

# Endocrine and Metabolic Aspects of Bronchogenic Carcinoma

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THERE HAS BEEN increasing interest in the extrapulmonary abnormalities associated with bronchogenic carcinoma<sup>30,3</sup> (Table 1). Since most of these abnormalities have been described with other tumors or non-neoplastic disease of other organs, they cannot be considered tumor- or organ-specific. Many of these syndromes have been related to a potentiality of the tumor to act as a functioning tissue mass. These endocrine and metabolic aspects of neoplasia have opened a new field of fruitful investigation.

Several of these syndromes will be considered. They may be the presenting manifestation of the carcinoma and do not per se imply non-resectability of the lesion; moreover, they may become evident as a complication during treatment. Awareness of these problems may therefore lead to earlier diagnosis and more effective treatment.

Bilateral adrenal hyperplasia, often with signs of Cushing's syndrome, and markedly elevated steroid levels has been described in as-

sociation with bronchogenic carcinoma, usually of the oat cell type.<sup>22,27</sup> Patients with overt Cushing's syndrome represent one extreme of the spectrum of adrenal hyperplasia associated with these tumors; they frequently show weight gain or maintenance of weight despite rapid progression of the cancer, acute development of the features of Cushing's syndrome, severe hypokalemic alkalosis which has been related to the high level of plasma steroids,<sup>7</sup> and a rapidly fatal course. The urinary excretion of steroids may not be suppressed by large doses of dexamethasone, but there is response to corticotropin (ACTH) stimulation.<sup>38</sup> These features serve to distinguish these patients from those with Cushing's syndrome of other etiology. Plasma corticotropin levels are high and an corticotropin-like material can be isolated from both the tumor and its metastases.<sup>38,35</sup> Less commonly, the corticotropin-producing tumor is of a low order of malignancy. The clinical course is prolonged and characterized by diffuse pigmentation which may disappear after subtotal adrenalectomy.<sup>13</sup> The manifestations of Cushing's syndrome may precede diagnosis of the tumor by many months. It has been suggested that cortisone facilitates tumor growth, and it has been shown that there is an inverse relation between the concentration of plasma steroids and the duration of life.<sup>48</sup>

The hypercalcemia of malignancy is usually due to diffuse skeletal metastases. Of interest are the cases of carcinoma and hypercalcemia without bone metastases demonstrable by x-ray or at autopsy.<sup>9,39,34</sup> Resection of the tumor has been followed by a prompt return of the serum calcium to normal, with reappearance of elevated levels upon recurrence of the disease.<sup>9,39</sup> The serum phosphorous in these cases has been variable.

TABLE 1.\*—*Extrapulmonary Abnormalities Associated With Bronchogenic Carcinoma*

1. Metabolic: adrenal hyperfunction, hypercalcemia, excessive ADH, carcinoid syndrome.
2. Neuromuscular: the carcinomatous neuromyopathies.
3. Connective tissue and osseous: clubbing and hypertrophic osteoarthropathy, dermatomyositis, scleroderma, acanthosis nigricans.
4. Vascular: migratory thrombophlebitis, nonbacterial thrombotic endocarditis.
5. Hematologic: anemia, polycythemia, fibrinolytic purpura, cryofibrinogenemia

\* Modified, from Knowles and Smith.



In most of these patients the parathyroids are normal,<sup>39,26</sup> and it has been suggested that the carcinoma may elaborate a substance, resembling parathyroid hormone, although no such substance has been isolated.\* In others there has been parathyroid hyperplasia<sup>46,36</sup> and return of elevated serum calcium levels to normal after subtotal parathyroidectomy.<sup>46</sup> It was therefore suggested that the tumor released an unknown agent which stimulated the parathyroids leading to bone reabsorption and hypercalcemia.

Neoplasms with hypercalcemia without apparent bone disease can present an obscure picture and mimic completely primary hyperparathyroidism.<sup>36</sup> Moreover, symptoms such as anorexia, weakness, and vomiting may be attributed to nonspecific effects of the cancer and the causative hypercalcemia go undetected. Hypercalcemia is potentially fatal and may be treated with intravenous fluids and steroids even if resection of the tumor is not possible.

A syndrome of excessive antidiuretic hormone has been described in some patients with bronchogenic carcinoma.<sup>43,44,41,28</sup> It is characterized by hyponatremia and serum hypotonicity, renal sodium loss, and urine persistently hypertonic to serum. These patients have normal renal and adrenal function, and show no evidence of extracellular fluid volume contraction. It is believed that antidiuretic hormone (ADH) continues to secrete at a time that the serum is hypotonic. Its secretion is therefore "inappropriate." Whether the tumor elaborates an ADH-like material, or stimulates the release of ADH is not known, although antidiuretic activity has been reported in neoplastic tissue of a patient with this syndrome.<sup>16</sup>

Because of the constant ADH effect these patients are in a state of chronic water retention and manifest an inability to excrete water normally. With the administration of water, dilutional hyponatremia and expansion of the extracellular fluid volume result. Renal sodium loss then occurs as a result of a reduction in aldosterone secretion and an increase in glomerular filtration rate, both secondary to expansion of the extracellular fluid volume.<sup>31</sup> However, sodium losing is better correlated with periods of positive water balance than the exact level of overhydration.<sup>29</sup> With the attainment of water balance and a new steady state of

TABLE 2.—*The Carcinomatous Neuromyopathies*

1. Cerebral
2. Cortical cerebellar degeneration
3. Cord syndromes
  - A. Anterolateral column syndrome
  - B. Posterolateral column syndrome
4. Peripheral neuropathy
  - A. Sensory, motor, mixed
  - B. Guillain-Barre
5. Autonomic nervous system insufficiency
6. Carcinomatous myopathy
7. Mixed forms

the dilutional hyponatremia, excessive urinary excretion of sodium may cease.<sup>29</sup>

A normal serum sodium does not rule out this syndrome. Water depletion may occur because of the anorexia, nausea, and vomiting commonly seen in bronchogenic carcinoma. In this way, the serum sodium concentration may be spontaneously corrected, only to be unmasked when water is again administered. This defect in water excretion should be sought in all patients with bronchogenic carcinoma so that fluid therapy can be rationally managed. The administration of what might ordinarily be considered a normal daily water requirement to a patient with this syndrome can lead to a rapid fall in the serum sodium concentration, and the development of severe symptoms of water intoxication.

A variety of neuromuscular disorders unrelated to the presence of metastases, may be associated with bronchogenic carcinoma.<sup>4,6</sup> They may be classified according to their clinical manifestations (Table 2).

The cerebral type manifests as an organic mental syndrome with depression or a confusional state.<sup>37</sup> Cortical cerebellar degeneration presents the picture of cerebellar ataxia, tremor, vertigo, and nystagmus.<sup>21,5</sup> Anterolateral and posterolateral column syndromes present as amyotrophic lateral sclerosis and combined system disease respectively.<sup>42</sup> Patients with autonomic nervous system insufficiency manifest postural hypotension, anhidrosis, impotence, and urinary retention.<sup>28,45</sup> The peripheral neuropathy may be purely sensory,<sup>11</sup> purely motor,<sup>32</sup> or, most commonly a mixed sensorimotor type.<sup>2</sup> Carcinoma of the lung will rarely be associated with an ascending paralysis of the Guillain-Barré type.<sup>33</sup> Carcinomatous myopathy causes proximal muscle weakness secondary to changes in muscle per se.<sup>6</sup> This may present a myasthenic or myotonic clinical picture. Com-

\* See Addendum.



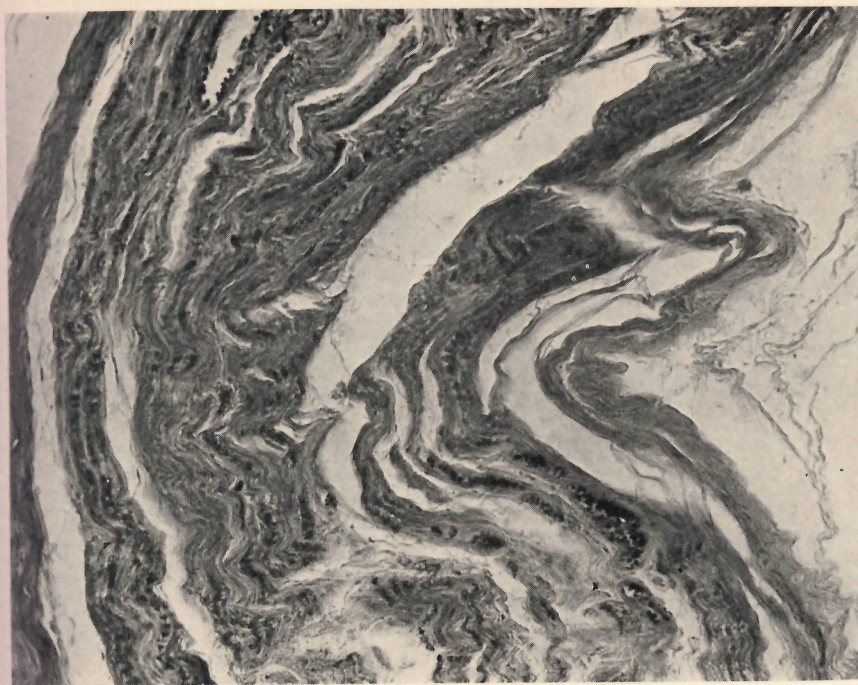


Fig 1.—Biopsy of right peroneal nerve. Myelin degeneration with droplet formation. Osmic acid; reduced about 24% from mag  $\times 90$ .

binations of the above disorders give rise to the mixed forms.

The pathologic changes within the nervous system are characterized by two processes: demyelination and neuronal degeneration. The former may involve peripheral nerve, posterior root, posterior column, lateral column, and white matter of the brain. The latter has involved brain stem nuclei, anterior horns, dorsal root ganglia, and Purkinje cells of the cerebellar cortex. Autopsy confirmation of cases with autonomic insufficiency is not available, but the relationship between the cancer and the clinical picture is strongly suggested.

### Report of Cases

**CASE 1.**—A 64-year-old white male, a heavy cigarette smoker, was admitted to the hospital because of weakness and weight loss of one month's duration. Generalized muscle wasting was most marked in the shoulder girdle and small muscles of the hands. There was generalized motor weakness with a right foot drop. Vibratory sense was absent below the pelvis. Biceps and ankle jerks were absent; all other reflexes were hypoactive.

Chest roentgenogram demonstrated a right upper lobe density. Examination of the cerebrospinal fluid showed a total protein of 84 mg%. A lumbar myelogram was normal. Biopsy of the right peroneal nerve showed extensive myelin degeneration with droplet formation (Fig 1 and 2).

At autopsy a poorly differentiated squamous-cell carcinoma was found arising from the main bronchus

of the right upper lobe. A lumbosacral dorsal root ganglion showed degeneration and disappearance of neurons (Fig 3 and 4). Several sections of the cord showed degeneration and loss of anterior horn cells (Fig 5).

Carcinomatous neuromyopathy was found to be associated with bronchogenic carcinoma in approximately 75% of cases.<sup>6</sup> No correlation has been noted between the onset of neurological symptoms and the time when the tumor becomes clinically manifest or diagnosed; the course of the neuropathy and that of the carcinoma; the size, type, or location of the tumor and the severity of the neuropathy. Surgical removal of the carcinoma and vitamin therapy have generally had no effect on the neuropathy. Marked spontaneous remissions have been observed.<sup>6,21</sup> It has been suggested that the tumor releases a substance which competes with or inhibits an enzyme or coenzyme necessary to maintain the integrity of neurons and myelin.<sup>11</sup> It is important to recognize that symptoms of neuropathy may precede the discovery of a carcinoma by as long as three years.<sup>2,20,12</sup>

The most frequent extrapulmonary manifestation of bronchogenic carcinoma is a thickening of the connective tissues about the terminal phalanges termed clubbing. This may or may not be associated with long bone subperiosteal osteitis with subperiosteal new-bone formation called hypertrophic osteoarthropathy. When



Fig 2.—Same as Fig 1.  
Reduced about 18% from  
mag  $\times 200$ .



both conditions are present, the clubbing usually occurs first and is regarded by many as an early or mild manifestation of hypertrophic osteoarthropathy.

Hypertrophic osteoarthropathy, usually associated with clubbed fingers, may occur in

diverse disorders including chronic pulmonary disease and congenital heart disease. In these conditions it is generally asymptomatic. When associated with carcinoma, it is usually manifested clinically by pain, swelling, heat, redness, tenderness, and limitation of motion, similar to

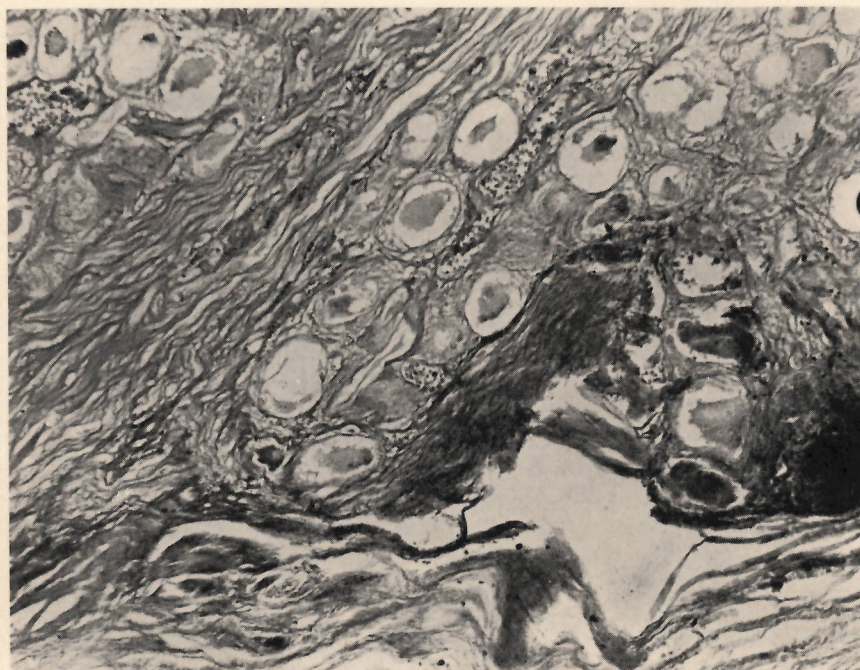
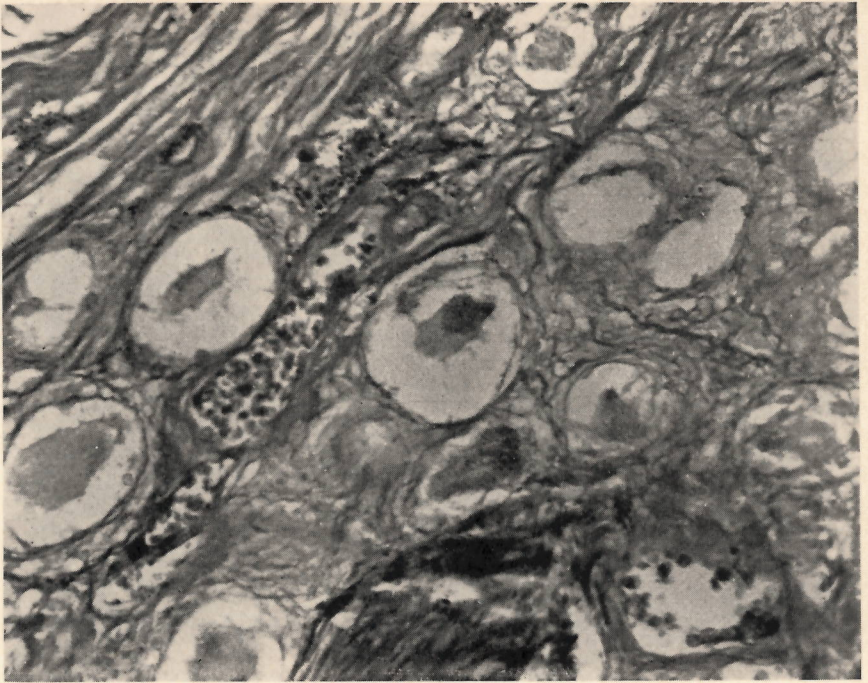


Fig 3.—Lumbosacral  
dorsal root ganglion. De-  
generation and disappear-  
ance of ganglion cells.  
Luxol fast blue-periodic  
acid-Schiff; reduced about  
24% from mag  $\times 90$ .



Fig 4.—Same as Fig 3. Reduced about 18% from mag  $\times 200$ .



the symptoms and findings encountered in rheumatoid arthritis and thrombophlebitis.<sup>40,47</sup> However, even with carcinoma the condition may be demonstrated by x-ray only.<sup>49</sup>

The incidence of these changes in bronchogenic carcinoma has been reported to be between 5% and 10%. Of diagnostic importance is the observation that osteoarthropathy may precede

the development of pulmonary symptoms due to a tumor by as much as 36 months.<sup>19</sup>

Surgical removal of the primary tumor has been followed by resolution of finger clubbing.<sup>19,24</sup> In contrast to carcinomatous neuropathy, the course of hypertrophic osteoarthropathy usually runs closely parallel to the tumor, and there may be dramatic relief of the often

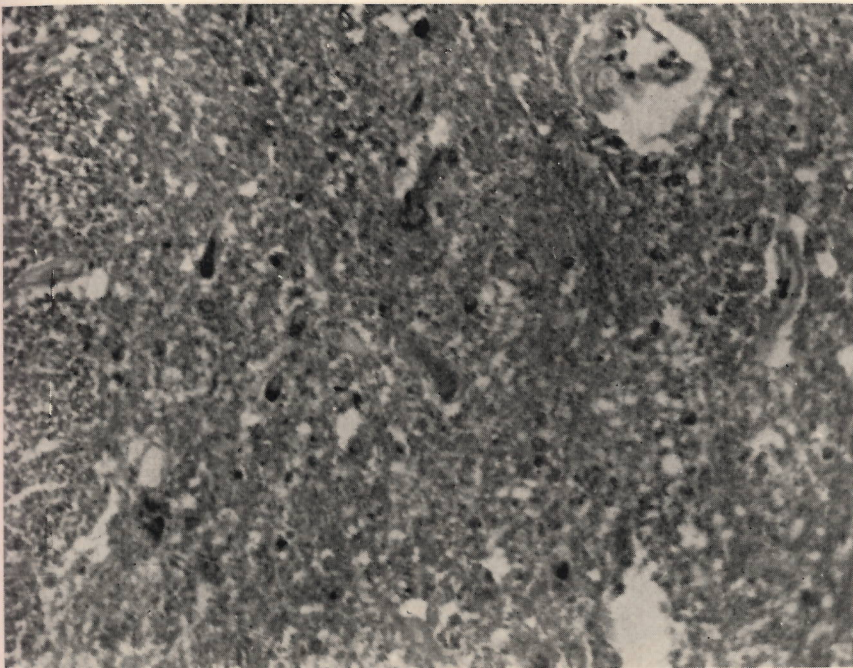


Fig 5.—Anterior horn from lumbo-sacral cord. Degeneration and loss of anterior horn cells. Reduced about 22% from mag  $\times 200$ .





Fig 6.—A 50-year-old white male with squamous-cell carcinoma. Swelling, tenderness, and limitation of motion in both wrists secondary to hypertrophic osteoarthropathy in the absence of clubbed fingers. Urinary estrogen normal.

disabling symptoms following only exploratory thoracotomy, hilar neurectomy, ipsilateral vagotomy, or intercostal nerve section.<sup>14,25</sup>

The overgrowth of vascular connective tissue and increased blood flow in the limbs of the patients with hypertrophic osteoarthropathy and carcinoma<sup>23</sup> may be the result of an increase in circulating estrogen. Increased estrogen excretion in these patients has returned to normal after removal of the tumor.<sup>17</sup> The relationship between nerve section and estrogen excretion, and the possibility that the tumor is a source of estrogen needs to be determined.

CASE 2.—A 50-year-old white male cigarette smoker noted the onset of polyarthritides four months prior to admission. Serological tests for rheumatoid factor were negative but he was placed on acetylsalicylic acid and chloroquine without relief of symptoms. In the month prior to admission he developed right-sided chest pain,

cough, and hemoptysis. He had swelling and tenderness of both wrists, knees, and ankles; there was no clubbing (Fig 6, 7).

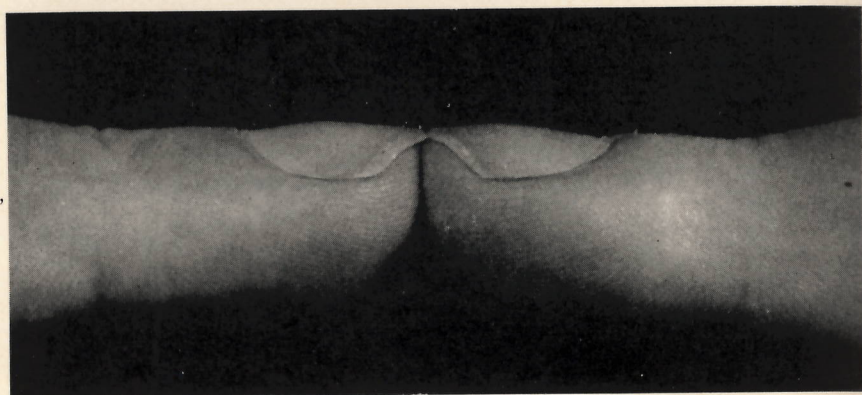
Chest roentgenogram showed prominence of the right superior mediastinum and accentuated bronchovascular markings in the right infrahilar region extending into the right lower lobe. X-rays of the long bones showed the typical changes of hypertrophic osteoarthropathy. The 24-hour urinary excretion of estrogen was normal.

On the seventh hospital day he developed pain and tenderness in the right side of the neck. On the eighth hospital day he underwent a right scalene node biopsy; the next morning a thrombosis of the right external jugular vein was noted (Fig 8).

The scalene nodes contained metastatic squamous-cell carcinoma. Subsequent autopsy confirmed the presence of a right lower lobe squamous-cell carcinoma with widespread metastases.

The coagulation disorders associated with bronchogenic carcinoma may assume either extreme. Fibrinolysis with hypofibrinogenemia

Fig 7.—See legend, for Fig 6.





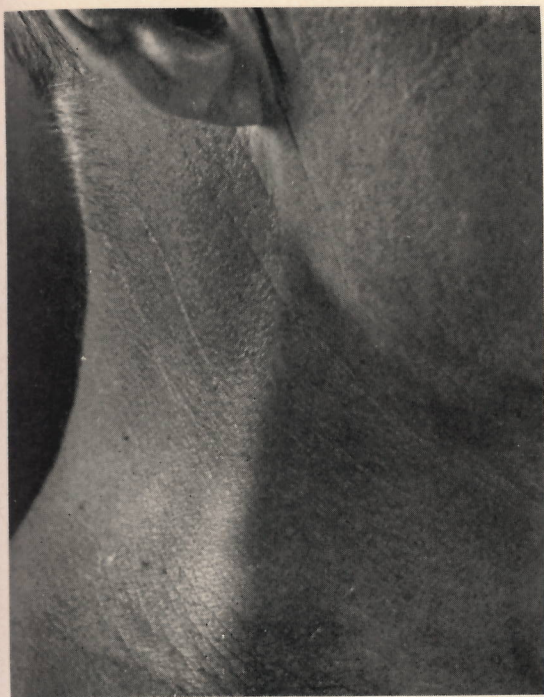


Fig 8.—Thrombosis of right external jugular vein. Pain and tenderness in right side of neck beginning one day before right scalene node biopsy. Thrombosis obvious one day after procedure.

and a hemorrhagic tendency may be part of the presenting picture of the carcinoma.<sup>10,15</sup> In one case, studies to prove fibrinolysis were not undertaken; the patient had a rapidly fatal course secondary to severe generalized hemorrhage with hypofibrinogenemia.<sup>15</sup> Biopsy of a supraclavicular lymph node containing metastatic deposits has initiated this syndrome.<sup>8</sup> Surgical removal of the neoplasm has resulted in a decrease in plasma fibrinolytic activity associated with a rise in the plasma fibrinogen level to normal.<sup>10</sup> It can therefore be postulated that the carcinoma is in some way related to activation of the fibrinolytic process.

A state of hypercoagulability is known to be associated with malignant disease and after operations of all types. This is especially prominent with bronchogenic carcinoma and after operations involving the lung. Elevated levels of antihemophilic globulin have been described<sup>1</sup> and may be etiologic in the migratory thrombophlebitis seen in association with carcinoma.

### Summary

Several of the metabolic abnormalities that may be associated with bronchogenic carcinoma

are reviewed and representative cases cited. The functional capabilities of these tumors is becoming increasingly apparent.

### Generic and Trade Names of Drugs

Dexamethasone—Decadron, Deronil, Dexameth, Gamacorten, Hexadrol.

Corticotropin—ACTH, Acthar, Corticotropin.

Cortisone acetate—Cortisone Acetate, Cortogen Acetate, Cortone Acetate.

Chloroquine phosphate—Aralen Phosphate.

### Addendum

Since the writing of this paper, a parathyroid hormone-like substance was isolated from tumor tissue of a patient with renal adenocarcinoma and hypercalcemia (*Amer J Med* 36:805, 1964). A substance with thyroid-stimulating activity may have been elaborated by an embryonal carcinoma of the testis (*New Eng J Med* 271:345, 1964). Another case of bronchogenic carcinoma with antidiuretic activity in the plasma and tumor tissue has been reported (*New Eng J Med* 271:934, 1964).

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