Growth Hormone and Adrenocortical Hormones in Relation to Experimental Tumors: A Review

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There is a vast literature on the influence of sex hormones and gonadotrophins on the incidence and growth of tumors, particularly those of the gonads and accessory sex organs. Less attention has been paid to the possible influence on tumors of other hormones, although aspects of the field now surveyed have been reviewed elsewhere (74, 76, 115, 150).

There is some justification for considering adrenocorticotrophin (ACTH) and adrenocortical hormones conjointly with growth hormone (GH, sometimes unnecessarily called somatotrophin or STH). This will be evident from the following survey of metabolic actions of these hormones in animals without tumors. For a fuller treatment of metabolic aspects and of the chemical nature of the hormones, reference may be made to other reviews (e.g., 45, 80, 112, 118, 114, 117, 146, 180).

With regard to chemical aspects, GH as isolated from bovine pituitary glands is a protein with a molecular weight of about 47,000. Until recently ACTH was considered to be a protein with a molecular weight of about 20,000. It now appears that a peptide constituent present in ACTH protein preparations is responsible for its activity in the Sayers test (lowering of adrenal ascorbic acid) and for some, if not all, of the other activities attributed to ACTH preparations. Until pituitary hormones can be isolated from blood, there must remain some uncertainty (cf. 102) as to the nature of GH and ACTH as actually secreted by the pituitary.

This question is now approaching solution in the case of the adrenal cortex. The adrenal secretes predominantly hydrocortisone (synonymous with 17-hydroxycorticosterone—F) or, in the rat, corticosterone (B), together with a steroid highly active in electrolyte metabolism. Metabolic studies have, however, usually employed cortisone (11-dehydro-17-hydroxycorticosterone), desoxycorticosterone, or adrenocortical extract, respectively abbreviated in the following Tables by E, DOC, and ACE (usually without distinction between acetates and free alcohols).

**Influences on Normal Metabolism**

**Growth and general metabolism.**—Following hypophysectomy body growth is arrested, either immediately (adult rats) or eventually (young rats). This arrest, although partly attributable to loss of appetite (79), can be prevented or reversed by administration of GH, even if food intake is restricted (121), without detectable stimulation of the atrophied thyroid or adrenal glands.

Although the growth-promoting action of GH can be annulled by ACTH (112) and can be obtained even in the absence of the adrenal glands (158, 164), the data do not rigorously establish that optimal growth can be induced in their absence. It has been suggested by Long and by Young (179) that a limited catabolism of protein occurring under the influence of adrenal hormones, as of thyroid hormone, might actually assist growth. The California school has shown that the promoting action of GH on nitrogen and potassium retention (and, transiently, on sodium and chloride retention) is unimpaired by adrenalectomy in rats maintained on cortical extract (164); but quantitatively satisfactory data are lacking for adrenalectomized rats maintained on salt or on...
graded doses of cortical hormone. It is, of course, well established that desoxycorticosterone alone can promote growth in adrenalectomized rats, and it has been stated, without statistical support, that young (not adult) adrenalectomized rats grew better when given low doses of cortical extract or cortisone than when maintained on salt (79, 85).

It is well established that the weight increase resulting from GH treatment represents true growth, associated with an increase in body protein and, if food intake is restricted, with a decrease in body fat (65, 118, 179). Conversely, the weight decrease resulting from ACTH treatment is associated with a decrease in body protein (112). But underlying such changes in body weight there may be disproportionate changes in the weights of certain organs, as illustrated by the data of Table 1. Clearly, however, few generalizations can be made. Differences among laboratories in the results obtained could depend on a number of experimental factors, possibly including variable contamination of GH or ACTH preparations with thyrotrophin or even with a distinct "renotrophic" factor (cf. 157).

In the case of the thymus, GH may have a stimulatory action in contrast with ACTH or cortical hormones, although effects on the thymus do not necessarily parallel effects on lymph nodes (42, 131). Either GH or ACTH may increase relative liver weight in intact rats fed ad libitum, the percentage of protein in the liver being unchanged (112, 118; but cf. 179); since no such increase was found in hypophysectomized rats, Li and Evans (118) suggested that endogenous thyrotrophin may mediate the effect. It may be noted that hypophysectomy results in a relative decrease in the size of the liver, as of the spleen and possibly the thymus, usually without disproportionately decreasing heart or kidney size (4, 42, 57; but cf. 46). With regard to the apparent discrepancies between the two short-term experiments in Selye's laboratory (151, 155; Table 1), it should be pointed out that data for the former series (151) suggest that the augmenting action of one GH preparation on liver and spleen was not replicated by a differ-

### TABLE 1

<table>
<thead>
<tr>
<th>TEST ANIMAL</th>
<th>EFFECT OF ADRENOCORTICAL HORMONES</th>
<th>EFFECT OF ACTH</th>
<th>EFFECT OF GH</th>
<th>REMARKS</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, intact (or hx.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male, young, intact (or hx.)</td>
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<td></td>
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<tr>
<td>Female, intact (or hx.)</td>
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<td></td>
</tr>
<tr>
<td>Female, young, intact (or hx.)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female, young, intact or unilaterally nephrectomized and given NaCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mice:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, castrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, both sexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Rats:       |                                   |               |              |          |            |
| Female      |                                   |               |              |          |            |
| Female      |                                   |               |              |          |            |

| Mice: |                                   |               |              |          |            |
| Both sexes; A, CSH, and C57BL strains |                                 |               |              |          |            |

Changes (as compared with equivalent untreated animals) in organ weight, relative to body weight, are denoted + (relative increase), - (relative decrease), or 0 (proportion unchanged); C.F. denotes controlled food intake (i.e., effect not due to changes in intake); Hx. denotes hypophysectomized.
ent GH preparation. In the latter series (155) with intact rats, the GH doses were very high; the effects of GH and cortisone given together were not additive, in partial support of Selye’s conclusion that cortisone antagonized the effects of GH.

Among the tissues adversely affected by adrenocorticoids are hair (9) and skin (27), which may show “regressive changes in all of the epithelial constituents.” In the case of mammary tissue, effects of adrenocorticoids or of GH appear to be functional rather than morphologic (cf. 49, 180).

Treatment of rats with GH may produce selective morphologic effects more subtle than those so far considered. Comparison of different muscles has shown that some, notably the diaphragm, may increase disproportionately (66), and comparison of the distal and proximal epiphyses of the tibia has revealed that only the latter is stimulated (5).

In view of a report (89) that GH preparations in high dosage may augment the adrenal size of hypophysectomized rats without depleting ascorbic acid, it is of interest that administration of a “labeled” GH preparation to rats led to the appearance of radioactivity in the adrenals, as well as in bone and pancreas. It may be recalled that Selye has postulated a “mineralocorticotropic” action of GH (151; cf. 164).

It is controversial whether regulation of the adrenals depends on only a single “adrenocorticotropic hormone.” In hypophysectomized rats, the adrenals can be maintained or restored by ACTH preparations which have little effect on ascorbic acid level (89, 142). Studies on eosinopenia (78) and diabetes (138, 139) likewise cast doubt on the assumption that ACTH is a unique substance. To confuse the issue further, there are reports that adrenalectomized animals treated with ACTH preparations (and usually with a “priming” dose of cortisone or cortical extract) give metabolic responses, viz., involution of the thymus (153), improved performance in Ingle’s “work test” (81), fat mobilization (6, 111), and reduced dermal spreading (26). It is, of course, difficult to ensure the absence of adrenal rests from “adrenalectomized” animals; moreover, the gonads may sometimes play a pseudo-adrenal role, as observed in a study of inhibition of wound healing by ACTH (31).

| Table 2 |

<table>
<thead>
<tr>
<th>Action or property</th>
<th>Mouse</th>
<th>Rat (adult)</th>
<th>Cat (adult)</th>
<th>Dog (adult)</th>
<th>Human</th>
<th>Other species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression of body wt. or N balance by ACTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise in body wt. or N balance by GH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetogenic action of ACTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetogenic action of GH given with ACTH (or corticoids)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketogenic or fat-mobilising action of GH preparations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


There is some evidence that GH can selectively stimulate the islet tissue of the pancreas. Certainly the growth-promoting action of GH is supported by insulin; but consideration of the role of insulin and possibly of “glucagon” (hyperglycemic factor) in synergizing, if not mediating, the growth-promoting action of GH is beyond the scope of this review (cf. 123, 179, 180).

It must be pointed out, in qualification of the above remarks on the growth-promoting action of GH in the rat, that there are important species differences in response to GH (Table 2). The eventual response to GH in the adult cat or dog is not growth, but diabetes—apparently reflecting failure of the pancreas to maintain an increased level of insulin secretion (180).

As further shown in Table 2, effects of GH are usually not readily demonstrable in the mouse or the human, and effects of ACTH also vary from...
one species to another, although it is of interest that a synergistic effect of ACTH on the diabetogenic action of GH has been shown in the force-fed rat (Engel, see 45) as well as in the cat (138).

Tissue metabolism and composition.—Exposure of tissues to insulin in vitro may result in stimulation of processes such as carbohydrate dissimilation in rat diaphragm (102) and lipogenesis in liver (70) or in rat mammary tissue (49), and in inhibition of amino acid oxidation (87). With pituitary and adrenocortical hormones there have been few satisfactory demonstrations of specific metabolic actions in vitro. Adrenocortical extract or glucocorticoids added in vitro have been reported to induce involution of lymphoid tissue (48), to inhibit lipogenesis by mammary tissue (18, 49), and to increase amino acid oxidation in rat liver (87) and aerobic glycolysis (but not glucose uptake) in rat tissues other than tissues normally having high aerobic glycolysis (122). In general, however, the effect of adrenocorticoids on carbohydrate dissimilation is inhibitory, as found in vitro with rat liver (30), rat diaphragm (69), and mouse diaphragm or lymphocytes (7). Here it may be pointed out that such in vitro experiments, as well as in vivo experiments, have given widely varying results for the relative efficacy of different 11-oxo-corticosteroids (Table 3). The type of phenomenon studied and the species may be determining factors, although it should be emphasized that in vitro experiments, particularly with the difficulty soluble corticosteroids, require careful scrutiny with respect to technics and interpretation.

In the case of GH, in vitro experiments have shown a depressing effect on the respiratory quotient of diaphragm (137), an effect on glucose uptake similar to that of insulin (102, 183) or converse to that of insulin (133; cf. 112), a conserving effect on preformed glycogen (147), and a stimulating effect on ketogenesis by liver tissue (170; cf. 70). In some of these experiments (137, 170), as in those showing an enhanced mobilization of fat to the liver by GH in vivo (111), there have been indications that the effectiveness of the GH preparation may vary from one batch to another.

Broadly speaking, then, the study of GH and

| TABLE 3 |

<table>
<thead>
<tr>
<th>Species</th>
<th>Action or effect</th>
<th>B compared to E</th>
<th>F compared to E</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Weight loss, N loss, glycosuria, atrophy of adrenal cortex and thymus, kidney lesions, etc.</td>
<td>Approx. twice</td>
<td></td>
<td>ACE most effective</td>
<td>88</td>
</tr>
<tr>
<td>Rat</td>
<td>&quot;Work test&quot; activity</td>
<td>At least 0.3</td>
<td>Approx. equal</td>
<td>B compared to E</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Fall in Na : K excreted</td>
<td>2.5</td>
<td>1.5</td>
<td>DOC/E = 17</td>
<td>41</td>
</tr>
<tr>
<td>Rat</td>
<td>Rise in liver glycogen</td>
<td>0.5</td>
<td>1.5</td>
<td>DOC/E = 70.3</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Revolving drum stress test</td>
<td>2.9</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>Rise in blood NPN</td>
<td>4.4</td>
<td>1.0</td>
<td>DOC/E = 10</td>
<td></td>
</tr>
<tr>
<td>Rabbit</td>
<td>Inhibitory effect on size of lymph nodes</td>
<td></td>
<td></td>
<td>ACTH qualitatively similar</td>
<td>93</td>
</tr>
<tr>
<td>Rabbit</td>
<td>Inhibitory effect on size of RNA content</td>
<td></td>
<td></td>
<td>similar, GH blocked B (but not E, F) effect</td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>Involvement of lymphatic tissue</td>
<td>0.8</td>
<td>3.5</td>
<td>DOC had converse effect</td>
<td>43</td>
</tr>
<tr>
<td>Mouse</td>
<td>Inhibition of phlogistic (inflammatory) response</td>
<td>0.03</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Inhibitory effect on granulation tissue</td>
<td></td>
<td></td>
<td>ACTH effect feeble; DOC may be converse</td>
<td>109</td>
</tr>
<tr>
<td>Chick, embryo</td>
<td>Inhibition of growth and development</td>
<td>30</td>
<td>100</td>
<td>Comparison of acetates of E and F</td>
<td>92</td>
</tr>
<tr>
<td>Chick, new-born</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>Lowering of resistance to influenza virus; type 2</td>
<td>Similar</td>
<td>Similar</td>
<td>ACTH inactive. GH acted like, and did not block, E</td>
<td>94</td>
</tr>
<tr>
<td>Rat</td>
<td>Inhibition of lipogenesis in vitro by mammary gland slices</td>
<td>Active</td>
<td>Similar</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Sheep</td>
<td></td>
<td></td>
<td>Inactive</td>
<td>DOC similar to E</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td></td>
<td></td>
<td>Active</td>
<td>DOC active; E inactive</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>Rise in aerobic glycolysis of tissues in vitro</td>
<td>Active</td>
<td>Inactive</td>
<td>E inactive; ACE most active; NaCl active</td>
<td>122</td>
</tr>
<tr>
<td>Rat</td>
<td>Fall in glucose dissimilation by diaphragm in vitro</td>
<td>Low</td>
<td>Low</td>
<td>At least 0.3?</td>
<td>69</td>
</tr>
</tbody>
</table>

Comparison of acetates of B and F

ACTH inactive. GH acted like, and did not block, E

Comparison of acetates of B and F

ACTH inactive. GH blocked B (but not E, F) effect

ACE most effective

DOC and E = 17

DOC/E = 70.3

DOC/E = 10

ACTH qualitatively similar, GH blocked B (but not E, F) effect

DOC had converse effect

ACTH effect feeble; DOC may be converse

Comparison of acetates of B and F

Reference:

83

84

41

10

43

54

169

122

92

94

12

122

69

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adrenocorti-accept to those of insulin. Before considering some in vitro effects of these hormones, attention may be drawn to some interesting preliminary results obtained with cultures of chick heart fibroblasts exposed to these hormones (109). In the presence of cortisone, itself almost inactive, GH markedly enhanced cell proliferation. Insulin alone acted similarly and also increased the amount of ribonucleic acid per cell. With GH alone there was some inhibition of mitosis. In general, there is no evidence that GH can stimulate mitosis in isolated tissues. Indeed, epidermal mitosis in mouse ear tissue can be inhibited by GH (as by cortisone); this effect of GH, and the converse effect obtained with insulin are considered to depend on changes in glucokinase activity (20, 21).

Our knowledge of the actions of pituitary and adrenocortical hormones still rests mainly on observations made after administration (or deprivation) of the hormones in vivo. In some circumstances adrenocortical hormones may reduce carbohydrate dissimilation, as in recent studies on hematopoiesis in Gordon's laboratory (69); in the bone marrow of adrenalectomized rats, the elevated glycolysis rates (both aerobic and anaerobic) could be lowered by administration of adrenocorticoids such as hydrocortisone, with no effect on respiration. Data emanating largely from Cori's laboratory (108) have established that GH may have an immediate insulin-like effect on carbohydrate dissimilation, e.g., on glucose uptake by isolated diaphragm, but that the eventual effect of GH—or perhaps of a product formed by some transformation in vivo—is anti-insulin in nature (inhibition of hexokinase?). This anti-insulin action of GH is not demonstrable in the absence of the adrenal glands, unless the animals are simultaneously treated with cortical extract or cortisone in a dose which itself has no influence on the glucose uptake of diaphragm (102). This role of adrenocortical hormones is analogous to their role in the diabetogenic action of GH (Table 2, rat or cat). Here it may be noted that the glycogen-maintaining (myoglycosastic) action of GH, on skeletal muscle in situ, requires the presence of some adrenocortical hormone in the case of rats fed carbohydrate, although not in the case of fasted rats (147).

An enhanced mobilization and catabolism of depot fat, reflected in ketosis and depression of R.Q., can be produced by glucocorticoids, or, at least with some preparations, by GH or ACTH, or conceivably by an unidentified factor present in these preparations (6, 65, 70, 111, 112, 170). Here again it appears that the effect of the pituitary preparations sometimes requires the support of adrenocortical hormones (8, 111, 170). Under some circumstances, however, ACTH or corticoids may have the converse effect on fat metabolism (45).

In the case of the protein-anabolic action of GH, there is evidence for a supporting role of insulin (128, 180) but not of adrenocortical hormones, with the possible exception of the above-mentioned effect on fibroblast cultures (109). It is generally accepted that the gluco-(11-oxy)-corticoids have a catabolic influence on tissue protein, as reflected in their glycogen-increasing action on liver (117). This catabolic influence may depend in part on a specific stimulation of the breakdown of proteins to amino acids, although intracellular peptide levels were found in Engel's laboratory to be unchanged after treatment with ACTH (45). In accord with the possibility that amino acid catabolism may also be enhanced, adrenalectomy impairs amino acid oxidation (n-amino acid oxidase?) by liver, essentially as previously found by Russell and Wilhelmi with respect to oxidation of D-alanine and L-glutamic acid by kidney (87). But Umbreit (178) has reported an inhibiting effect of adrenalectomy, reversed by cortisone, on the D-amino acid oxidase of liver but not of kidney, and on the proline oxidase of kidney but not of liver. It is at least open to doubt whether such changes in amino acid oxidase activity, or analogous changes in the arginase activity of kidney and liver (51, 64, 97), are specifically correlated with the protein-catabolic action of the glucocorticoids.

Among other liver enzymes which appear to be deficient in the absence of the adrenals are alkaline phosphatase (97) and catalase (mice [2], rats [16]). With GH there was no marked effect on alkaline or acid phosphatase (liver or kidney) or on arginase (liver) in mice (99); but in hypophysectomized rats GH did further decrease the low level of liver arginase (51). Extensive and careful studies (e.g. 13, 54) by Gaebler and associates in hypophysectomized rats have shown that GH can elevate the alkaline phosphatases of kidney and liver (levels lowered and raised, respectively, by hypophysectomy) and also liver catalase. Other enzymes included in these studies were cathepsins in liver, kidney, and spleen (reduced by hypophysectomy, slightly enhanced by GH), aspartic-glutamic transaminase in liver (lowered by hypophysectomy, markedly enhanced by GH), and aspartic-glutamic transaminase in muscle—which showed converse changes, consistent with the hypothesis that the effect of GH, on a restricted food intake, was to stimulate protein synthesis in muscle at the expense of liver protein. Enzymes which were little affected by GH included suc-
cinoxidase, d-amino acid oxidase (see also 87), glutamic acid dehydrogenase, and dehydropeptidase I.

Short-term experiments with intact, fasting rats have indicated that GH can decrease liver arginase and alanine-glutamic (but not aspartic-glutamic) transaminase in adult animals, although in young animals GH had no effect or even the converse effect (15). Another enzyme which is decreased in intact rats by GH treatment (chronic) is "myofibrillar ATP-ase" (77).

In view of the possible relationships of nucleic acids to protein synthesis and to neoplasia, hormonal influences on nucleic acids deserve consideration in some detail. The terms RNA and DNA will be used for ribo (pentose) nucleic acid and for the deoxy analog, respectively. Much of the work is based on isotope incorporation studies rather than on classical analyses, and here the opinion may be expressed (cf. 146) that the former may, especially if unaccompanied by the latter, give misleading results unless carefully performed and interpreted. A particular pitfall in the assessment of P uptake is the possible presence of traces of rapidly metabolized P, presumably derived from phosphoprotein (58), in DNA or RNA fractions as studied by many authors (e.g., 59). Moreover, in many studies (e.g., 58), the interpretation of values for relative specific activity may be complicated by the possible metabolic inconstancy of the tissue P-containing constituent chosen as "denominator." There are, of course, sources of error in classical analyses also; thus, the Schmidt-Thannhauser "RNA" fraction may contain a considerable amount of P not derived from RNA, and the Schneider procedure may give an incomplete recovery of nucleic acid P (cf. 58). A further point, neglected by many authors, is that the amount of liver RNA and its rate of formation may be influenced, not necessarily in parallel (cf. 32, 131), by dietary changes.

In the rat, adrenalectomy has been variously reported to lower liver RNA but elevate DNA (44; high-protein diet), to slightly raise both RNA and DNA (24), and to decrease RNA with no change in DNA (25; restricted food intake). Liver regeneration was, in one study (25), unaffected by adrenalectomy although the DNA and RNA content of the regenerating liver was increased; in another study (44) regeneration was actually enhanced by adrenalectomy although, conversely to the change in nonadrenalectomized rats, the process of regeneration was associated with a rise in RNA and fall in DNA.

In the initial stage of liver regeneration in mice, cortisone in high dosage impaired mitosis (with no reduction in intestinal mitosis) and resynthesis of DNA, although not of RNA (149). In intact rats, cortisone in enormous dosage somewhat decreased liver DNA and RNA and markedly altered the distribution of cytoplasmic RNA, depleting the mitochondrial and microsomal RNA (119). The effect in rabbits as previously studied in the same laboratory was a depletion of RNA and especially of DNA in liver (not kidney), with an increase in cell size. But in another investigation of tissue nucleic acids in cortisone-treated rabbits, changes were found in RNA (decreased in liver) rather than in DNA (68). A decrease in RNA but not in DNA was likewise found in the lymph nodes of rabbits treated with cortisone or ACTH (93; cf. Table 3). In a study of nucleic acid turnover rate, in rat liver and thymus, a slight increase was produced by adrenocortical extract (60).

Administration of ACTH to rats raised the level, but not the rate of formation, of RNA (not DNA) in liver, spleen, kidney, and intestine (52). Other reports on ACTH-treated rats indicate enhanced P incorporation into liver RNA (140; hypophysectomized rats), but a decreased level of RNA in liver cytoplasm (8).

Hypophysectomized rats, even with a constant food intake, show a decrease in liver RNA but not DNA (24, 25), this decrease exceeding that of liver protein (24). A paper from Li's laboratory (57) on liver nucleic acid concentrations in hypophysectomized rats (fasted for 24 hours before sacrifice!) also reports a fall in RNA and possibly a rise in DNA, although in view of the reported fall in liver weight the total DNA may have decreased. Administration of GH was stated to prevent these effects, on the basis of analyses on dry defatted liver residues (yields unstated). However, in Tepperman's laboratory (163) the concentrations of DNA and RNA were, after hypophysectomy, respectively raised and unchanged (but raised by treatment with a GH preparation which, in the reviewer's experience, had poor growth-promoting activity).

These findings were confirmed in the same study (163) by microspectrophotometric measurements on parenchymal cells. The effect of hypophysectomy (reversed by GH) was to decrease the content per cell of RNA and of protein, these changes occurring in both nucleus and cytoplasm, each of which decreased in volume. Neither hypophysectomy nor the GH treatment induced depolymerization of DNA (judged by a staining method) or altered the amount of DNA per cell. Verification of this apparent constancy of DNA content would be desirable, in view of the occurrence of polyploidy in liver and also of a reported effect of...
hypophysectomy, reversed by GH, in raising the DNA content of "B" cells of rat liver (17).

A decreased turnover rate of nucleic acids has been observed after hypophysectomy in rat liver and thymus (30), the opposite effect being obtained with GH in hypophysectomized rats (50) or in intact rats (33; liver). A similar effect of hypophysectomy on liver RNA was noted in another laboratory (141), and some reversal of the effect was obtained with ACTH but not with GH, although GH did prevent the increased turnover of plasma inorganic P which normally follows hypophysectomy.

In these studies on P incorporation, the effects of hypophysectomy (50, 141) and of GH (50) on nucleic acids were paralleled by effects on phospholipids, the influence of GH on the latter being demonstrable even in intact rats (33, 58); but the actual concentration of liver phospholipid may not change in parallel with the turnover rate (58). Although the incorporation of P into liver phospholipid is stated to be unaffected by adrenalectomy (165), an increased incorporation has been observed in intact rats given cortical extract (50) and also, according to one report (58), not confirmed elsewhere (140), in hypophysectomized rats given ACTH.

Other hormonal effects could be mentioned as possibly relevant to the metabolic changes underlying neoplasia. Thus, ACTH can decrease non-protein sulfhydryl groups in liver and muscle (59) and can augment the tryptophan peroxidase-oxidase system (liver), the increase in which induced by tryptophan administration is known to be prevented by hypophysectomy, though not by adrenalectomy (56). In rats given radioactive calcium, the tissue/plasma ratios in muscle and large intestine were respectively decreased and raised after adrenalectomy; cortisol or desoxycorticosterone raised the ratio in both tissues in male rats, but cortisol lowered the ratio for muscle in female rats (176). These effects were obtained with high doses or prolonged treatment, and no changes in the ratio were observed in the case of liver. Effects on bone calcium will not be discussed here (cf. 112).

Space does not allow further consideration of hormonal effects on "normal" metabolism, but consideration of neoplasia may be usefully prefaced by an outline of effects on certain other pathological phenomena. The wide field of "stress" and "diseases of stress" cannot, however, be considered here, although it may be mentioned that treatment with cortisone may prevent the induction by GH or by desoxycorticosterone of pathological states such as "nephrosclerosis" (151). It may also be pointed out, with reference to the concept of "hypercorticalism," that there is much evidence to favor Ingle's view that "the adrenal hormones play a 'permissive' rather than causative role in certain diseases and in certain metabolic responses to stress" (80, cf. 45).

Influences on Certain Pathological Phenomena

Infections.—The effect of cortisone or ACTH on virus growth is usually adverse to the host, although factors such as dosage and virus strain may determine the effect obtained (cf. 88, 145). Cortisone can enhance the proliferation of influenza B virus in eggs or tissue culture (95). In influenza-infected mice, there are reports of a similar effect of cortisone (not counteracted by GH—see Table 3; 94), of little effect with ACTH (118), or even of the converse effect of cortisone or ACTH (88), an aggravation being produced by GH (89). Yet pre-treatment of mice with GH may abolish cortisone-induced sensitivity to Coxsackie virus (134).

With bacterial infections, particularly in species other than the rat or mouse, an aggravation usually results from administration of cortisone in doses likely to induce adrenal atrophy (145, 171). This effect is not always obtainable with ACTH (see Table 3; 94); moreover, the survival of infected adrenalectomized mice may actually be enhanced by low doses of cortisone (145). The aggravating action of cortisone has been considered to depend on a diminution not only in response to bacterial toxins, but also in inflammatory response (see below), in antibody formation—reflected in changes in lymph node RNA concentration (Table 3; 93), and in phagocytosis especially by the reticulo-endothelial system (23, 43, 145, 171). The effect of GH may be similar to that of cortisone, as in pneumococcus-infected mice (94), or converse, as in rats harboring microbes which are normally nonpathogenic (152). It has been stated (54), with inadequate supporting data, that GH has a "synergistic action" with cortisone in diminishing allergic sensitivity, as judged by the response to intradermal tuberculin in guinea pigs injected with B.C.G.

Inflammation and related phenomena.—In a literature too extensive to cover adequately here, reports by Taubenhaus and collaborators (169) are of particular interest. Hypophysectomy, adrenalectomy, or administration of cortisone (even locally) reduced the formation of granulation tissue around turpentine abscesses in rats. Administration of a GH preparation (which the reviewer found to have poor growth-promoting activity) enhanced fibroblastic proliferation, except in intact rats given high doses; a similar enhancement
could be obtained with thyroxin or desoxycorticosterone. In adrenalectomized animals, GH was without effect. The enhancing effect of GH recalls the one hand its local action, mentioned by Selye (151), in stimulating fibroblastic granuloma formation, and on the other hand its action, in conjunction with cortisone, in stimulating the growth of fibroblast cultures (109).

In general the effect of adrenocortical hormones on granulation tissue and wound healing is inhibitory, at least with high doses and in species other than the guinea pig; but the mechanism of the effect is evidently complex (28, 48, 148, 145, 162). Cortisone may directly inhibit fibroblasts (although in some circumstances desoxycorticosterone may be stimulatory rather than inhibitory —cf. 109) or influence the resistance of the ground substance (97). Other reported effects of cortisone include inhibition of chondroitin sulfate synthesis (108) and reduction in the tissue content of mast cells (89) and also of plasma cells, the content of which can be raised by GH (88).

With GH in rather low dosage, either alone or jointly with cortisone, there was no effect on wound healing in mice (162); nor did GH, given to rats, have any marked effect on dermal spreading (96). In the latter study, as in a study of wound healing in mice (31), ACTH had a marked inhibitory action even in adrenalectomized animals. Hormonal effects on liver regeneration have been mentioned above in connection with nucleic acids, and will not be further discussed here.

**"Endogenous" carcinogenesis.**—Before considering hormonal influences on carcinogen-induced or transplanted tumors, consideration must be given to the possibility that the hormones under discussion may be carcinogenic, or may at least govern the appearance of "spontaneous" tumors. There are reports that the development of mammary tumors in mice may be suppressed by adrenalectomy (156) although not by hypophysectomy (55), and that adrenalectomy may have the converse effect (and adrenocortical extract an inhibiting effect) on the development of lymphoid tumors in C58 mice (106, 107).

There is little direct evidence for a definite carcinogenic action of the hormones under consideration, with the possible exception of desoxycorticosterone (124). Woolley (178) has shown that adrenocortical carcinomas (or nodular hyperplasia) secreting sex hormones, and secondary tumors in sites such as the pituitary and mammary glands, may develop in mice gonadectomized at birth (provided that the pituitary is intact; see [46]); but there is no direct evidence to attribute these effects to hypersecretion of ACTH. No success was obtained in attempts to convert the nodular hyperplasia to carcinoma by a 4-month treatment with pituitary hormones, viz., ACTH, GH, or gonadotrophins. With one dubious exception (47), there is no report of a carcinogenic action of administered ACTH. Were it possible to achieve hepatic inactivation of adrenocorticoids by the use of intrasplenic adrenal transplants, some light might be thrown on this question. A long-term study of intact animals in parabiosis with adrenalectomized partners would be of much interest, particularly in view of a recent report (72) that intact rats in parabiosis eventually develop, in one or both partners, a high incidence of lymphoid and other tumors.

Widespread interest has been aroused by the reports by Moon and collaborators, from the University of California (100, 126, 127, 128), of the appearance of tumors in intact female rats treated with GH for a year or longer. This effect was not demonstrable in mice (180)—possibly because of inadequate dose or shorter life span—or in rats (strain difference?) treated for a shorter period in Selye's laboratory (154). The tumors, which were not successfully transplanted, included lymphosarcomas of the lung (the extra-thoracic lymph nodes being normal), tumors in the adrenal medulla, ovary, and mammary glands (but not the uterus), and anterior-pituitary adenomatous tumors. There was little evidence of metastases, and no histological studies are reported on other organs of potential interest, such as the pancreas and liver.

As Lipschütz (115) points out, the GH-treated rats in the above experiments, conducted with no restriction of food intake, developed extreme gigantism. Clearly there is a possibility, supported by the fact that certain of the neoplasms occurred also in some of the control animals, that the effect of GH was nonspecifically to accelerate the onset of "spontaneous" tumors. It would be of particular interest to know if GH-treated rats have a higher tumor incidence than older untreated rats of comparable weight (necessarily male rats). Although "there was no correlation between specific pituitary lesions and the neoplasms of any given type occurring in the other organs" (100), the absence of neoplasms (except possibly in the ovaries) in GH-treated hypophysectomized rats—admittedly in poor condition at the end of the experiment—suggested that a necessary factor is an "altered physiology of the anterior pituitary" (129). There is, however, no evidence for Li's suggestion (112) that treatment with GH can induce the pituitary to secrete a "tumor-producing hor-
mone” — a suggestion reminiscent of earlier claims, (e.g., 175) that the pituitary contains lipid-soluble carci

Effects on the action of carcinogens. — D. L. Smith and collaborators (160) investigated the effect on carcinogenesis (by methylcholanthrene) of the deprivation or administration of various hor-

mones, the timing of hormone treatment being

unstated (Table 4). Although the study was very thorough, the results were essentially negative, possibly because (as the authors remark) the dose of the carcinogen was so high as to induce tumors in 100 per cent of the control rats.

Experiments by Moon and collaborators (125) and by other authors (Table 4) have shown that the action of some carcinogens can be retarded by hypophysectomy, the retardation being reversed if anterior-pituitary extract is administered. No conclusive results could be obtained with 2-acetylaminofluorene because of its high toxicity in hys-

gophysectomized rats, and in the case of other carci-

genins (Table 4) it is possible that differences in their dosage could account for the varying effect-

iveness of hypophysectomy. With benzpyrene, the latent period for carcinogenesis in rats was unaffected by hypophysectomy (181).

With 3'-methyl-4-dimethylaminoazobenzene, as studied in Griffin’s laboratory (67), the hypophy-

sectomized rats admitted ate less food than the controls; but evidence has been adduced (144) that this could not account for the striking retardation. Preliminary attempts at replacement therapy in a few animals have suggested that ACTH (144), GH, and gonadotrophin(s) may each have a supporting role in carcinogenesis.

There is no clear-cut evidence for an inhibitory effect of adrenalectomy. With azo-dye feeding, salt-maintained adrenalectomized rats survived poorly; some developed tumors but had “nODULES OF REID—Hormones and Experimental Tumors: A Review 257

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### Table 4 - Some Hormonal Effects on Induction or Growth of Experimental Tumors

<table>
<thead>
<tr>
<th>Test animal</th>
<th>Tumor</th>
<th>Hypophysectomy (hx.) effect</th>
<th>Adrenalectomy (adx.) effect</th>
<th>Adrenocorticoid effect</th>
<th>ACTH effect</th>
<th>GH effect</th>
<th>Remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats, Denver males</td>
<td>Sarcoma (methylicholanthrene)</td>
<td>None</td>
<td>None (maintenance on ACE!)</td>
<td>Feebly inhib. (ACE, not DOC)</td>
<td>None (dubious GH?)</td>
<td></td>
<td></td>
<td>160</td>
</tr>
<tr>
<td>Rats, Long-Evans males</td>
<td>Sarcoma (methylicholanthrene or 9,10-dimethyl-1,2-dibenzanthracene)</td>
<td>Inhib.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>185, and personal commun.</td>
</tr>
<tr>
<td>Rats, albino</td>
<td>Dibenanthracene, subcut.</td>
<td>Inhib. (hx. after treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Rats, males</td>
<td>Liver. DAB*</td>
<td>Inhib. (feebly?)</td>
<td>Inhib. (DOC; less in adx. than in intact?)</td>
<td>Stim. (in hx., not intact)</td>
<td>Stim. (in hx. rats)</td>
<td>C.F. in study of hx. effect</td>
<td>67, 144 and personal commun.</td>
<td></td>
</tr>
<tr>
<td>Rats, e.g., Holtzman-Sprague-Dawley males</td>
<td>Liver. 9’-Methyl-DAB (Benspyrene or methylicholanthrene)</td>
<td>Inhib.</td>
<td>None (accessory adrenal tissue?)</td>
<td>None (E, in diet; hx. or intact)</td>
<td>Stim. (in hx., rats)</td>
<td></td>
<td></td>
<td>101</td>
</tr>
<tr>
<td>Mice, hybrids</td>
<td>Papillomas and carcinomas (5,4-benspyrene)</td>
<td>Feebly inhib.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mice, Carworth Farms, both sexes</td>
<td>Sarcoma (methylicholanthrene)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>Mice, C57BL, both sexes</td>
<td>Lymphoid (irradiation)</td>
<td>None (or feebly stim.)</td>
<td>Stim.</td>
<td>Inhib. (E or F, not ACE or DOC)</td>
<td></td>
<td></td>
<td></td>
<td>90, 91</td>
</tr>
<tr>
<td>Guinea pigs, castrated females</td>
<td>Fibroma (estrogen)</td>
<td>None</td>
<td>Inhib. (E, F, and esp. DOC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120, 174</td>
</tr>
<tr>
<td>Rabbits</td>
<td>Epithelioma (benspyrene)</td>
<td>Inhib.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats, Sprague-Dawley males</td>
<td>Walker 256 carcinoma</td>
<td>Inhib.</td>
<td>None (ACE, in hx. rats)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C.F. 11</td>
</tr>
<tr>
<td>&quot;(young)&quot;</td>
<td></td>
<td>Inhib.</td>
<td>Inhib. (E)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C.F. 82, 86</td>
</tr>
<tr>
<td>&quot;(300 gm.)&quot;</td>
<td></td>
<td>Inhib. (esp. if hx. also)</td>
<td>Inhib. (E or ACE, not in intact)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Rats, Sprague-Dawley (sex ?)</td>
<td>Fibrosarcoma (unspecified)</td>
<td>Inhib. (stim. relative to body growth)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C.F. E or ACE in low dosage 76, 108</td>
</tr>
<tr>
<td>Rats, &quot;pure strain&quot;</td>
<td>K7 adenocarcinoma</td>
<td></td>
<td></td>
<td>Inhib. (E)</td>
<td></td>
<td></td>
<td></td>
<td>116</td>
</tr>
<tr>
<td>Mice, both sexes</td>
<td>Sarcoma 97</td>
<td></td>
<td></td>
<td>Inhib. (ACE)</td>
<td></td>
<td></td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>Mice, Carworth albino females</td>
<td></td>
<td></td>
<td></td>
<td>Inhib. (ACE) or stim. (E or DOC)</td>
<td></td>
<td></td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Mice, A, both sexes</td>
<td>Mammary adenocarcinoma</td>
<td></td>
<td></td>
<td>E as a low single dose</td>
<td></td>
<td></td>
<td></td>
<td>149</td>
</tr>
<tr>
<td>Mice, C3H, both sexes</td>
<td>Mammary adenocarcinoma</td>
<td></td>
<td></td>
<td>None</td>
<td>GH dose low</td>
<td></td>
<td></td>
<td>161</td>
</tr>
<tr>
<td>Mice, hybrids</td>
<td>Mammary carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>101</td>
</tr>
<tr>
<td>Mice, BALB/c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>Rats</td>
<td>Leukemic</td>
<td>Stim.</td>
<td>Inhib. at certain doses (ACE, DOC)</td>
<td>None</td>
<td>Feebly inhib. (E); none if dose low</td>
<td>None</td>
<td>Asbestos-producing sarcoma not inhib.</td>
<td>132</td>
</tr>
<tr>
<td>Mice</td>
<td>(Ak-4)</td>
<td></td>
<td></td>
<td>Inhib. (some doses (ACE, DOC) batches)</td>
<td>None</td>
<td></td>
<td></td>
<td>159</td>
</tr>
<tr>
<td>Mice, young adult</td>
<td>Lymphosarcoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Mice</td>
<td>Lymphosarcomas or osteogenic sarcomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>166</td>
</tr>
<tr>
<td>Chicks</td>
<td>Lymphoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>105</td>
</tr>
<tr>
<td>Rabbits</td>
<td>Carcinoma (Brown-Pearce)</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&quot;Hx.&quot; by irradiation 104</td>
</tr>
</tbody>
</table>

* DAB = 4-dimethylaminostilbene.
* Effects denoted "stim." (stimulatory) or "inhib." (inhibitory).

C.F. denotes controlled food intake, i.e. elimination of possible influence of changes in intake.
For some early references to effect of hypophysectomy or crude hormonal preparations, see (70, 116, 160).
with adrenalectomized rather than intact animals. Androgens secreted by the adrenal are possibly of importance in this connection (cf. 76).

Meticulously performed experiments by Huggins and collaborators (76, 168) showed that the restraining influence of hypophysectomy on tumor growth (the percentage of “takes” being unaltered) cannot be attributed merely to adrenal atrophy. Thyroid atrophy could be the other factor responsible, but the deprivation of GH by hypophysectomy may also be important, as suggested by the few data for effects of GH on transplanted tumors (Table 4).

**Effects on tumor metabolism.**—There are few data bearing on the postulate (cf. 1, 110) that tumors have “escaped” from hormonal influences which regulate the function of normal tissue. A paper from Barron’s laboratory (96) states that the uptake of labeled carbon, in the form of glycine, phenylalanine, or acetate, was depressed by in vitro addition of cortisone of hydrocortisone to normal lymphatic cells, but not to lymphosarcoma tissue. This finding is of dubious significance, particularly since the normal cells were from rabbits or rats and the tumor cells from mice. A recent abstract (?) from the same laboratory reports similar findings for glycolytic activity. On the other hand, it has been reported (177) that an increase in anaerobic glycolysis can be effected in vitro by insulin with mouse melanoma but not with mouse brain. Carbohydrate utilization is considered to be the process adversely affected by cortisone in suppressing mitosis in normal skin (carcinogen-treated skin being unaffected) (20, 62).

A study with “internal controls,” in mice carrying a mammary adrenocarcinoma, has been reported in abstract form (14). The incorporation of glycine into several “normal” tissues, but not into the tumor, was reduced by prior injection of adrenocortical extract or of cortisone acetate. Since different normal tissues are known to show some differences in metabolic responses to hormonal influences, it is of interest that in this study the adrenocortical extract, in contrast with the cortisone, had little effect on glycine uptake by intestine and none on that by muscle.

Adrenal influences on liver catalase have been mentioned in a previous section. In studies with normal mice injected with homogenates of Sarcoma 37, Adams (1) has obtained data suggesting that “the adrenal and testicular factors normally influencing liver catalase are prevented from operating. This failure appears to be due to the inability of the liver to respond to the hormonal stimuli.” In tumor-bearing rats, Begg (16) was unable to restore the reduced level of liver catalase by administration of adrenocortical extract.

**DISCUSSION AND CONCLUSIONS**

Such satisfactory data as exist in the literature do encourage the view that tumor growth (in common with virus growth) is not influenced pari passu with body growth by the hormones under consideration. A survey of the data obtained with transplanted tumors, other than lymphoid, has indicated an ameliorating influence of adrenalectomy or hypophysectomy, the effect of the latter being largely explicable in terms of ACTH and possibly GH. The possibility that these effects are indirect (vascular changes?) (cf. 109) does not detract from their interest. Tumors in which a virus is known to be a participating factor appear to have been rather neglected from the present aspect.

Hormonal effects on induced tumors (or on their induction) appear to be broadly similar to those on transplants, although it is possibly significant that stimulatory effects of adrenocorticoids have been reported with the latter but not with the former (Table 4). However, this field requires much further study, particularly with reference to the effect of adrenalectomy and of GH treatment. Bilschowsky and Hall (18) may be right in suggesting that GH is unlikely to be “the most important pituitary hormone involved in carcinogenesis,” but their arguments are based on the unproved assumption that estrogen treatment or thyroidectomy inhibits the secretion of GH.

As Lipschitz (115) and Selye (150) have remarked, there is no satisfactory evidence that the hormones under discussion could play a significant role as actual carcinogens. Although prolonged treatment of intact rats with GH may result in tumors, this action may well be “co-carcinogenic” (endogenous carcinogens?) or even nonspecific, consequent on increased food intake and vastly increased somatic growth. There is no warrant for Li’s extrapolation of these findings to carcinogenic hydrocarbons, viz., “it seems reasonable to assume that a tumor-producing hormone is secreted from the anterior pituitary under the stress of these toxic (carcinogenic) substances” (112).

Depending on the carcinogen and on its mode of administration, there is a well known specificity in the site of induced tumors. Any influence of GH, ACTH, or adrenocortical hormones on primary tumors might well depend on the tumor site, in view of the selective effects of these hormones on the growth (Table 1) or metabolism of certain organs. This possibility is receiving particular attention in the Sloan-Kettering laboratories (168), but
Unfortunately few generalizations can be made as to which organs are influenced selectively. Only in the case of the thymus on the one hand, and lymphoid tumors on the other hand, is there clear evidence for a correlation of effects (91). A search for such relationships need not be deterred by the postulate that tumors are unresponsive to hormones in comparison with the corresponding normal tissues.

Metabolic comparisons between tumors and normal tissues, with respect to hormonal influences, need to be widely extended. It is hoped that the foregoing survey of hormonal influences on normal metabolism will suggest endocrinological avenues to be explored in the cancer field. A number of tissue constituents are known to change in amount or activity—possibly nonspecifically—both with neoplasia and with a change in hormonal environment. These include calcium, catalase, arginase, D-amino acid oxidase, hyaluronidase, and certain intracellular proteolytic enzymes. The nucleic acids merit particular attention, their level being influenced by GH and, sometimes conversely, by adrenocorticoids; data for their changes in malignancy are admittedly conflicting, but point to a rise in RNA and especially in DNA. The possibility that hormones may influence the metabolism of carcinogens also deserves investigation.

In chemical comparisons between tumors and normal tissues, increasing attention is rightly being paid to the possibility that differences will be found in "fine structure" rather than in gross composition. Particularly in the case of constituents such as "protein," "free amino acids," and even "DNA" and "RNA," analyses for gross content are of limited value unless checked by a study of the chemical composition and cell distribution of the constituent under investigation. Surprisingly, subtle differences of this kind have been little investigated in the field of hormonal effects on normal tissues. A recent study (77) from Young’s laboratory on the nature of the "protein" laid down in muscle under the influence of GH points the way to other studies of this kind.

It is pertinent to consider what test conditions, and what forms of hormone treatment, are most likely to yield fruitful results in relation to the incidence, growth, or metabolism of tumors. The rat is "an abnormal" species in some respects (Table 2), and its insensitivity to the diabetogenic action of GH renders rather pointless a comment by Hertz (74) on the above-mentioned study by Moon and collaborators—that no determinations were made of carbohydrate tolerance. However, there are no data to contra-indicate use of the rat in the present connection. The mouse is perhaps less suitable, in view of its insensitivity to the growth-promoting or to the "carcinogenic" action of GH.

Hypophysectomized or adrenalectomized animals are to be preferred to intact animals in studying effects of administered hormones, particularly adrenocorticoids. Since adrenal output can vary enormously, even attaining the equivalent of 20 ml/day of adrenocortical extract in the stressed rat (80), effects obtained with moderate doses of adrenocorticoids, in animals with actively functioning adrenals, could conceivably be due to an actual reduction in circulating adrenocorticoids (doubtless differing in nature from those administered).

A general point which has been neglected too often is that data for food intake are highly important, in evaluating effects seemingly due solely to deprivation or administration of hormones. Vitamin intake may also be a limiting factor; thus, the effectiveness of GH may be impaired if the intake of pyridoxine is inadequate.

The possible importance of factors such as diet, temperature, age, and sex has been lucidly discussed by Ingle (79). With regard to age, it may be noted that inhibition of hair growth by adrenocortical extract is less marked in immature rats than in adult rats (9). As already mentioned, the acute effect of GH on certain liver enzymes may depend on age (15). Tepperman (170) noted that liver from old rats, but not from relatively young rats, showed a ketotic response to certain GH preparations in vitro. Moreover, ketogenesis was enhanced by GH treatment in recently hypophysectomized rats, but not in long-term hypophysectomized rats unless cortisone was also given.

This last observation, indicating a "permissive" role of adrenal hormones in relation to the activity of GH, recalls other examples cited above. In fields such as carbohydrate metabolism, bacterial infections, and possibly even somatic growth it is clearly false to regard GH and adrenocorticoids as always mutually antagonistic, although they are certainly antagonistic in many circumstances (cf. 135). The net effect of GH and adrenocorticoids given concomitantly, or even their single effects, may depend not only on the phenomenon studied but also on the doses (cf. 79). Here it may be pointed out that inadequate study of dosages vitiate at least one report (54) of a "synergistic action." Increasing the dose of a hormone may actually reverse the direction of an effect, as shown in vitro with respect to lipogenesis by mammary tissue exposed to corticosterone (49).

In studies with adrenocorticoids, attention must be paid to the possible importance not only of dose
level, but also of the mode of administration (important also in the case of ACTH, and even of GH—see 139, 180), and of the nature of the adrenocorticoid. There is already some evidence suggesting qualitative differences among different adrenocorticoids in relation to tumors (Table 4), as in other fields (Table 3); hydrocortisone is notably effective in the chick (92, 105). An unavoidable complication is that injected adrenocorticoids may undergo metabolic transformations in vivo; thus desoxycorticosterone may acquire an 11-oxo group. The natural adrenocortical secretion cannot, of course, be precisely simulated by therapy with a single steroid such as cortisol, as clearly shown by Ingle (84) with respect to his "work test." The use of known mixtures of steroids may be advantageous, as suggested by preliminary experiments in Gordon's laboratory (60) on bone marrow metabolism.

It cannot be overemphasized that investigators in the endocrine field should be conversant with the characteristics of the hormonal preparations employed, and avoid the use of dubious material. Fortunately, reliable pituitary preparations are now becoming available from commercial sources, although in the case of GH (cf. 139) it should not be assumed that material prepared by the Raben-Westermeyer method (136) is equivalent to material prepared by the methods developed in Li's and Wilhelm's laboratories. It is unwise to designate as "pure" any anterior-pituitary preparation, commercial or otherwise, even if contaminants appear to be absent. Data reviewed above indicate the need for caution in the case of both "ACTH" and "GH" preparations, although a claim (196) that GH preparations contain a diabeticogenic factor distinct from GH itself has been disproved (188).

In conclusion, a guess may be hazarded as to the possible applicability to the human of research on this aspect of neoplasia. Attempts to treat lymphoid tumors with ACTH or cortical hormones have met a difficulty often encountered in long-term hormone studies, that there may be a transient response succeeded by a "refractory state." It is controversial whether ACTH or GH may be sufficiently antigenic in animals to account for eventual failure to respond. An alternative explanation, applicable particularly to adrenocorticoids (cf. 27), is that some change in the tissues accounts for their failure to respond. In the case of GH-treated rats, this change may be merely depletion of fat reserves (cf. 65) or, in long-term experiments, attainment of a maximal growth limit as suggested by Selye (154), who claimed that GH eventually became ineffective in rats fed ad libitum, but not in rats on a restricted food intake.

With tumors other than lymphoid, it seems likely that aggravation rather than amelioration would result from treatment with GH, ACTH, or adrenocorticoids. Adrenalectomy or even hypophysectomy may have a beneficial effect at least with certain mammary or prostatic tumors (cf. 76). An alternative to such drastic operative procedures would be to administer a "blocking" agent which would suppress the secretion or the activity of the supposed tumor-favoring hormone. No agents of proved efficacy are yet available, although an unsuccessful attempt has been made (35; cf. 115) to suppress the growth of transplanted carcinomas (Walker) by administration of p-hydroxypropiophenone, a drug alleged to block pituitary secretion. Irradiation of the pituitary might be worth re-investigation, in view of alleged beneficial effects in some early clinical studies (quoted in 150).

Data for the blood levels of GH, ACTH, and adrenocorticoids in humans are at present virtually lacking, although some preliminary data suggest that the level of blood GH is not significantly higher in cases of advanced breast cancer than in control subjects. Until more data are available, speculation as to hypersecretion of these hormones during or preceding cancer must rest on indirect evidence. There are reports of enlarged adrenals in cancer patients, as in tumor-bearing rats, although such enlargement has been considered to reflect adrenocortical exhaustion rather than hypersecretion (cf. 16, 19). The urine of cancer patients may differ qualitatively, as well as quantitatively, from normal urine with respect to steroid constituents believed to be of adrenocortical origin (40).

A survey of the incidence of cancer in acromegals might throw some light on the possibility that GH may be an etiologic agent in cancer. No such conclusion can safely be drawn from reports of an association between cancer and diabetes (cf. 74), since it has not been proved that GH or adrenocortical hormones are commonly etiologic factors in diabetes.

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