pheochromocytoma from vasomotor crises, which should show lower blood catechol-amine levels for a given rise in blood pressure than a secreting tumor.

Using the method of fluorimetric estimation, Lund has been able to show unequivocally that the blood catechol-amine levels were greatly increased in several cases of chromaffin-cell tumors, the values varying between 14 and 98 $\mu g./L.$ as against less than 1 $\mu g./L.$ in normal peripheral venous blood (table 4).

**Adrenal Cortical Activity in Cases of Pheochromocytoma**

The eosinopenic action of epinephrine was earlier taken as evidence for a release of cortical hormones. Direct estimation of corticoid hormones have failed, however, to show any increase after infusion of epinephrine.

Normal or low 17-ketosteroid figures in urine have been reported by several authors. Normal 17-OH-CS values in the blood were found in a case of norepinephrine-producing pheochromocytoma, while an increased 17-OH-CS level, 17 $\mu g./100$ ml., was observed by Querido in a case of a tumor that released epinephrine as well as norepinephrine.

Eosinopenia has been noted in certain cases of pheochromocytoma but neither the white cell count nor the corticosteroid level in blood or excretion in urine seem to be of any specific diagnostic value in pheochromocytoma.
## Table 3. Thirty-five Cases of Pheochromocytoma with Urine Analysis of Catechol Amines, in Most Cases Verified at Operation and by Microscopic Examination.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Hypertension</th>
<th>Localization</th>
<th>Urinary NE mg./24 hr.</th>
<th>Urinary E mg./24 hr</th>
<th>Tumor NE mg./Gm.</th>
<th>Tumor E mg./Gm.</th>
<th>Tumor size (Gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>F</td>
<td>—</td>
<td>in right adrenal</td>
<td>125-153</td>
<td>59-103</td>
<td>2.1</td>
<td>1.5</td>
<td>525 (cyst)</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>F</td>
<td>perm.</td>
<td>close to adrenal</td>
<td>234-387</td>
<td>28-138</td>
<td>1.3</td>
<td>0.15</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>F</td>
<td>perm.</td>
<td>close to aorta at umbilical level</td>
<td>437-1240</td>
<td>11-54</td>
<td>4.6</td>
<td>0.1</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>F</td>
<td>perm.</td>
<td>in right adrenal</td>
<td>113-660</td>
<td>110-750</td>
<td>0.75</td>
<td>0.75</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>F</td>
<td>parox.</td>
<td>at site of right adrenal</td>
<td>345-384</td>
<td>164-224</td>
<td>7.4</td>
<td>2.3</td>
<td>147</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>F</td>
<td>perm.</td>
<td>between aorta and duodenum</td>
<td>1790-2250</td>
<td>18-24</td>
<td>8.4</td>
<td>0.1</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>M</td>
<td>—</td>
<td>in left adrenal</td>
<td>240</td>
<td>68</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>M</td>
<td>perm. +</td>
<td>in right adrenal</td>
<td>104</td>
<td>not determined</td>
<td>—</td>
<td>—</td>
<td>28</td>
</tr>
<tr>
<td>11</td>
<td>23</td>
<td>M</td>
<td>perm.</td>
<td>adherent to left adrenal</td>
<td>1010-1200</td>
<td>16-19</td>
<td>0.63</td>
<td>0.07</td>
<td>40</td>
</tr>
<tr>
<td>12*</td>
<td>30</td>
<td>F</td>
<td>perm.</td>
<td>between abdominal aorta and vertebral column</td>
<td>415</td>
<td>11</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>40</td>
<td>F</td>
<td>perm.</td>
<td>in left adrenal</td>
<td>240-327</td>
<td>8.4-26</td>
<td>5.2</td>
<td>0.1</td>
<td>ca 4</td>
</tr>
<tr>
<td>15†</td>
<td>56</td>
<td>F</td>
<td>perm.</td>
<td>refused operation</td>
<td>1290</td>
<td>38</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>61</td>
<td>M</td>
<td>—</td>
<td>at site of right adrenal</td>
<td>918</td>
<td>540</td>
<td>—</td>
<td>—</td>
<td>500</td>
</tr>
<tr>
<td>17</td>
<td>—</td>
<td>M</td>
<td>—</td>
<td>close to right adrenal</td>
<td>23-83</td>
<td>49-126</td>
<td>0.001</td>
<td>0.003</td>
<td>26</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>M</td>
<td>perm.</td>
<td>adherent to left adrenal</td>
<td>3000</td>
<td>5</td>
<td>4.0</td>
<td>0.1</td>
<td>19</td>
</tr>
<tr>
<td>19</td>
<td>44</td>
<td>M</td>
<td>perm.</td>
<td>at site of left adrenal</td>
<td>450, 640</td>
<td>430, 540</td>
<td>0.63</td>
<td>1.3</td>
<td>270</td>
</tr>
<tr>
<td>20</td>
<td>13</td>
<td>M</td>
<td>perm. +</td>
<td>close to right adrenal</td>
<td>1450</td>
<td>7.5</td>
<td>—</td>
<td>—</td>
<td>ca 50</td>
</tr>
<tr>
<td>21</td>
<td>26</td>
<td>F</td>
<td>perm.</td>
<td>at left renal hilus</td>
<td>418-1600</td>
<td>10-12</td>
<td>3.8</td>
<td>0.1</td>
<td>17</td>
</tr>
<tr>
<td>22</td>
<td>26</td>
<td>F</td>
<td>perm.</td>
<td>at aortic origin of inf. mesent., art.</td>
<td>750, 800</td>
<td>3.1</td>
<td>1.1</td>
<td>0.1</td>
<td>37</td>
</tr>
<tr>
<td>23</td>
<td>47</td>
<td>M</td>
<td>perm. +</td>
<td>close to left adrenal</td>
<td>450</td>
<td>2.9</td>
<td>—</td>
<td>—</td>
<td>walnut</td>
</tr>
<tr>
<td>24†</td>
<td>—</td>
<td>M</td>
<td>perm.</td>
<td>suspected general spread</td>
<td>8800</td>
<td>low, not demonstrable</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>26</td>
<td>34</td>
<td>F</td>
<td>perm.</td>
<td>in right adrenal</td>
<td>213-618</td>
<td>2.1-15</td>
<td>1.5</td>
<td>0.1</td>
<td>20</td>
</tr>
<tr>
<td>27</td>
<td>41</td>
<td>M</td>
<td>parox.</td>
<td>at site of left adrenal</td>
<td>396</td>
<td>538</td>
<td>—</td>
<td>—</td>
<td>ca 40</td>
</tr>
<tr>
<td>29</td>
<td>29</td>
<td>M</td>
<td>perm. +</td>
<td>at site of left adrenal</td>
<td>1040, 1160</td>
<td>4.5, 14</td>
<td>2.8</td>
<td>0.25</td>
<td>85</td>
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<tr>
<td>30</td>
<td>31</td>
<td>M</td>
<td>perm.</td>
<td>multiple tumors in thorax</td>
<td>1400-1800</td>
<td>1.5-9</td>
<td>0.2</td>
<td>0</td>
<td>ca 76</td>
</tr>
<tr>
<td>31</td>
<td>46</td>
<td>M</td>
<td>perm.</td>
<td>tumor not found at operation</td>
<td>390</td>
<td>19</td>
<td>—</td>
<td>—</td>
<td>900 (cyst)</td>
</tr>
<tr>
<td>32</td>
<td>40</td>
<td>F</td>
<td>perm. +</td>
<td>close to right adrenal</td>
<td>1390, 1400</td>
<td>3, 4, 6.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>33</td>
<td>59</td>
<td>F</td>
<td>perm.</td>
<td>two tumors between adrenal and kidney</td>
<td>162, 300</td>
<td>170, 310</td>
<td>—</td>
<td>—</td>
<td>small egg</td>
</tr>
<tr>
<td>34†</td>
<td>35</td>
<td>M</td>
<td>perm.</td>
<td>between aorta and vertebral column at duodenal level</td>
<td>520</td>
<td>33</td>
<td>—</td>
<td>—</td>
<td>large egg fist</td>
</tr>
<tr>
<td>35</td>
<td>51</td>
<td>M</td>
<td>parox.</td>
<td>in right adrenal</td>
<td>280</td>
<td>294</td>
<td>—</td>
<td>—</td>
<td>plum</td>
</tr>
<tr>
<td>36</td>
<td>45</td>
<td>M</td>
<td>perm.</td>
<td>between aorta and duodenum</td>
<td>2100</td>
<td>4.3</td>
<td>—</td>
<td>—</td>
<td>440</td>
</tr>
<tr>
<td>37</td>
<td>6</td>
<td>F</td>
<td>perm.</td>
<td>in right adrenal</td>
<td>2060</td>
<td>7.4</td>
<td>3.3</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>38</td>
<td>49</td>
<td>F</td>
<td>perm.</td>
<td>close to right adrenal</td>
<td>352</td>
<td>22</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>39</td>
<td>45</td>
<td>M</td>
<td>perm.</td>
<td>in right adrenal</td>
<td>398</td>
<td>9.3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>40</td>
<td>37</td>
<td>F</td>
<td>perm.</td>
<td>at site of left adrenal</td>
<td>1420</td>
<td>280</td>
<td>—</td>
<td>—</td>
<td>fist</td>
</tr>
</tbody>
</table>

Perm. = permanent
Parox. = paroxysmal.
* Case 12: ganglioneuroma + pheochromocytoma
† Case 15 and 24: not operated.
†† Case 34: adrenal cortical carcinoma, probably including pheochromocytoma.
TABLE 4.—Epinephrine (E) and Norepinephrine (N) in Venous Blood from Patients with Pheochromocytoma (Lund 1952)\textsuperscript{14}

<table>
<thead>
<tr>
<th>Case no.</th>
<th>During attack (blood pressure)</th>
<th>After attack (blood pressure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>a) 2.4 μg. % N + E (300 mm. Hg)</td>
<td>&lt;0.3 μg. % N + E (150 mm. Hg)</td>
</tr>
<tr>
<td></td>
<td>b) 2.1 μg. % N (300 mm. Hg)</td>
<td>&lt;0.3 μg. % N + E (after operation)</td>
</tr>
<tr>
<td>4</td>
<td>0.8 μg. % N + E (260 mm. Hg)</td>
<td>&lt;0.4 μg. % N + E (130 mm. Hg)</td>
</tr>
<tr>
<td>5</td>
<td>a) 3.4 μg. % N (+E)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>b) 3.8 μg. % N (+E)</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>1.4 μg. % N + E (260 mm. Hg)</td>
<td>1.4 μg. % N + E (? mm. Hg)</td>
</tr>
<tr>
<td>7</td>
<td>4.4 μg. % N + E (235 mm. Hg)</td>
<td>&lt;0.1 μg. % N + E</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
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</table>

**Drug Tests for Pheochromocytoma**

A large number of papers have been published on the diagnostic use of various drug tests in pheochromocytoma. The basic principles for these tests have been either release of active amines from the tumor or depression of their actions. Although these tests may supply information as to the presence or absence of a chromaffin-cell tumor they not infrequently give false positive or false negative results, which restrict their clinical value. In many instances they cause inconvenience or incur risks to the patients, even with fatal results. As a general rule the attack-producing drugs should not be given unless the blood pressure is normal or only slightly elevated, whereas the antisymptomimetic drugs are only useful during increased blood pressure. Since simple clinical laboratory methods for the estimation of the catecholamine output in urine now are available, it would seem that the less reliable drug tests should be used in exceptional cases only, in conjunction with urine analysis, or as an emergency method when urine analysis is not available.

Some of the most widely used drug tests are, however, briefly reviewed.

1. **Histamine Test** (Roth and Kvale\textsuperscript{39}). This test is based on the direct stimulating effect of histamine on the chromaffin cells, causing a release of catechol amines and rise in blood pressure. After intravenous injection of 25 to 50 to 100 μg. of histamine (in terms of the base) a large rise of blood pressure is usually recorded in cases of pheochromocytoma while the rise in other cases is as a rule either absent or relatively small.

2. **Mecholyl Test** (Guarneri and Evans\textsuperscript{40}). This test like the foregoing one depends on direct stimulation of the chromaffin cells. The doses used are 10 to 25 mg. subcutaneously. Both the histamine and the mecholyl tests are relatively nonspecific and may give misleading results. In addition, these tests may cause inconvenience and even certain risks for the patients by raising the blood pressure to very high levels in tumor cases and by producing a fall of blood pressure in other cases. Before the injection of Mecholyl the patient should be given 1 mg. of atropine sulfate. In this group also falls 1,1-dimethyl-4-phenyl piperaazonium iodide (DMPP), a ganglionic-stimulating agent.\textsuperscript{41}

3. **Benzodioxane Test**. This was introduced by Goldenberg and associates.\textsuperscript{42} The injection of 0.25 to 0.50 to 0.75 mg./Kg. body weight causes a prompt drop in blood pressure, which returns to the pre-injection pressure in a few minutes or up to about 1 hour later. A usual test dose is 15 to 20 mg. of benzodioxane hydrochloride intravenously.

Although this test is said to be more specific than the foregoing ones, it is not entirely innocuous. Thus strong and rapid pressor responses (over 300/200 mm. Hg) have been observed.\textsuperscript{43}

4. **Dibenamine Test**. Slow intravenous injection (over 1 to 2 hours) of 400 mg. of dibenamine hydrochloride in 500 ml. of 5 per cent glucose solution causes a slowly developing but long lasting (11 hours) lowering of the blood pressure in pheochromocytoma.\textsuperscript{44} Dibenamine in a dose of 10 mg./Kg. body weight may also block the releasing effect of histamine.\textsuperscript{45}

5. **Phentolamine (Regitine) Test**. This drug, which blocks the effector cells for the action of epinephrine and norepinephrine like Benzodioxane and Dibenamine, was introduced by Longino and co-workers.\textsuperscript{46} It has been claimed to be the safest of the antisymptomimetic test drugs. When given in a dose of 5 to 10 mg. intravenously, it causes a fall in blood pressure often lasting for more than an hour in tumor cases. False positive reactions are not infrequent.\textsuperscript{37, 47}
6. Tetraethylammonium Test (LaDue, Muri- 
sion, and Pack48). This drug acts as a 
ganglionic- 
blocking agent and is thought to increase 
the 
pressor action of circulating norepinephrine and 
epinephrine by blocking the regulating mecha-
nism. In addition it seems to cause an increased 
release of the chromaffin cells by direct action. 
It is seldom used.

LOCALIZATION OF TUMOR

It is highly desirable that the exact localiza-
tion of the tumor or tumors in the body is 
known before operation. In some cases the 
tumor is relatively large and therefore possible 
to palpate or to observe on a plain roentgeno-
gram (10 to 30 per cent of cases7, 49, 50). Usually 
it is small (weight less than 100 Gm.) but pal-
pation may nevertheless give information if the 
arterial blood pressure is found to increase 
significantly when the suspected site is pal-
pated.51, 52 Other examinations may give suc-
cessful results, such as intravenous or retro-
grade pyelography (positive result in 20 to 50 
per cent of cases7, 49), selective arteriography,53 
tomography, and retroperitoneal gas insuffla-
tion (positive result in about half the examined 
cases7).

Suggestive information may also be obtained 
from analyses of the catechol-amine concentra-
tion in urine and blood. As is evident from 
table 3, a pheochromocytoma releasing norepi-
 nephrine as well as epinephrine is usually lo-
calized in direct connection with 1 of the 
adrenal glands, while a tumor producing only 
norepinephrine is usually situated more or less 
away from the adrenal glands. There are excep-
tions to this rule, however.

A new approach has recently been tried.54 By 
introduction of a radiopaque catheter (the 
usual cardiac catheter or better the special type 
used by Ödman44) under fluoroscopic control, 
blood samples can be drawn from selected parts 
of the venous system. Venous blood from the 
tumor may have a sufficiently high concentra-
tion of catechol amines to allow a relatively 
precise estimation. The catechol amines become 
diluted in the caval veins but if samples are ob-
tained just central and distal to the level of 
entrance the result may be conclusive. If the 
catheter tip is introduced into the renal veins 
(and exceptionally into the right adrenal vein) 
the result may indicate that an adrenal tumor 
is right-sided or left-sided. In 1 case54 (case no. 
21 in table 3) an extra-adrenal tumor at the 
left renal hilus was observed at operation to be 
drained by a vein entering the inferior caval 
vein caudal to the level of the renal veins. The 
catheterization study had shown that norepi-
 nephrine was absent in the superior caval vein 
but present in increasing concentration when 
the catheter tip was moved down toward the 
iliac bifurcation of the inferior caval vein. In a 
second case of malignant pheochromocytoma55 
(case no. 24 in table 3) with suspected general 
spread of metastases, high norepinephrine con-
centrations were found in the inferior as well as 
the superior caval systems (but not in arterial 
blood). In a third case56 (case no. 30 in table 3) 
of a multiple, possibly malignant, intrathoracic 
pheochromocytoma, samples from the inferior 
caval vein and the brachiocephalic veins did 
not contain norepinephrine, but a high concen-
tration appeared in the superior vena cava at 
the level where the azygos vein usually enters. 
To judge from these 3 cases, selective venous 
catheterization with blood analysis of catechol 
amines may be of clear value for the topical 
diagnosis of continuously secreting pheochro-
mocytomas. A similar procedure has been used 
for evaluation of unilateral adrenal cortical ac-
tivity;57 in the case of a unilateral adrenal pheo-
chromocytoma it may be of value to examine 
the cortical function of the contralateral ad-
renal gland before operation.

TREATMENT

The adequate treatment of pheochromocytoma is the complete surgical removal of the 
tumor.12, 58 This may be difficult, since the tu-
mor often is situated near the aorta and the 
inferior vena cava, and since it may easily rupture 
even if it is encapsulated. The mortality 
rate of operations has hitherto been high (20 to 
30 per cent)59 but will probably become lower 
with more adequate postoperative treatment. Antisymphathomimetic agents (Benzodioxane, 
Dibenamine, or preferably Regitine) can be 
used temporarily to combat a spontaneous 
paroxysmal attack, or an attack provoked by 
pharmacologic diagnostic stimulation, or diag-
nostic palpation, or by the anesthesia and the manipulation of the tumor during operation.

Difficulties may arise in keeping the arterial blood pressure within reasonable limits during operation. For the exact and rapid pharmacologic treatment of sudden changes in arterial pressure, it is of advantage to register the pressure continuously, e.g., with the technic for intra-arterial recording described by Holmgren. The body position of the patient during operation and the choice of anesthetics may be of importance for the catechol-amine release from the tumor. When the tumor has been removed, intravenous administration of norepinephrine for a variable length of time and sometimes in high dosage is usually necessary to prevent the arterial blood pressure from falling below the normal range.

The urinary output of catechol amines should be determined after operation in order to ascertain the completeness of the surgical treatment. A high arterial blood pressure after an apparently successful operation may be due to essential hypertension existing before the appearance of the tumor, or to vascular changes secondary to the period of elevated blood pressure caused by the tumor, or may be produced by remaining undetected tumor tissue. Urinary analysis of catechol amines may help to differentiate these possibilities.

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All patients with established atrial fibrillation admitted to the Nordland County Hospital during a period of 18 months were treated with quinidine in an attempt to restore normal sinus rhythm. The patients were treated with digitalis and Dicumarol before and during the period of quinidine therapy. Of a total of 74 patients, normal sinus rhythm was achieved in 45 (60.8 per cent). It was found that the lowest percentage of conversions occurred in patients with rheumatic heart disease. The longer the duration of the atrial fibrillation the greater was the difficulty in achieving normal rhythm. When normal rhythm was produced, the circulation time was found to be shorter and the roentgenologic heart volume was found to decrease, but the venous pressure did not change appreciably. Nausea, vomiting, or diarrhea during treatment occurred in 19 per cent of the patients. Sixteen per cent of the patients showed quinidine effects upon the electrocardiogram including ventricular premature beats, widening of the QRS complexes, nodal rhythm, atrioventricular block, and nodal tachycardia, which required discontinuance of quinidine treatment. After the drug was stopped, one half of the patients developed sinus rhythm. Eight patients developed atrial flutter during the quinidine treatment. The authors believe that nothing is to be gained by increasing the quinidine dosage when this happens. However, by continuing the quinidine in a dosage of 0.3 Gm. 4 times daily and increasing the digitalis dosage to 0.1 Gm. 4 times daily, it was possible to produce sinus rhythm in 6 of these 8 patients. Of the 45 patients who were converted to normal rhythm, the conversion was maintained in 32 (71 per cent) during an observation period ranging from 3 to 24 months.

In connection with the conversion to sinus rhythm 2 patients developed emboli and 1 patient had a period of syncope that was attributed to cardiac standstill. Eleven of the patients had 1 or more emboli before treatment. It is thought that pretreatment with anticoagulants will reduce the danger of embolization. The toxic effects of quinidine on the heart necessitate close and constant supervision of the patients with daily electrocardiograms and even more frequent observations if disorders of rhythm occur. For this reason it is believed that quinidine therapy of the kind used in these patients can be carried out only in the hospital. Discontinuance of treatment is indicated if the QRS complex widens by more than 25 per cent.

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Circulation. 1957;15:5-13
doi: 10.1161/01.CIR.15.1.5
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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