An Appraisal of the Concepts of Endocrine Influence on the Etiology, Pathogenesis, and Control of Abnormal and Neoplastic Growth*

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In the attempt to orient ourselves to the mass of existing endocrinological data bearing on the cancer problem, it is essential to consider the general biological framework upon which endocrinology rests. With the evolution of multicellular organisms, there have developed innumerable patterns of functional integration among their constituent cellular units. These patterns range all the way from the intercellular canals of the primitive metazoa, through such complex patterns as the nerve nets of certain invertebrates, and thence to the more elaborate neural and vascular systems of higher forms. The essential function of these systems is the integration of the vital processes of the organism as a whole. Traditionally, those integrative functions which appear to be physically mediated through specialized neural structures have become the province of the neurologist. The endocrinologist takes over when such integrative effects are thought to be mediated by purely chemical means. However, modern physiologists, largely conditioned by Loewi's demonstration of the humoral nature of the "vagal impulse" and by a growing knowledge of the molecular products of the autonomic nervous system, are increasingly aware of the large area of overlap between endocrinology and neurology. One evidence of this is the current interest in the influence of the hypothalamus upon pituitary function. Accordingly, we shall return in the ensuing discussion to this general area of "neuroendocrinology."

In contrast to the historically natural connection between neurology and endocrinology, many clinical and biological disciplines have claimed in recent years some degree of relationship to endocrinology. Thus, the immunologist, pediatrician, gynecologist, orthopedist, ophthalmologist, obstetrician, allergist, cardiologist, urologist, and many others look to endocrinology for guidance and help. This pivotal position of endocrinology stems quite naturally from its primary concern with the central integrative functions already referred to. Hence, some endocrinologists have become emboldened to generalize certain limited endocrine phenomena into the concept of "stress" or "general adaptation" (68), a suggestion which will receive further appraisal below.

A hormone is a substance which mediates the integrative functions of an endocrine gland. Hormones are characteristically distributed via the vascular system, but some examples of direct tissue diffusion giving rise to local field effects are becoming apparent. Moreover, hormones are considered to possess a high degree of chemical specificity which presumably imparts to them their essential biological properties. They are regarded as acting in trace amounts and may therefore be classed with other biologically active trace elements such as vitamins and enzymes. In fact, their actual distinction from these closely related metabolic agents may be regarded as somewhat arbitrary. Whereas the nutritionist has been able to clarify the metabolic relationship between such dietary trace factors as, for example, pyridoxine and transaminase or pantothenate and coenzyme A, the endocrinologist has thus far learned little concerning the intimate biochemical mechanisms involved in bringing about hormonal effects.

Accordingly, endocrine responses are described in relatively crude terms. One of these terms refers to the "trophic" action of certain steroid and pituitary hormones upon specific tissues and organs. This term implies that (a) the hormone under discussion increases the size or mass of a given tissue or organ and (b) the hormone increases the rate of function (or functions) commonly identified with this tissue or organ. Thus, the adrenotrophic hormone in its "trophic" action upon the adrenal cortex increases the mass of...
adreno-cortical tissue and induces an increased output of certain adrenal steroids. There is general agreement that such “trophic” effects represent, with few exceptions, quantitative rather than qualitative alterations.

Closely allied to this concept of the “trophic” action of the hormones is the concept of “hormonal dependency.” One sees that certain tissues and organs become relatively atrophic and hypofunctional in the absence of critically required “trophic” hormones or when such hormones are effectively antagonized by hormonal or pharmacological means. It is important again to emphasize that this concept of “hormonal dependency” refers with few exceptions to a relative rather than an absolute functional dependency.

There is also a widely held thesis that these principles of the “trophic” action of the hormones and of “hormonal dependency” are applicable not only to normal tissues and organs but also to neoplasms derived from them. This thesis holds that there are certain functional common denominators between hormone-induced tissue growth and neoplasms of the breast, prostate, and uterus or of such hormone-producing organs as the pituitary, thyroid, adrenal, pancreas, ovary, and testis.

The nature of this relationship between hormone-induced tissue growth and neoplasia and its full exploitation for therapeutic purposes constitutes the central theme of endocrine oncology. It should therefore be profitable to consider the salient features of similarity and difference between the manner in which a normal tissue grows in response to hormonal stimulation and the process whereby tumors are induced in hormonally sensitive organs. Both processes lead to a rapid and disproportionate increase in tissue mass. However, for normal tissues this increase in mass follows closely reproducible quantitative features so that statistically valid dose–response curves may be derived (11, 25). Hormonally induced neoplasia, on the other hand, appears to be in the nature of an “all-or-none” phenomenon with somewhat indecisive threshold requirements (18). The latent period for normal tissue response to endocrine stimulation is usually quite short. That for neoplasia usually constitutes a major portion of the life span of the species involved. Moreover, withdrawal of the endocrine stimulus to normal tissue deposition is followed promptly by rapid involution of the enlarged organ (32). Tumors may remain hormonally dependent or in time may become completely independent of hormonal support (15, 18, 56). Even though a normal organ may grow under hormonal stimulation to massive size and may thus encroach upon surrounding organs, it reaches a maximum mass beyond which further increments in dose of hormone will have no further effect (11). Neoplasms, however, when activated by appropriate hormonal stimuli have no specific quantitative limitations in potential mass. However, when a normal organ is stimulated to undue growth by excess hormone, it acts like a growing tumor in depleting the limited nutritional reserve of the host even in a fasted animal. Yet, hormonally proliferated tissue usually differs only quantitatively from its normal counterpart, whereas neoplastic tissue by definition differs qualitatively from that normally seen in the species under study. Certain reversible metabolic changes may accompany sustained hormonal stimulation of previously normal tissue and thus provide a morphological bridge between hormone-induced tissue growth and neoplasia (83, 49, 59).

These similarities and differences suggest that the malignant process in hormone-sensitive tissues may represent a deviation from the normal pattern of endocrine growth response (18). This inference is strengthened by numerous experimental demonstrations of the induction of tumors by derangement of functional endocrine relationships within the body (5, 15, 17–19, 35, 57, 77). Nearly every organ known to be endocrinologically reactive, with the exception of the pancreas and parathyroid, has succumbed to experimental tumorigenesis by endocrine manipulation. The common denominator of these manipulations appears to be a prolonged and intensive derangement of the normal trophic or regulatory relationship between hormone and end organ. Such derangements are effected in some cases by hormonal excess and in others by hormonal deprivation. However, the principle of “hormonal imbalance,” early enunciated by Gardner and Pfeiffer, seems to pervade all the experimental material (18).

Clinically, similar phenomena are observed both with respect to derangements of endogenous hormonal relationships and also following hormonal administration. Thus, the frequent association of hormone-producing tumors of the ovary with cancer of the endometrium suggests such a disturbed hormonal balance (26). The occurrence of ovarian tumors in female acromegalics may also reflect an altered pituitary-ovarian relationship. The syndrome of multiple endocrine tumors of parathyroid, pancreatic, and pituitary origin has now been well characterized (70, 73). The pituitary dependence of thyroid adenomas is reflected in their frequent regression under pituitary-depressant doses of thyroid hormone. The alteration of functional status in metastases from thyroid can-
cancer by suppression of hormonal output of the remaining normal thyroid tissue indicates a functional similarity between tumor and parent tissue (60, 67).

However, the picture is not so distinct with respect to the tumorigenic action of exogenous hormones in the human subject. Breast cancer in the male following prolonged estrogen therapy for prostate cancer has been repeatedly documented (1, 16, 20, 47). However, the lack of endometrial cancer in intensively estrogenized women is noteworthy.1 Furthermore, prolonged androgen therapy in middle-aged males has apparently not led to the lighting-up of occult prostatic carcinomas which are known to occur in from 14 to 46 per cent of the older male population. This marked difference between the tumorigenic action of exogenous hormones in man and animals may be attributed to the fact that even prolonged clinical therapy occupies only a limited segment of a person's life expectancy, whereas the animal studies usually extend through a major portion of the subject's life-span.

The exploitation of the overlap between hormone-induced tissue growth and neoplasia has led to some remarkable and challenging therapeutic accomplishments. The earliest of these was Beatson's incisive demonstration in 1896 of the beneficial effects of ovariectomy in patients with breast cancer (4). This firmly established clinical effect is seen in about half of the patients who undergo ovariectomy. It is noteworthy that this observation antedated Loeb's initial study on the reduced incidence of breast cancer after ovariectomy in certain strains of mice (48). No reliable criteria exist to permit the prior selection of those patients in whom a favorable effect may be anticipated, although certain metabolic and histological indicators have been suggested. It may be inferred from the uniformity of the preventive effect of ovariectomy on breast cancer in highly inbred strains of mice that, perhaps, the genetic heterogeneity of the human population may be a factor in determining the variable effects obtained. In any case, more complete clinical and metabolic characterization of the difference between patients who subsequently obtain substantial regression following ovariectomy and those who do not is urgently needed.

The male counterpart of this effect is seen in the often prompt and spectacular improvement in patients with prostatic cancer following orchietomy (37, 58). Here again, we have no criteria for the selection of those patients who will derive major benefit from castration. These effects of gonadectomy in both male and female constitute the most direct and unequivocal evidence we have of the clinical applicability of the principle of endocrine dependency of tumors in hormone-sensitive organs. Thus, the nature of the process whereby such organs involute following hormonal deprivation demands emphasis equal to that already given to the phenomena of hormonally conditioned tissue growth. Preliminary studies of our own indicate that the regressive changes in the prostate and in the uterus after gonadectomy follow a well regulated and orderly course both in relation to time and amount. Moreover, this regression seems to be independent of such other metabolic manipulations as starvation, induced hyperthyroidism or hyperadrenocorticism, thyroidec
tomy, adrenalectomy, or hypophysectomy (32). Means for the accentuation of such regressive effects would presumably be of value in increasing the degree and frequency of therapeutic responses following gonadectomy.

These effects of gonadectomy have suggested that extirpation of the adrenal glands, which constitute a major additional source of gonadal steroids, should result in further regression of cancer of the breast and prostate (37, 38). Sufficient clinical observations are now available to permit the conclusion that a limited and short-lived palliative effect is obtainable in about one-third of patients with breast cancer and in a very occasional patient with prostate cancer. One of the difficulties in evaluating these effects is the possibility that the role of the cortisone given the adrenalectomized patient for maintenance, since cortisone therapy per se may exert palliative effects somewhat similar to those seen following adrenalectomy. However, some patients who have definitely failed to show a pre-operative response to cortisone have been reported to show a subsequent response to adrenalectomy. The possible role of accessory adrenal tissue in adrenalectomy failures has not thus far been adequately evaluated. Dao (8) has offered limited data purporting to show a marked reduction in urinary estrogen excretion following adrenalectomy in women with breast cancer. Thus, we lack any decisive information as to the mechanism of action of adrenalectomy in providing the limited palliation thus far reported. However, there is a growing clinical impression that patients who have previously experienced regression following ovariectomy will obtain the most distinct benefit following adrenalectomy.

Experimentally, breast tissue is known to be affected in its growth differentiation and function by gonadal, adrenal, and pituitary hormones (14).
Hence, hypophysectomy would promise to offer the most effective hormonal deterrent to the advancement of breast cancer. Recent progress in surgical technic and in pre- and postoperative endocrine management certainly renders this procedure practicable even in patients with advanced disease. Also, excellent criteria for the determination of the completeness of hypophysectomy have been developed (50, 74). The writer feels, however, that in the present context any attempt at evaluation of the therapeutic potential of this remarkable technic would be premature. Still, the soundness of the endocrinological rationale of hypophysectomy in breast and prostate cancer does merit full emphasis. It would seem equally rational to consider hypophysectomy to be indicated as a primary endocrine procedure in such cases.

The ultimate reversibility of even the most remarkable regressive changes in breast and prostate cancer following either gonadectomy, adrenalectomy, or hypophysectomy presents a major challenge in cancer therapy. Emphasis is placed by some upon compensatory phenomena which tend to reestablish the presumed initial endocrine environment. For example, in keeping with Woolley’s findings in mice, the adrenals are thought to replace the extirpated gonads as sources of gonadal steroid (75). We actually have no specific clinical data which can support such an inference. This deficiency results from serious limitations in existing methods of assay for gonadal hormone activity in the human subject.

An alternative explanation of the transient character of endocrine palliation relates these changes to more intricate alterations in the intrinsic metabolic functions of the cancer cells involved. Histochemical and morphological analyses have not thus far yielded even the remotest lead as to the nature of these adjustments (41). In other fields of tumor chemotherapy, as in the case of antifolic resistance in leukemia cells, the enhanced synthesis of a specific metabolite, such as folic acid, provides some initial understanding of the phenomenon of resistance (45). The endocrinologist must set as his goal similar comprehension of the factors leading to reactivation in previously hormone-dependent tumor cells.

Just as surgical extirpation procedures have proved of practical and theoretical interest, the alteration of normal hormonal production or hormonal action by medical means has provided therapeutic and physiological data of great importance. These medications have been developed in some cases along rational lines. Thus, the use of estrogens in the control of prostate cancer is predicated on the so-called “anti-androgenic” effect of the female sex hormone. This interpretation has considerable basis in experimental findings (39), but we have only indirect evidence that estrogens do in fact exert an “anti-androgenic” effect in the human subject. Still, a great variety of estrogenic agents of stilbene or steroidal structure are found to be effective in proportion to their respective estrogenic potencies. This suggests that their therapeutic effects probably stem from the estrogenic property of the several compounds in use. Moreover, resistance to one of these estrogens is usually accompanied by resistance to each of them.

Another property of estrogens, namely, the capacity to inhibit pituitary gonadotropin secretion, may also play a role in the therapeutic effects obtained both in breast and prostate cancer patients (66). This effect is quantitatively demonstrable in both men and women by bioassay of the urine for gonadotropin content. Further experience with the effects of hypophysectomy in prostatic cancer will provide indirect information as to the part this pituitary-depressant action may play in therapy with the gonadal hormones.

Estrogens also exert a considerable array of general systemic actions which may mediate their therapeutic effects. These include: (a) depression of the beta lipoprotein fraction of the serum, (b) increase in protein-bound iodine of the serum without concomitant evidence of increased formation of thyroid hormone, (c) increase in caeruloplasmin content of serum, (d) alterations in mineral metabolism manifested chiefly by sodium and water retention, and occasionally by reduced calcium excretion which may be accompanied by hypercalcemia (5, 10, 12, 42, 68). These more general effects may, in fact, be of major importance in mediating the therapeutic effects observed.

It is of some interest that the estrogen-induced pituitary tumors and also the marked adrenal enlargement which follow estrogen administration in rodents are not encountered in human subjects exposed to even massive doses of estrogen for prolonged periods (37, 69). The other aspects of the tumorigenic potency of exogenous estrogens in men and women have been discussed above.

Recently, Hisaw and Velardo (34) have directed attention to the fact that estradiol is capable of inducing only a submaximal uterotrophic effect in the rat irrespective of the dose administered. Also, estradiol, when given with otherwise maximally effective doses of estrone or estradiol, actually impairs the expected uterine response to the potent estrogens. These findings have led Huggins and Jensen (40) to characterize estradiol and related compounds as “impedestrogens.” This unique
biological property may provide a basis for as yet unobtainable therapeutic effects in breast and prostate cancer.

The status of steroid therapy of breast cancer has been repeatedly and extensively evaluated elsewhere (7). It is sufficient to state here that the therapeutic effects which have been thus far observed, limited as they may be, constitute a major chemotherapeutic accomplishment despite a rather tenuous rationale and highly detrimental side-effects. In this area the most urgent needs are: (a) some understanding of the mechanism of steroid-induced regression and (b) the development of compounds of increased oncostatic action and reduced androgenic, estrogenic, or corticoid potency. The progress toward this latter objective has been, in the writer's view, too fragmentary to justify many of the claims made for some of the newer steroids. There is as yet no adequate bioassay which can substitute for direct clinical assessment in appropriately selected and thoroughly studied cases.

Even under ideal circumstances clinical evaluation becomes a difficult and involved task. We would define a therapeutic effect as an induced deviation from the natural course of disease. Our limited knowledge of the natural course of breast cancer often provides too indistinct a base-line for accurate therapeutic appraisal. Clinical and ethical considerations usually preclude the use of untreated control subjects. Hence, such studies must be purely descriptive and uncontrolled. This creates an urgent need for the utmost objectivity in such evaluations. A beginning has been made toward group definitions of therapeutic criteria to be employed in joint efforts of clinical appraisal. It may be expected that such efforts will aid in clarifying some of the problems of clinical testing of newer agents as they become available.

Several working hypotheses may facilitate the ultimate development of more potent steroidal agents. One of these relates to the possible application of the principle of molecular antagonists to the planned synthesis of compounds capable of neutralizing the biological effect of endogenous hormones. The writer has previously reviewed this approach and was obliged to conclude that the direct applicability of this principle has yet to be demonstrated (28). Nevertheless, such biological antagonisms as that observed between estrogen and androgen, or between estrogen and progesterone, exhibit certain quantitative features which suggest that such a competitive mechanism may be operating. It would therefore seem desirable to pursue this approach further.

Existing knowledge of the relation of steroid structure to biological or clinical activity warrants no generalization as to the potential value of previously untested compounds. However, we do have some tenuous basis for correlating certain endocrinological effects with potential therapeutic value. As already indicated, the estrogenic effect is clearly correlated with a suppressant action in prostate cancer whether the estrogen be of steroid or stilbene type. In breast cancer, regression is seen following the administration of a wide variety of estrogenic or androgenic compounds. It may, therefore, be in order to list the biological endocrine effects which may be considered to reflect some promise of therapeutic potential:

1. Androgenic effect and anti-androgenic effect.
2. Estrogenic effect and anti-estrogenic effect.
3. Corticoid effect and anticitocoid effect.
4. Protein anabolic action.
5. Protein catabolic action.
6. Pituitary-depressant action; this includes suppression of any or of all phases of pituitary function with special emphasis upon gonadotropin, thyrotropin, adrenotropin, prolactin, and possibly growth hormone production or action.
7. Progestational action and antiprogestational action.
8. Inhibitory or destructive effects upon spontaneous or transplanted tumors, preferably those originating in hormone-sensitive organs.

At the same time, it must be emphasized that therapeutic potential may be completely independent of such endocrine effects or may relate to as yet undefined humoral relationships. A most fertile field for the latter possibility is the further exploration of the biological effects of such endocrinologically potent substances as placenta, pregnancy urine, ovarian, testicular, or adrenal tissue, amniotic fluid, and a host of related natural materials. This is a seriously neglected area of investigation which has become overshadowed by the more recent interest in synthetic compounds. It would seem desirable that endocrinologists should direct their attention to the products of the endocrine glands as well as to the products of the steroid chemists.

It is equally important to consider by what indirect means the trophic action of a hormone may be mediated. The deposition of new tissue involves the mobilization of each of its essential constituents, namely, amino acids, purines, nucleotides, water, minerals, vitamins, and a host of other specific ingredients. As these various elements are marshaled forth for each tissue, a host of
enzymatic and metabolic processes come into play. Thus far, only beginnings have been made in our understanding of these phases of hormone-induced tissue growth. For example, Awapara (2) has described the shift in amino acid composition of the prostate under androgenic stimulation. Meyer et al. (54) have described alterations in succinic dehydrogenase content of the corpus luteum in various functional phases. Fishman (13) has related β-glucuronidase content of the uterus to estrogen action, and the Gutmans (23) have shown the relationship of the acid phosphatase content of the prostate to androgenic activity. Although numerous additional examples of such clear quantitative relationships could be cited, we still have little understanding of their basic implications as to the mechanism of hormone action.

Similarly, estrogen-induced tissue growth has been shown to be quantitatively dependent upon available reserves of folic acid, and both folic acid antagonists and purine antagonists will effectively block the growth of the genital tract of several species in response to endogenous or exogenous estrogen (30, 31). Conversely, thiamin and riboflavin are critically required for the normal hepatic metabolism of estrogens (27).

Such fragments of knowledge offer indirect routes for the potential interference with neoplastic growth in hormone-dependent tissue. Thiersch has applied this principle in the use of folic acid antagonists for the interruption of pregnancy (72). Li et al. have extended this effect to the suppression of tumor tissue of trophoblastic origin such as that encountered in choriocarcinoma of the uterus (46). This indirect approach to some of the more subtle phases of dependence of hormone-induced tissue growth merits systematic exploration.

Still another tangential approach to the control of hormone-induced tissue growth relates to a further understanding of the challenging neuroendocrine phenomena currently engaging only a few endocrinologists and even fewer oncologists. Scharer has shown that simple nerve severance will induce tumors in insects (65). Greer (21) has shown that the thyroid-enlarging effect of propylthiouracil can be blocked by appropriately located hypothalamic damage. Similar interference with release of adrenotropin and gonadotropin has been shown to follow damage to somewhat different hypothalamic sites (23, 24, 52). Moreover, there is a growing literature on the pharmacological interference with endocrine function through the presumed hypothalamic action of such drugs as reserpine and chlorpromazine (9). The essential consideration for the oncologists is that growth effects in hormone-sensitive tissues can be modified by neuro-endocrine manipulation. Meanwhile, neurosurgery is exploring more extensive surgical procedures in the control of various dysfunctions of the nervous system. It may be expected that the endocrinologist in his quest for better means of control of tissue growth may yet guide the neurosurgeon's hand to the further reaches of the midbrain. However, Sawyer has shown that gonadotropin release may be effectively blocked by certain adrenolytic drugs (64). Hence, rapidly developing pharmacological means for neuro-endocrine control may render these surgical undertakings superfluous.

More general pharmacological control of endocrine function by nonhormonal agents also presents numerous possibilities. Within the past decade the development of increasingly potent and less toxic antithyroid drugs has provided practicable means for nearly complete medical control of thyroid function. Two compounds, namely, Amphenone and D.D.D., have offered a beginning toward similar pharmacological control of hormonal function of the normal adrenal cortex and of malignant tumors derived from the adrenal cortex (29, 44). Alloxan can specifically destroy insulin-producing islet tissue, and the newer antidiabetic sulfonamides appear to enhance endogenous insulin production or effectiveness. The endocrine oncologist must be ready to exploit these pharmacological developments. He is also in a particularly strategic position to extend our knowledge in this area.

One of his major advantages in this regard is the characteristically high hormonal output of many tumors arising in hormone-producing organs. This provides an excellent quantitative reflection of the functional activity of such tumors. With appropriate chemical and bio-assay procedures the level of hormone production can be followed as an index of the inhibitory action of therapeutic agents which aim either at specific functional interference or at more general tumor destruction. It is equally important to ascertain in what way these various effects may be causally or circumstantially related.

At a more basic level, the phenomenon of excessive hormonal output associated with neoplastic change represents one of the most palpable of all known metabolic distinctions between benign and malignant cells. In the light of Greenstein's enzymatic characterization of the malignant change as a progressive loss or reduction of specific functional potentialities of the cell, this increased hormonal output may represent the failure of normal inhibitory mechanisms of great
practical interest. Meanwhile, endocrinologically characterized animal tumors of thyroid, adrenal, and ovary in both functional and nonfunctional forms have become available. Also, in vitro systems for the biosynthesis of both thyroid and adrenal hormones in amounts sufficient to quantitate by modern techniques have been worked out (61, 70). These combined developments provide a most unique opportunity to study specific biosynthetic mechanisms which have become deranged through neoplastic change.

The frequent occurrence of excessive hormone production in tumors of the endocrine glands suggests that very probably equally characteristic alterations in biosynthetic capacity occur in nonendocrine organs undergoing malignant change. The endocrinologist may simply be dealing with the more obvious instances of these manifestations which need to be more extensively sought for through increased basic physiological study of the several "nonendocrine" organs which may become involved with malignancy. A good example of a recent triumph in this direction is the demonstration of excess serotonin production leading to a clinical syndrome of specific intoxication by the carcinoid tumor of the bowel, a lesion which a few years ago would certainly not have been regarded as an "endocrine" tumor (71). With extended study many more such relationships should become apparent and thereby provide new sites of potential vulnerability to the action of appropriately devised chemotherapeutic agents.

Immunological phenomena are at hand which provide at least the beginnings of control of hormone-induced tissue growth. It is known that at least two of the pituitary hormones, namely, thyrotropin and gonadotropin, will induce specific antibodies which will negate their respective biological effects in test animals (6, 53). These inhibitory effects are not species-specific either in relation to the species providing the antigen or receiving the antiserum. Thus, sheep antigonadotropic serum prepared by prolonged administration of pig pituitary extracts will inhibit effects of endogenous or exogenous gonadotropin in rats, rabbits, and mice. One can, by continued administration of such inhibitory sera, keep the gonads of the rat in an infantile state throughout adult life. Maddock et al. (51) have shown that prolonged administration of sheep gonadotropin to young girls exhibiting sexual precocity will induce biologically demonstrable antigonadotropic formation in their sera, and this is associated with clinical evidence of regression of their precocity. These antigenic properties of thyrotropic and gonadotropic extracts are lost when the extracts are freed of a major portion of accessory protein. This suggests that the hormones provide the specificity for the immune response, but carrier protein is needed for the full antigenic response. An extension of this principle to hormones other than gonadotropin and thyrotropin seems feasible. Moreover, the implications of even such rudimentary knowledge for the potential immunological control of many phases of hormone-induced tissue growth and neoplasia urgently demand active extension of work in this field.

It is apparent that the areas of contact between endocrinology and oncology are numerous and diverse. The breadth of these considerations has led some to ascribe to endocrine factors a more or less universal role in the pathogenesis of tumors. Thus, some observers have been led to consider the adrenal gland as of focal significance in tumorigenesis. Also, the similarity in structure of certain pentanophenanthrene carcinogens to the steroid hormones and bile acids has permitted the inference that such carcinogens may arise endogenously through faulty steroid metabolism. Other observers have attributed a key function in tumorigenesis to the pituitary growth hormone (55) because of the occurrence of tumors in rats treated for extended periods with growth hormone. Furthermore, hypophysectomy appears to reduce the biological effectiveness of certain chemical carcinogens (62). Whereas these and related phenomena certainly have great intrinsic significance, the writer feels that undue generalization of them to cover all of tumorigenesis is unwarranted.

Similarly, we encounter the concept that many diseases represent varying patterns of failure of a specific mechanism of adaptation necessarily involving the pituitary-adrenal axis (68). In the writer's view, such a thesis presumes too much upon the unknown to provide a truly adequate basis for further thought or investigation. In a biological sense, "life is strife." This begins with the sperm's active competition with its fellows in finding the ovum and with the ovum's violent reaction to this encounter. It is not surprising, therefore, to find that many of life's phenomena can be characterized as a response to stress. Indeed, it would be difficult to state which of the organism's adjustments to its environment is not accompanied by "stress." Thus, the concept appears to add simply another layer to the already dense semantic fog with which we are surrounded.

The foregoing fragments of knowledge and suggestion are offered simply as dim clues to the nature of the cancer problem. It is a mistake to accept the coin of limited therapeutic accomplishment as the true currency of comprehension. It
simply reflects a small part of the shadow of the enemy which has not even yet exposed its full countenance to us.

In closing, the writer is constrained to offer a simple plea for a research environment of sustained tolerance with emphasis on new ideas rather than upon presumption and arbitrary direction.

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