Beginning of Summary

Neoplasia of a tissue occasionally results in the production of a substance with hormonal activity similar to that produced by one of the endocrine glands. This leads to syndromes that may simulate hyperfunction of an endocrine gland. The syndromes that have been well documented are: hypoglycemia, Cushing's syndrome, polycythemia, hypercalcemia, precocious puberty, the atypical carcinoid syndrome, inappropriate secretion of an anti-diuretic substance, and hyperthyroidism. In Cushing's syndrome and polycythemia, the substances produced have many of the physicochemical characteristics of the normal hormones, adrenocorticotropic hormone and erythropoietin respectively. However, the syndromes of hypoglycemia and hyperthyroidism are clearly not due to the production of insulin or thyroid-stimulating hormone but rather to substances that have these biologic activities. Recognition of these syndromes will result in adequate medical management and occasionally cure.

It is clear from the 2 previous discussions that some tumors occasionally produce substances with hormonal activity. These hormonal syndromes are but one of the intriguing set of effects caused by cancer acting on distant tissues. Whether all of these effects are humoral or are manifestations of autoimmune responses precipitated by cancer is not clear in many instances and some of these ambiguous situations are worth considering briefly.

There are several dermatologic syndromes commonly associated with cancer such as acanthosis nigricans, herpes zoster, and dermatomyositis (15). The more than casual occurrence of these entities with cancer testifies to the significance of relationship although even plausible suggestions about etiologic mechanisms are lacking. There are several other nonspecific dermatoses reported to occur in cancer that can be significant clinically but are, in fact, quite rare (15). Recently 2 cases of anhidrosis secondary to cancer have been described (11, 41). The anhidrosis was due to pathologic changes in the eccrine secretory cells and occurred in association with multiple myeloma and Hodgkin's disease.

Only within the past 15 years were the neurologic disorders associated with cancer clearly defined. Brain (6) reviewed these syndromes recently and classified them according to the sites of involvement (Table 1). The 1st group is composed of carcinomatous encephalomyeloneuropathy. This includes patients with cerebellar disorders due to degeneration of the Purkinje cells, the neuropathies, motor, sensory, and mixed, and the rare case of dementia. The neuropathies have been known to antedate the discovery of cancer by several years and oat-cell carcinoma of the bronchus has been the most frequent offender.

The 2nd group includes the patients with either poly-myositis or the myasthenic syndrome. The myasthenic syndrome has been studied in some detail by Rooke et al. (36) in 14 patients with cancer. Eleven of these had oat-cell carcinoma. This myasthenic syndrome differs from true myasthenia gravis in several respects: (a) The large proximal muscles are impaired predominantly, (b) There is a temporary increase in muscle strength after repetitive muscular activity, (c) The stretch reflexes are either diminished or missing, (d) The response to the pharmacologic agents used in treating myasthenia is poor. These patients, however, are sensitive to curariform drugs and the surgeon and anesthesiologist have on occasion become acutely aware of this association. (e) There may be an associated sensory neuritis.

In the 3rd category are the progressive multifocal leukoencephalopathies. This syndrome is less common than the others and is most frequently associated with the lymphomas. In the reported cases, the disease generally had a brief course and occurred terminally in most patients. The pathologic findings are multiple demyelinating lesions throughout the cerebrum, cerebellum, and brain stem. It is, of course, apparent that in none of these cases was local invasion by tumor a part of the syndrome.

Since Brain's review, there have been 2 cases of orthostatic hypotension described in association with oat-cell carcinoma (18, 42). In one of these cases, the hypotension was the presenting complaint occurring approximately 1 year before the clinical recognition of the carcinoma. It is thus difficult to implicate local effects such as infiltration of sympathetic ganglia in the genesis of the syndrome.

There are a host of other manifestations of cancer such as anemia, thrombophlebitis, and hypertrophic pulmonary osteoarthropathy that should probably not be included in this discussion. This decision may be the result of inade-
quately, however, and Ginsburg and Brown (12) have reported increased estrogen excretion in men with carcino
goma of the bronchus and pulmonary osteoarthropathy.

In the discussion of tumors producing ACTH-like ma-
terial, Dr. Liddle pointed out that tumors derived from
other endocrine glands occasionally produced ACTH. In
thinking about other hormonal activities associated with
tumors, it is reasonable to include tumors of endocrine
glands if the hormonal activity is one that is not normally
produced by the gland. Thus the release of a thyrotropin-
like substance by a tumor of the placenta or the produc-
tion of serotonin by an islet-cell tumor of the pancreas would
fit into this category. Perhaps arbitrarily then, I have
excluded from the discussion the polycythemia associated
with hypernephroma, since the kidney is the chief source
of erythropoietin, and the catecholamine-secret ing neuro
blastomas because the embryonic origin of the tumor is the
same as that of the cells of the adrenal medulla.

CATECHOLAMINES AND CAROTID
BODY TUMORS

In 1962, Glenner et al. (13) reported the case of a 12-
year-old boy with hypertension who had a tumor of the
carotid body that most probably secreted norepinephrine.
The tumor had none of the histologic characteristics of
functional adrenal medullary tumors or of the catechola-
mine-secreting neuroblastomas or ganglioneuromas. Two
similar cases have been reported, in one of which the tumor
secreted norepinephrine (10) and in the other norepineph-
rine and perhaps small amounts of epinephrine (3).
This syndrome is difficult to classify since it is known that
neural crest components accumulate in the human carotid
body during embryonic development. It may be recalled
that these are the cells from which the chromaffin cells of the
adrenal medulla are derived. Furthermore, this year it was
shown that the normal human carotid body contains catecholamines (27) so that tumors arising from this struc-
ture might be predicted to possess occasionally the capac-
ity for the elaboration of excessive amounts of catechola-
mines.

ATYPICAL CARCINOID SYNDROME

The discovery that the carcinoid syndrome can occur
with tumors other than carcinoids of the small intestine

<table>
<thead>
<tr>
<th>Encephalomyeloneuropathy</th>
<th>Excretion mg/24hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical cerebellar degeneration</td>
<td>0.7</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>5 - HYDROXYINDOLE ACETIC ACID</td>
</tr>
<tr>
<td>Sensory</td>
<td>0.7</td>
</tr>
<tr>
<td>Motor</td>
<td>SEROTONIN</td>
</tr>
<tr>
<td>Mixed</td>
<td>50</td>
</tr>
<tr>
<td>Dementia</td>
<td>15</td>
</tr>
<tr>
<td>Myopathies</td>
<td></td>
</tr>
<tr>
<td>Myositis</td>
<td></td>
</tr>
<tr>
<td>Myasthenic syndrome</td>
<td></td>
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<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td></td>
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</tbody>
</table>

has led to further study of the functional characteristics
of carcinoid tumors. The term "carcinoid" was intro-
duced initially to designate tumors of the small bowel
somewhat less aggressive than the usual cancer. It has
come to mean, however, any tumor containing argentaffin
cells similar to the Kulchitsky cells of the small intestine.
Unfortunately argentaffin staining disappears from tissues
a few hours after death so that its absence in autopsy ma-
terial does not necessarily serve to classify the cells cor-
crectly. Since 1958 about 25 cases of bronchial adenomas
have been reported with atypical carcinoid syndromes. In
general these tumors show a resemblance to intestinal car-
cinoids and argentaffin cells are present in small numbers
in some of them (52). The tumors are easily distinguished
from the classical cylindroma type of bronchial adenoma.

Since functionally these bronchial adenomas are quite
similar to the other tumors producing the atypical carci-
noid syndrome, they will be discussed together. The atypical carcinoid syndrome was first outlined by Sandler
and Snow in 1958 (38) in a patient with gastric cancer.
The distinctive clinical feature was a patchy, vivid red
flush unlike that of the typical carcinoid syndrome. Dur-
ing the flush, linear stroking of the skin in a pale area pro-
voked a red flare (28). In several patients urinary histo-
mine excretion has been increased and it has been suggested
(28) that the tumor produces histamine. This syndrome
has been reviewed in detail by Oates and Sjoerdsma (28).

When one compares the excretion of tryptophan metab-
lites between the patients with the typical and atypical
carcinoid syndromes, the differences are striking (Chart
1). In the typical carcinoid, 5-hydroxytryptamine (sero-
ytriptophan-producing gastric and bronchial carcinomas demonstrated that the tumor tissue of an oat-cell carcinoma contained 200 μU of anti-diuretic substance per mg of tissue. However, the amount of tumor tissue may be several thousand times that of posterior lobe. The ratio of 5-HIAA and serotonin at other sites. This has some clinical significance, since the administration of α-methyldopa, a decarboxylase inhibitor, greatly decreased the severity of symptoms in a patient with atypical carcinoid syndrome by preventing the further metabolism of 5-hydroxytryptophan (28), whereas its effect was negligible in the patient with the typical carcinoid.

This pattern of metabolites characteristic of the atypical carcinoid syndrome has been reported with pancreatic duct-cell carcinoma (31), oat-cell carcinoma of the bronchus (14), gastric carcinoma (28), neuroblastoma (4), and bronchial adenomas as outlined above. A unique case of a metastasizing islet-cell carcinoma of the pancreas that produced both hypoglycemia and the atypical carcinoid syndrome has recently appeared (49). This last case is a telling argument against the hypothesis that the 5-hydroxytryptophan-producing gastric and bronchial carcinomas are really carcinoid tumors since in this instance a histologically and functionally typical islet-cell carcinoma produced the atypical carcinoid syndrome.

There have been several cases of oat-cell carcinoma and bronchial adenoma in which histological and biochemical examination of the tumor tissue revealed the presence of serotonin and 5-hydroxytryptophan although the patients were asymptomatic. The secretion of relatively small amounts of serotonin by an oat-cell carcinoma in a patient without the clinical syndrome has also been demonstrated (30). These findings suggest that the synthesis of these compounds by oat-cell carcinomas may be more common than is generally recognized and raises the possibility that the measurement of their excretion may serve to gauge the metabolic activity of the tumors.

INAPPROPRIATE SECRETION OF ANTI-DIURETIC SUBSTANCE

I would like to turn now to the syndrome of inappropriate secretion of anti-diuretic hormone. This was first described by Schwartz et al. in 1957 (40) in 2 patients with oat-cell carcinoma of the bronchus. The syndrome consisted of secretion of an anti-diuretic substance at a time when plasma osmolality was low. The resulting water retention caused a decrease in aldosterone secretion and an increase in glomerular filtration rate, both factors favoring sodium loss (Chart 2). In subsequent case reports (8, 35), the possibility was raised that the anti-diuretic substance might be produced by the tumor. Amatruda et al. (1) demonstrated that the tumor tissue of an oat-cell carcinoma contained 200 μU of anti-diuretic substance per mg of tissue by bioassay. To put this in perspective, the normal human posterior lobe has 1–2 units of anti-diuretic material per mg of tissue. However, the amount of tumor tissue may be several thousand times that of posterior lobe. In another similar patient (5), both tumor and metastasis contained 50–150 μU/gm of tissue. In this case, however, the posterior lobe had been destroyed by metastatic cancer proving that anti-diuresis was not due to ADH secretion. Thorn and Transbol (47) studied the excretion of anti-diuretic substance in a man with oat-cell carcinoma and hyponatremia. He excreted 3100 mU in 24 hr, whereas the normal hydropenic subject excretes only 80 mU/day. Thus, the evidence from these 3 cases points towards the elaboration of a substance with anti-diuretic properties by the oat-cell carcinoma. Although this material had some of the properties of arginine vasopressin (1) it is premature to conclude that it is identical with it.

PRECOCIOUS PUBERTY

An equally rare syndrome is that of precocious puberty associated with hepatoblastoma. Seven cases of this have been reported and an 8th patient has been studied at the National Cancer Institute. The patients have been boys ranging in age from 1 to 8 years. In all cases, there was evidence of penile development and early maturation of secondary sexual characteristics. Interstitial cells were present in the testes and an increased excretion of testosterone was demonstrated in 1 patient by Hung et al. (17). These authors have also summarized previous reports in their paper.

It is clear from studies in 5 of the cases that the genesis of the precocious puberty was the production of a substance with interstitial cell-stimulating properties probably by the tumor. Since tubular development did not occur in these testes, presumably there was no follicle-stimulating hormone present. In 1 case (17), chemotherapy produced a decrease in the size of the tumor and a concomitant fall in testosterone excretion. The gonadotropins have not been adequately characterized, but McArthur (24) stated that they differed immunologically from normal human chorionic gonadotropin.

The hepatomas in these children are histologically the same as other childhood hepatomas that are unaccompanied by virilization. In no instance were teratoid structures or trophoblastic cells encountered that could be implicated as the source of the gonadotropin. We are thus forced to conclude that a small number of otherwise typical hepatomas achieve the capacity for synthesis of a substance with interstitial cell-stimulating activity. Since such activity would be clinically unnoticed in girls, it would

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**Chart 2.**—Genesis of the hyponatremia in “inappropriate anti-diuretic hormone secretion.” GFR, glomerular filtration rate.
be of interest to measure gonadotropins in girls with hepatomas.

**HYPERTHYROIDISM**

Hyperthyroidism too has been noted in association with cancer. A series of miscellaneous types of cancer with coexisting hypothyroidism was reported by DeGennes et al. (7), but there are no studies relating to etiology. There is a well-documented association of hyperthyroidism with tumors of the trophoblast. Obstetricians have long been aware of signs and symptoms suggestive of hyperthyroidism in some women with hydatidiform mole. There have been 3 reports (9, 19, 48) documenting this hyperthyroidism by means of appropriate thyroid-function tests such as thyroidal $^{131}$I uptake and serum protein-bound iodine levels. In all instances, following delivery of the mole, the hyperthyroidism subsided.

Similar findings have been reported in 7 women with metastatic choriocarcinoma (29) and in 1 man with embryonal carcinoma (45). The evidence for hyperthyroidism and the effects of therapy directed towards the tumor are summarized in Chart 3.

In 4 of the patients with metastatic trophoblastic disease, plasma thyroid-stimulating activity was increased when measured by a bioassay technic and, in 2 of these patients, extracts of tumor tissue contained large amounts of a thyrotropin-like material (29).

These data in conjunction with the response to chemotherapy point to the trophoblast as the source of the thyroid-stimulating activity. As with the ACTH-producing tumors, these tumors appeared autonomous since exogenous thyroid did not suppress the $^{131}$I uptake (29). Although the placenta is a multi-functioned endocrine organ, under normal circumstances it does not appear to produce appreciable amounts of thyrotropin. Nevertheless, tumors of this organ have occasionally achieved the capacity for the production of a thyroid-stimulating substance. Since the hyperthyroidism that is produced is clinically mild, it may be that the syndrome is considerably more common than is realized.

**HYPOGLYCEMIA**

The hypoglycemia due to cancer of tissues other than the pancreatic islet cell has been the subject of several recent reviews (23, 43). An almost constant characteristic of these tumors has been their large size, the tumor weights ranging from 800 to 10,000 gm. The tumors have been largely of mesenchymal origin, the retroperitoneal fibrosarcoma being the most common. However, a wide variety of cancers has been reported in association with hypoglycemia and significant in frequency have been hepatic and adrenal cortical carcinomas.

Several hypotheses have been advanced to explain the hypoglycemia. The large size of the tumors has provoked speculation that excess glucose utilization by the tumor is the important factor. Although the rate of disappearance of glucose is rapid in these patients, measurements of tumor glycogen and glucose utilization by the tumor have not generally supported this view (22).

It seemed possible that the tumor produced hypoglycemia either by increasing pancreatic secretion of insulin or by inhibiting an hepatic insulinase. Both of these possibilities were rendered less likely by the failure of subtotal pancreatectomy to ameliorate the hypoglycemia in 2 cases (26). Similarly, in an experimental tumor system in the mouse, pancreatectomy did not reduce the hypoglycemia (44).

The results of bioassay and immunoassay of both tumor and plasma from these patients were recently reviewed (22). Using the deposition of glycogen or the uptake of glucose by rat diaphragm, insulin-like activity was found in extracts of 10 of 25 tumors studied but in only 1 of 11 plasmas. Adding the results of Samols' (39) recent studies to the results of the immunoassays previously reported, an immunologic cross reaction with insulin antibodies has been noted with the plasma of only 1 of 7 patients and with none of the tumor extracts (Table 2).

Since the bioassays are not specific for insulin (32, 34), a positive result may have little significance. The immunoassays seem conclusive, however, and make it highly likely that the hypoglycemic substance produced by these tumors is not insulin. This conclusion should be accepted cautiously, however, since Lacy and Williamson (20), using an immunofluorescence assay, could not demonstrate insulin in an islet-cell adenoma whereas it was found in the normal islet cell. This study raises the possibility that insulin in the tumor cell may exist in a state different from insulin in the normal $\beta$-cell.
TABLE 2
INSULIN-LIKE ACTIVITY IN BLOOD AND TUMOR EXTRACTS OF PATIENTS WITH HYPOGLYCEMIA-PRODUCING TUMORS

<table>
<thead>
<tr>
<th></th>
<th>Immunoassay</th>
<th>Bioassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>1/7</td>
<td>2/10</td>
</tr>
<tr>
<td>Tumor</td>
<td>0/6</td>
<td>10/25</td>
</tr>
</tbody>
</table>

* No. of patients positive/no. of patients assayed.

The clinical differentiation of the islet-cell adenoma from the hypoglycemias-producing sarcoma may be difficult. The prolonged hypoglycemia response produced by tolbutamide in the patient with islet-cell adenoma is a reasonable diagnostic tool although the patient with the nonpancreatic neoplasm has developed similarly prolonged hypoglycemia—on rare occasions. The plasma immunoassay for insulin seems to separate the 2 groups since it has been invariably elevated in patients with insulinomas (37). In this diagnostic setting, however, there is still room for clinical acumen, since the almost invariably large size of the extrapancreatic neoplasm will in general betray it to the careful observer. This is more than an academic exercise since these tumors often grow slowly and surgical resection can produce either long-term remissions or occasionally a cure.

ERYTHEMIA

Erythremia has been noted to occur with a variety of tumors. Since the kidney is the important source of erythropoietin, erythremia associated with carcinoma of the kidney is analogous to hypoglycemia associated with islet-cell adenoma and as such will not be considered here. Polycythemia has been seen with tumors of the adrenal cortex producing either virilization or Cushing’s syndrome. It is probable that in the 1st case this is due to testosterone-induced stimulation of erythropoiesis. In the 2nd case, the polycythemia is mild and there may not be an actual increase in red cell mass. Both uterine fibroids (46) and hepatic carcinoma (25) have been found in association with erythremia, but the genesis of the erythremia is unknown. McArthur (24) has tabulated the findings in 12 reported instances of the association of erythremia with uterine fibroids. In only 1 hepatoma (21) was the tumor assayed for erythropoietin activity and found to be negative. Waldmann et al., however, have demonstrated increased erythropoietin-like activity in the tumor tissue from subjects with cerebellar hemangioblastoma (51) and pheochromocytoma (50) associated with erythremia. In each case, both the tumor tissue and the plasma showed this activity. Waldmann et al. (51) summarized the evidence that the erythropoiesis-stimulating material may be erythropoietin.

It is curious that hypernephroma, cerebellar hemangioblastoma, and pheochromocytoma, the tumors that have been associated with polycythemia and the production of an erythropoiesis-stimulating substance, may also be associated in the patient with the von Hippel-Lindau syndrome. Although kidney tubules arise from a different germ-cell layer than the adrenal medulla and cerebellum, these associations suggest an early fundamental relationship among these 3 tissues.

MULTIPLE HORMONAL SYNDROMES ASSOCIATED WITH A SINGLE TUMOR

Awareness of these syndromes has led to the finding that some tumors may produce several types of hormonal activities. Becker et al. (2) reported a case of a patient with a hepatoma and associated hypoglycemia, polycythemia, and hypercalcemia. Another hepatoma was accompanied by polycythemia and hypoglycemia (39). There have been 2 patients with oat-cell carcinoma who demonstrated both Cushing’s syndrome and the carcinoid syndrome (16, 33). None of these cases has had adequate characterization of the hormonal substances produced by the tumor.

It is also noteworthy that tumors of endocrine glands may continue to secrete their own characteristic hormonal substances and simultaneously develop the capacity to produce an unrelated hormonal substance. Thus when choriocarcinoma has been associated with hyperthyroidism, the production of gonadotropin by the tumor has been at its characteristic high level. Functioning islet-cell adenomas have been accompanied by Cushing’s syndrome and by the carcinoid syndrome. A masculinizing tumor of the ovary produced hypercalcemia without bone involvement. Functional adrenocortical carcinomas have been noted to produce hypoglycemia on several occasions. These examples suggest that functionally well-differentiated tumors can acquire the ability to produce other hormonal substances.

For the cancer biologist, the development of new characteristics by the neoplastic cell must open new avenues of exploration. Since all cells have the same information coded on the same complement of DNA, it is pertinent to ask how all cells are prevented from synthesizing all of the same products. The development of the concept of the repressor may answer this question in part. If this is a sufficient answer, then neoplasia may occasionally modify repressor activity and thereby unmask new coding instructions on the DNA molecule. Thus these syndromes should lead us from intriguing clinicopathologic correlations to events occurring at the molecular level.

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