Pituitary microadenomas may present with subtle or no mass effect. They may appear lucent, dense, or heterogeneous on computed tomographic (CT) images. The normal pituitary gland may also have a nonhomogeneous CT appearance with intermingled lucent and dense areas. This heterogeneity is related in part to microscopic variation within the anterior and posterior lobes. Thirteen autopsy specimens of the pituitary gland were examined by coronal CT and histologically sectioned in similar coronal planes. The CT-lucent and CT-dense areas of the anterior and posterior lobes were correlated with corresponding areas on microscopic examination. To determine the effects of contrast infusion during CT, density measurements of lucent and dense areas in the anterior lobes of 26 normal contrast-enhanced pituitary glands in vivo were compared with density measurements of adjacent vascular structures at the time of scanning. Microscopic features corresponding to increased CT density in the anterior lobe included increased tissue compactness and increased cellular granularity, both of which usually occurred together in areas composed of tightly compacted and heavily granulated acidophilic cells. Conversely, microscopic features corresponding to decreased CT density in the anterior lobe included decreased tissue compactness and decreased cellular granularity, both of which frequently occurred together in areas containing chromophobic and/or mildly to moderately granulated basophilic cells. The degree of contrast enhancement within the anterior lobe appeared primarily to depend on vascularity, which in turn often depended on the degree of tissue compactness. In the posterior lobe, CT-lucent areas appeared to correspond to less compact and/or less vascular neurohypophyseal tissue.

Computed tomography (CT) is particularly valuable for recognizing microadenomas in patients with normal serum hormone levels [1–6]. CT can also help to rule out microadenomas in patients who have suspicious serum hormone levels but in fact have other lesions. Since small microadenomas may present with subtle or no mass effect [7] and therefore may be confused with normal glandular tissue, a thorough understanding of the CT appearance of the normal pituitary gland and its normal variations is important [8].

Part 1 of this study (pp. 927–935, this issue) discussed variations in CT density within the pituitary gland caused by gross structural interrelations of the anterior lobe, pars intermedia, and posterior lobe. This paper examines variations in CT density resulting from microscopic anatomic features in the anterior and posterior lobes.

Materials, Subjects, and Methods

The materials, subjects, and scanning techniques were described in part 1. However, additional methods were used to evaluate the CT-lucent and CT-dense areas within the anterior and posterior lobes and to determine the effects of contrast enhancement.

Focal CT-lucent areas in both the autopsy specimens and clinical subjects were evaluated for CT density, configuration, height, and width; focal CT-dense areas were evaluated for CT density. The CT density measurement for each focal area was determined by averaging
multiple 4-pixel values. In order to make the pituitary density measurements more valid, they were compared with those of ventricular cerebrospinal fluid (CSF). Since the latter values varied between 0 and 12 H (Hounsfield units), they were standardized to 8 H and any differences from this value were added to or subtracted from the pituitary measurements.

To determine the effects of contrast infusion during CT, density measurements of lucent and dense areas in the anterior lobes of normal contrast-enhanced pituitary glands in vivo were compared with density measurements in vascular structures at the time of scanning (fig. 1). The CT density measurement in the densest region in the adjacent cavernous sinus was taken to represent the vascular structures in each instance.

Results
Anterior Lobe

The CT-lucent areas in the anterior lobes of the combined clinical and autopsy series (n = 39) had the following configurations: 49% round, 28% oval, 22% elongated with parallel sides, and 1% elongated but wedge-shaped. They had a maximum height of 3.2 mm and maximum width of 4.0 mm.

On the unenhanced CT sections of our autopsy specimens, the two most significant histologic features contributing to a lucent as opposed to dense appearance were a low or moderate degree of tissue compactness (table 1, areas B vs. C and E vs. F) and a low degree of cellular granularity (table 1, areas A and B).

Frequent CT patterns emerged as a result of the anatomic relations of the CT-dense and CT-lucent areas to each other. These patterns were similar in unenhanced and enhanced glands. In the anterior and mid parts of the anterior lobe, CT-lucent and CT-dense areas of similar configuration often alternated with each other from one side of the gland to the other, creating a repetitive pattern (figs. 2B and 2C). The CT-lucent areas corresponded to loosely packed chromophobes and/or mildly to moderately granulated basophilic cells with a few moderately to heavily granulated acidophilic cells scattered throughout; the CT-dense areas corresponded to densely compacted and heavily granulated acidophilic cells (fig. 2A).

In another, less frequent pattern, CT-dense areas were located on both sides of the gland, lateral to centrally-located CT-lucent areas (figs. 3B and 3C). Histologically these lucent and dense areas were the same as those seen in the repetitive pattern (fig. 3A).

In addition, in the mid part of the anterior lobes of enhanced glands, CT-lucent areas were often seen along the superior border (fig. 3B). Histologically these areas consisted of loosely packed fibrous tissue with a few acidophilic, chromophobes, and/or basophilic cells embedded in a vascular stroma; they were contiguous posteriorly with similar areas at the base of the infundibulum. These lucent areas were rarely identifiable in enhanced glands, presumably because of their high degree of vascularity. The superior borders of the most-enhanced glands were CT-dense throughout, which may reflect not only the above feature but also the presence of intercavernous sinuses on their surfaces and the presence of an enhancing diaphragma sellae.

Often, CT sections through the anterior and mid parts of the anterior lobe were relatively homogeneous. In these instances there was a relatively uniform degree of tissue compactness with cells of various degrees of granularity either interspersed throughout or scattered as small foci of individual cell types.

CT-lucent areas were occasionally seen between the anterior lobe and cavernous sinus, especially superiorly and inferiorly (figs. 3B and 3C); these areas corresponded to extraglandular areas of adipose and/or connective tissue.

The posterior parts of the anterior lobe usually were relatively homogeneous and dense on CT (figs. 4B and 4C). They corresponded histologically to the areas with the most densely compacted and heavily granulated acidophilic cells in the anterior lobe (fig. 4A) and were located superolateral to the pars intermedia on both sides of the gland.

On either side of the midline in the mid and posterior parts of the anterior lobe, compact bands of dense connective tissue and vessels referred to as fibrous cores [9] coursed in an anteroposterior direction (fig. 5). They did not differ significantly in CT density or in vascularity/unit volume from the adjacent loosely packed glandular tissue and were not discernible from adjacent areas on plain or contrast-enhanced CT.

Except for the above-mentioned vascular areas on the superior border of the mid part of the anterior lobe, the degree of vascularity appeared to be similar throughout the anterior lobe or to be greater in some regions of increased tissue compactness. Such regions of increased tissue compactness were usually CT-dense in their unenhanced state and, being more vascular, had the greatest potential for vascular contrast enhancement. Therefore, the relative contrast between unenhanced dense areas and lucent areas
TABLE 1: CT Density–Histologic Correlation in Autopsy Specimens of Normal Pituitary Glands

<table>
<thead>
<tr>
<th>Pituitary Region: Histologic Area</th>
<th>Degree of Compactness</th>
<th>Predominant Tissue Type</th>
<th>CT Density (Hounsfield units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Anterior lobe:</td>
<td></td>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>A</td>
<td>Loose</td>
<td>Chromophobes</td>
<td>24–45</td>
</tr>
<tr>
<td>B</td>
<td>Loose</td>
<td>Heavily granulated acidophils</td>
<td>33.90 ± 6.45</td>
</tr>
<tr>
<td>C</td>
<td>Dense</td>
<td>Heavily granulated acidophils</td>
<td>41–51</td>
</tr>
<tr>
<td>D</td>
<td>Moderate</td>
<td>Heavily granulated basophils</td>
<td>57–69</td>
</tr>
<tr>
<td>E</td>
<td>Moderate</td>
<td>Fibrous connective tissue</td>
<td>56*</td>
</tr>
<tr>
<td>F</td>
<td>Dense</td>
<td>Fibrous connective tissue</td>
<td>21–36</td>
</tr>
<tr>
<td>G</td>
<td>Moderate</td>
<td>Chromophobic microadenoma</td>
<td>37–45</td>
</tr>
<tr>
<td>H</td>
<td>Dense</td>
<td>Moderately granulated acidophilic microadenoma</td>
<td>54*</td>
</tr>
<tr>
<td>Pars intermedia:</td>
<td></td>
<td></td>
<td>34*</td>
</tr>
<tr>
<td>I</td>
<td>Dense</td>
<td>Colloid cysts</td>
<td>23–50</td>
</tr>
<tr>
<td>Posterior lobe:</td>
<td></td>
<td></td>
<td>36.63 ± 10.21</td>
</tr>
<tr>
<td>J</td>
<td>Loose and/or poorly vascular Neurohypophysis</td>
<td>26–51</td>
<td>35.43 ± 4.65</td>
</tr>
<tr>
<td>K</td>
<td>Dense and/or highly vascular Neurohypophysis</td>
<td>44–62</td>
<td>49.75 ± 5.49</td>
</tr>
</tbody>
</table>

Note.—A–K differentiate areas according to their particular histologic composition.
* One specimen only.

would be expected to be preserved or increased with contrast infusion, if contrast enhancement is based solely on vascularity.

To determine how contrast infusion actually affected CT density within the anterior lobe, the density measurements of the lucent and of the densest areas, respectively, were correlated with the density measurements of adjacent vascular structures at the time of scanning (represented by the densest region in the adjacent cavernous sinus). Separate linear relations were found (fig. 1). For each unit-increase in CT density of the adjacent sinus, the CT density of the lucent areas increased less than that of the densest areas (fig. 1). Thus their CT density difference increased with increasing contrast enhancement. The difference in CT den-
Fig. 3.—Middle part of anterior lobe. A, Coronal histologic section (H and E stain). B, Closely corresponding CT section of specimen. Strongly staining areas in A (large arrows) are densely compacted tissue with heavily granulated acidophilic cells; they correspond to CT-dense areas in B (large arrows). Weakly staining areas in A (small arrow) are loosely packed tissue with chromophobic and/or mildly to moderately granulated basophilic cells; they correspond to CT-lucent areas in B (small arrow). Weakly staining areas along superior surface of gland in A (arrowhead) are vascular, loosely packed fibrous tissue with few glandular cells; they correspond to CT-lucent areas in B (arrowhead). Another weakly staining area in A (curved arrow) is extraglandular adipose and fibrous tissue, corresponding to CT-lucent area in B (curved arrow). C, Contrast-enhanced coronal CT scan in normal patient demonstrates similar CT-dense (white arrows) and CT-lucent (small arrow) areas within anterior lobe. Most-lucent area located centrally (short thick arrow) probably corresponds to colloid cyst in anterior-most pars intermedia. Lucent area located laterally (curved arrow) probably corresponds to extraglandular fat and/or connective tissue.

Fig. 4.—Mid region of gland. A, Coronal histologic section (Masson trichrome stain). B, Closely corresponding CT section of specimen. Strongly staining posterior parts of anterior lobe in A (large arrows) are densely compacted tissue with heavily granulated acidophilic cells; they correspond to CT-dense areas in B (large arrows). Weakly staining anterior part of posterior lobe in A (arrowhead) is compact and highly vascular neurohypophyseal tissue, corresponding to central CT-dense area in B (arrowhead). Colloid-cyst-containing pars intermedia in A (small arrows) separates the two lobes; it corresponds to CT-lucent areas in B (small arrows). C, Contrast-enhanced coronal CT scan in normal patient shows less enhancement of posterior parts of anterior lobe (large arrows) than of more vascular anterior part of posterior lobe (arrowhead). CT-lucent pars intermedia (small arrow) is seen on only one side in this patient.

Fig. 5.—Coronal histologic section (PAS-orange G stain) of anterior lobe of autopsy specimen with symmetric fibrous cores (arrows).
TABLE 2: CT Densities of Lucent and Dense Areas in Contrast-Enhanced Normal Pituitary Glands in vivo (n = 26)

<table>
<thead>
<tr>
<th>Pituitary Region: Contrast-Enhanced Areas</th>
<th>CT Density (Hounsfield units)</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior lobe:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucent</td>
<td>34-95</td>
<td>55.70 ± 18.30</td>
<td></td>
</tr>
<tr>
<td>Dense</td>
<td>44-117</td>
<td>74.89 ± 20.11</td>
<td></td>
</tr>
<tr>
<td>Pars intermedia:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucent</td>
<td>19-58</td>
<td>37.60 ± 11.34</td>
<td></td>
</tr>
<tr>
<td>Posterior lobe:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lucent</td>
<td>35-60</td>
<td>46.19 ± 9.00</td>
<td></td>
</tr>
<tr>
<td>Dense</td>
<td>64-131</td>
<td>83.25 ± 21.00</td>
<td></td>
</tr>
</tbody>
</table>

Density between the lucent and the densest areas was greatest when the density of the cavernous sinus was the highest (fig. 1).

**Pars Intermedia**

The CT-lucent areas in the pars intermedia regions of the combined clinical and autopsy series (n = 39) had the following configurations: 47% elongated with parallel sides, 16% elongated but wedge-shaped, 30% round, and 7% oval. Their maximum height was 5.2 mm and the maximum width was 3.0 mm. There was a higher percentage of elongated lucent areas in the pars intermedia than in the anterior lobe. The lucent areas of the pars also had a greater maximum height and a lesser maximum width than those of the anterior lobe. These features reflect the narrow and elongated configuration of the pars itself, as discussed in part 1 of this study.

On histologic examination, in all but one instance, the lucent appearance of the pars intermedia corresponded to the presence of large and/or frequent colloid cysts. In the single exception the lucent appearance was related to an area of fibrosis with cavitation.

In our unenhanced autopsy specimens, the mean and range of CT densities of the colloid cysts (table 1, area I) were similar to the mean and range of CT densities of the areas of loosely packed chromophagic cells in the anterior lobe (table 1, area A) as well as to the mean and range of CT densities of the less vascular and/or loosely packed neurohypophyseal tissue of the posterior lobe (table 1, area J). The mean CT density of the colloid cysts was also similar to that of the chromophagic microadenoma (table 1, area G).

In our contrast-enhanced clinical series (table 2), the mean and the range of CT densities of the lucent areas within the pars intermedia were similar to those seen in our unenhanced autopsy population (table 1, area I). This indicates their failure to enhance and reflects their avascular nature. Their contrast-enhanced mean density was less than the contrast-enhanced mean density of the lucent areas in the anterior and posterior lobes (table 2), thus helping to identify their nature. Moreover, after contrast infusion the lucent areas of the pars intermedia were more easily distinguished from the adjacent tissue than were lucent areas in other regions. This was attributable to several factors: (1) Since the lucent areas of the pars intermedia did not enhance, unlike most lucent areas in other regions, the density difference between them and the adjacent tissue increased; (2) the regions adjacent to the pars intermedia normally were the most-dense regions of the anterior and posterior lobes (figs. 4B and 4C), providing maximum available contrast; and (3) the cysts of the pars intermedia often were better margined than the poorly defined lucent areas in other regions.

**Posterior Lobe**

CT examination of the posterior lobe frequently demonstrated multiple round lucent areas intermingled with dense areas. The maximum height of these lucent areas was 3 mm and the maximum width was 2.2 mm.

On histologic examination, bundles of homogeneous-appearing neurohypophyseal tissue were seen with various degrees of vascularity and compactness (fig. 6). The more lucent areas on CT examination corresponded to the less compact and/or less vascular bundles on histologic examination (table 1, area J). Conversely, the denser areas on CT examination corresponded to the more compact and/or more vascular bundles on histologic examination (table 1, area K).

The most anterior part of the posterior lobe usually corresponded to both compact and vascular neurohypophyseal tissue (fig. 4A). It was generally the most vascular region of the posterior lobe, receiving vessels directly from superior and inferior vascular networks on the immediately adjacent glandular surface [9-11]. On coronal CT examination, both with and without contrast enhancement, this region usually corresponded to a very dense and homogeneous central area, sometimes flanked on either side by a lucent pars intermedia (figs. 4B and 4C). After contrast enhancement it was typically the most CT-dense area of the entire gland.

The more posterior parts of the posterior lobe corresponded to bundles of neurohypophyseal tissue with various degrees of compactness and vascularity (fig. 6A). Overall, this tissue was less vascular than that in the anterior part of this lobe. On CT examination it frequently had a "multicystic" appearance (figs. 6B and 6C), with the lucent "cystic" areas corresponding to the less compact and/or less vascular neurohypophyseal tissue.

In our unenhanced autopsy specimens, the mean CT density of the lucent areas in the posterior lobe (table 1, area J) was similar to that of the lucent areas in the anterior lobe (table 1, area A) and pars intermedia (table 1, area I). In the contrast-enhanced clinical subjects, however, the mean CT density of lucent areas in the posterior lobe was less than that of the lucent areas in the anterior lobe but greater than those in the pars (table 2).

In our unenhanced autopsy specimens, the mean CT density of the dense areas of the anterior lobe (table 1, area C) was greater than that of the dense areas of the posterior...
Microadenomas

Two asymptomatic microadenomas found in our autopsy specimens provided direct information about their CT-histologic correlation. The first microadenoma appeared lucent on CT and was composed of sheets of moderately compacted chromophobic cells with no detectable granularity. Glandular follicles with central lumina containing a colloid substance were scattered throughout. The second microadenoma corresponded to a relatively dense area on CT that could not be differentiated from the adjacent tissue. This microadenoma was composed of densely compacted and moderately granulated acidophilic cells. Its relatively more dense appearance was attributed to its increased granularity, increased tissue compactness, and absence of colloid material as compared with the first microadenoma (table 1, areas G and H). Both microadenomas contained less fibrous tissue and were less vascular than the other regions of the anterior lobe.

Discussion

Retrievable parts of microadenomas excised at surgery often are structurally distorted, incomplete, and fragmented. For this reason, it is hazardous to attempt to correlate the histologic appearance of surgical specimens with the presurgical CT appearance of the structurally intact tumor. As a result, it is difficult to increase our diagnostic acumen for microadenomas by studying surgical material alone. We approached the problem of diagnosing pituitary microadenomas by attempting first to understand and define the CT appearance of the normal pituitary gland.

Our results show that the CT density of normal pituitary tissue depends primarily on its degree of compactness, granularity, and vascularity and on the presence or absence of colloid cysts. Typical CT patterns (fig. 7) may result from various combinations of these factors in different parts of the gland. Pattern distortion with associated asymmetry suggests an abnormality. This is true particularly if the suspected abnormality is a lucent area located in the anterior lobe and > 3.2 mm high or > 4 mm wide.

Since there is a difference between the degree of contrast enhancement of the CT-lucent areas as compared with the densest areas, the question arises as to the source of this enhancement, that is, the relative contributions of the vascular versus the interstitial compartment. Theoretically, since the pituitary gland resides outside the blood-brain barrier, contrast media can rapidly equilibrate between the intravascular and extravascular interstitial spaces [12, 13]. The degree of tissue enhancement then depends on the volumes of these compartments, the diffusibility of the specific contrast agent, the dose and rate of administration, and the state of hydration, age, renal function, and body habitus of the patient [14, 15].

Our results demonstrate that the lucent areas in the anterior lobe, which usually consist of loosely packed tissue, increase less in density with increasing vascular contrast concentration than the densest areas, which usually consist of densely compacted tissue (fig. 1). As previously discussed, the more compact anterior-lobe tissue may have a higher concentration of vessels than at least some of the less compact tissue, hence, a greater potential for vascular enhancement. The more compact tissue generally appears also to have less available interstitial space. Thus, it is likely that vascular enhancement is primarily responsible for the greater increase in CT density of the dense as compared
 PITUITARY MICROSCOPIC ANATOMY–CT CORRELATION

Two clinically "silent" microadenomas were found in the anterior lobes of our autopsy specimens. One was an acidophilic and the other a chromophobic microadenoma. The chromophobic microadenoma was lucent on CT. Since it was hypovascular compared with adjacent tissue and had sparse interstitial tissue, this microadenoma could be expected to remain lucent, at least initially, after contrast enhancement. The unenhanced acidophilic microadenoma, however, was isodense on CT. Since it was also hypovascular and had sparse interstitial tissue, it theoretically could be expected to become less dense than its adjacent, more vascular tissue, at least initially, after contrast enhancement. There is evidence to suggest that on delayed scans the relative concentration of contrast agent in some microadenomas may be greater than in adjacent tissue owing to sequestration or delayed concentration [18].

The chromophobic microadenoma was more vascular than the more compact acidophilic microadenoma. This raises the possibility of a vascular basis for the findings of Sakoda et al. [17], who report greater overall enhancement of prolactin-secreting adenomas (which are usually chromophobic) as compared with growth-hormone-secreting adenomas (which are usually acidophilic). However, because of their lower initial density, the prolactin-secreting adenomas in the series reported remained relatively less dense than their growth-hormone-secreting counterparts, even though they enhanced more [17].

Other potentially CT-lucent areas in the anterior lobe have been reported by other investigators [19–21] after histologic reviews of autopsy specimens. They include areas of infarction with fibrosis, old hemorrhage, and hypovascular metastases. We have a single clinical example of biopsy-proven metastatic adenocarcinoma, which extended from the orbit into the cavernous sinus immediately adjacent to the lateral aspect of the pituitary gland. It was hypodense relative to the nearby pituitary tissue.

Knowledge of normal structural patterns within the pituitary gland is helpful not only in detecting abnormal focal areas but also in differentiating these focal abnormalities from abnormal glandular hyperplasia. In our very limited experience, abnormal hyperplastic glands have not demonstrated a definite distortion of structural patterns. They have tended to increase the overall size of the gland, causing a superior convexity on its surface and/or bony erosion of the sellar floor. Theoretically, since certain regions of the pituitary gland contain specific cell types, selective regions may be stimulated in glandular hyperplasia to increase in compactness and/or vascularity and/or to alter their degree of granularity. This could result in a selective increase in either CT-dense or CT-lucent areas simulating microadenomas. Conditions linked to glandular hyperplasia include the use of L-dopa antagonists [1, 5, 6], hypothyroidism [2–5], and hypogonadism.

In summary, although normal pituitary glands often appear heterogeneous on CT, they frequently exhibit predictable and symmetric structural patterns. Distortion of these structural patterns, especially by abnormally large CT-lucent
areas, suggests the presence of a microadenoma, even in the absence of mass effect.

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