Hormonal Imbalances in Tumorigenesis*

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We are now probably all more aware of "hormonal imbalances" than ever before. Investigators of problems in experimental endocrinology have been aware of hormonal imbalances or balances for many years. Now the terms are used more frequently because they are being considered in connection with the production and treatment of tumors and cancer. An environment in which both the applied and fundamental aspects of a problem are being investigated in the clinic and in the laboratory simultaneously accelerates the expansion of that particular field of investigation. It is of interest that two groups of investigators here in Chicago have contributed significantly to the understanding of hormonal interreactions. Moore and Price (27) first expanded the theory of hormonal interreactions involving the reproductive organs. Huggins and his associates (20, 21) were the first to modify hormonal balances to affect the treatment of prostatic cancer.

There are undoubtedly differences of interpretation of hormonal imbalances but that is natural, it is so hard to define a "normal" balance of hormones, particularly in connection with some systems of hormones. In fact, the hormonal balances change from day to day, year to year, or even moment to moment in some instances. Such changes are essential as the body develops, is adapted to different stresses and as it ages. The flexible state of many hormonal activities is worthy of contemplation, because, when appreciated, it implies that hormones are regulators or inciters of functions; that they do not initiate or need not initiate any new function or functions to which organized aggregates of living cells are not already subject. One cannot expect a hormone to do something that the body cannot do but it can modify or regulate functions for which the body has intrinsic and sometimes even nascent potentialities. Consider the thyroid, for example; energy can be used by the living body in the absence of the thyroid gland, but under normal conditions, the thyroid regulates some aspects of the level of metabolism. Although the adrenal glands function in the regulation of protein mobilization and carbohydrate storage and utilization, these functions are known to occur in adrenalectomized animals. Ovogenesis probably, and certainly some growth of ova and ovarian follicles occur in the absence of the pituitary gland, the source of gonadotrophic hormones that regulate the rate and the number of ova maturing and ovulating. The vaginal epithelium grows and heals and even cornifies in response to trauma in the castrated animal, and in the absence of known estrogenic hormones although the estrogens have profound effects on the growth of the vaginal epithelium.

Hormones should be looked upon, therefore, as substances regulating functions for which the body has inherent capabilities and usually some independent or autonomous basic level of response. The apparent responses of the body to some hormones do not appear until relatively late. The prostate gland of the child is capable of responding to testosterone, but normally is small until puberty because the gonads are not stimulated adequately by, or do not respond to, the hypophyseal gonadotrophins. There is evidence that growth may occur in rats hypophysectomized when very young, whereas growth fails in older animals subsequent to hypophysectomy.

At least three variable elements must be considered in hormonal imbalance: 1. rate of production of hormones, 2. rate of destruction, elimination or utilization of hormone, and 3. the capacity of the "end organs" to respond. To this might be added a fourth possible variable, namely, the kind or quality of hormone produced (Table I). Each

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of these variables is influenced by what might be termed (a) genetic or inherited influences that are characteristic of the strain, species or individual, (b) age or the stage of ontogenesis of the endocrine glands and end organs, and (c) nutritional status of the animal. All of these variables have been associated with the induction of specific imbalances in one or more, if not in all, instances. Additional influences may modify the three major elements that contribute to hormonal imbalances. Imbalances once induced may be temporary and may disappear or they may persist and incite irreversible changes in the end organs or associated structures. The entire problem of endocrine balances invites much further investigation.

First consideration will be given two classical experimental endocrine or hormonal imbalances involving the reproductive organs and then the hormonal pathogenesis of experimentally induced tumors of the anterior pituitary gland, testes, adrenal cortex and ovaries will be discussed. The humoral factors in the etiological background of some tumors of these organs have been studied most satisfactorily. Hormonal imbalances also are undoubtedly involved in cancer of the mammary glands in mice, in experimentally induced leukemia and possibly in cancer of the uterine cervix (11).

For the greater part, the exceptions to be noted later, the following investigations have been undertaken in our laboratories. Dr. C. W. Hooker, Dr. C. A. Pfeiffer, and Dr. Min Hsin Li have partici-
Pituitary tumors occur in estrogen-treated mice of some strains; in our experience they occur most frequently in estrogen-treated mice of the C57 black strain or in hybrids involving this strain (12). Estrogen-treated mice of at least 6 other strains rarely or never acquire such tumors, and they are extremely infrequent in control mice. The only untreated mouse with a pituitary tumor that the writer has observed also had bilateral granulosa
Fro. 2.—Schema of endocrine imbalances induced by parabiotic union of castrate and intact female rat. Inability of ovarian hormones to attain threshold levels in castrated member of pair results in (a) atrophy of its genital organs, and (b) excessive production and liberation of gonadotrophic hormone, primarily follicle stimulating hormone. Excessive gonadotrophin attains threshold levels in intact member and results in excessive ovarian stimulation and coincident stimulation of accessory genital tissues and of pituitary hyperplasia (Witschi [34]).

cell tumors (8). The proper endocrine and genetic influences must co-exist for tumors of the pituitary to develop.

The hypophyseal tumors that develop in estrogen-treated mice are chromophobe adenomas. They arise in localized areas of hyperplastic glands and may attain large size; up to 300 mgms., a mass almost as large as a normal mouse's brain (10). The tumors are usually fleshy and pink, are separated from the brain by the meninges and are not invasive. A few tumors contain large blood filled "cysts" and a few more contained one or more small cysts.

The tumors usually consisted of enlarged chromophobic cells arranged in cords. The cells contain large Golgi bodies and look like actively secreting cells. The tumors, however, contain little gonadotrophic hormone as revealed by bioassay in hypophysectomized mice (17). The low content of hormone in the hypertrophied glands is reminiscent of the iodine content of the thyroid of thiourea-treated animals. Some tumors contain dilated sinusoids or hemorrhagic areas. They grow, once they have started, after the discontinuance of estrogenic treatment; they grow subsequent to transplantation in other mice of the same strain if the hosts are given estrogen. In our laboratory they have not grown in mice that have not received estrogen and are thus not completely autonomously. The simultaneous injection of androgen will reduce the incidence of such tumors.

The tumors usually appear in animals that have received estrogen for 350 days or more and at an earlier age in males than in females. For purposes of classification any enlargement of the pituitary gland in excess of 12 mgm. has been considered a tumor. Some of these, however, are markedly hypertrophied glands, although they exceed by at least 6 times the size of a normal female mouse's pituitary. However, even small glands contain localized adenomatous nodules. Many of the tumors may exceed 50 mgm. in weight (Fig. 3).

The tendency for estrogen-treated mice of the C57 strain to acquire hypophyseal tumors is transmitted genetically, by both the males and the females (10). The incidence of hypophyseal tumors in estrogen-treated backcrossed mice is roughly

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**TABLE II: THE INCIDENCE OF PITUITARY TUMORS AMONG ESTROGEN-TREATED HYBRID AND BACKCROSS MICE**

<table>
<thead>
<tr>
<th>Group</th>
<th>Origin of group</th>
<th>Sex</th>
<th>Number of mice</th>
<th>With pituitary tumors</th>
<th>Average age of tumor</th>
<th>Average age at death non-tumor animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC1*</td>
<td>C57♀ × CBA♂♀</td>
<td>♂</td>
<td>23</td>
<td>19, 83</td>
<td>513</td>
<td>326-671</td>
</tr>
<tr>
<td>CC2*</td>
<td>CBA♀ × C57♂♀</td>
<td>♀</td>
<td>24</td>
<td>18, 75</td>
<td>480</td>
<td>380-543</td>
</tr>
<tr>
<td>CC3</td>
<td>(CBA♀ × C57♂♀)♀ × CBA♂♀</td>
<td>♂</td>
<td>38</td>
<td>8, 21</td>
<td>517</td>
<td>390-592</td>
</tr>
<tr>
<td>CC4</td>
<td>(C57♀ × CBA♂♀)♀ × CBA♂♀</td>
<td>♀</td>
<td>34</td>
<td>7, 21</td>
<td>525</td>
<td>324-647</td>
</tr>
<tr>
<td>CC5</td>
<td>(CBA♀ × C57♂♀)♀ × C57♂♀</td>
<td>♂</td>
<td>41</td>
<td>26, 63</td>
<td>419</td>
<td>263-577</td>
</tr>
</tbody>
</table>

*Data published in Cancer Research, 1:345. 1941.

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Fig. 3.—Scatter chart of weights of pituitary tumors from mice that had received estradiol benzoate beginning at ages 21 to 45 days and continuously thereafter until death.
43 mice—16.6 or 25.0 μg estradiol benzoate weekly
proportional to the amount of C57 chromatin that the animals carry (Table II). From 75 to 83 per cent of the male mice of the F1 generation acquired chromophobe adenomas of the pituitary subsequent to estrogen treatment at an average age of 480 to 513 days. Only 21 per cent of the animals derived by backcrossing the first generation hybrids to the CBA strain acquired pituitary tumors, whereas 63 per cent of the backcrosses to the C57 strain had chromophobe adenomas at death. The incidence of tumors in the latter group would be higher if corrections were made for age; the average survival of mice in this group was 419 days.

In summary it may be said that (a) chromophbic adenomas of the pituitary glands of mice develop when the proper animals received estrogenic hormones, (b) the tendency for the tumors is transmitted by both males and females to their hybrid offspring (Fig. 4), (c) the tumors produce little hormone of any type but do apparently produce some hormone, (d) simultaneous administration of androgens reduces the incidence of these tumors, (e) the tumors appear at an earlier age in estrogen-treated males than in females, (f) the tumors are transplantable in estrogen-treated mice, and (g) once the tumors become established they develop in the absence of the environment necessary for their inception or origin.

Do such observations prove that chromophbic adenomas that occur rarely in untreated mice and in man are attributable to an abnormal presence of estrogens? It would be rash to be dogmatic on this point. Nevertheless, there is no reason to believe that mice of one strain differ from mice of another strain any more than one person differs from another. One person but not another might acquire a pituitary tumor if subjected to prolonged treatment with estrogen. In man the pituitary gland of the female is larger than that in the male, it enlarges during pregnancy and its gonadotropic function decreases subsequent to estrogen treatment. In man the pituitary gland thus shows responses that resemble those of the mouse. Estrogens act on the pituitary gland much as thiourea acts on the thyroid in that they prevent or reduce the secretion of some, but not all, of the hormones that the hypophysis normally produces. Under such conditions the gland hypertrophies and in the pituitary adenomas form in animals of some strains.

**Interstitial-cell tumors of the testis** developed in estrogen-treated mice of two strains in our laboratory, the A and JK strains, but very rarely in mice of other strains when they are treated similarly (14, 19) (Fig. 5). There is no apparent tendency for untreated mice of any one strain to acquire interstitial cell tumors because the few “spontaneous” tumors that have been observed have occurred in mice of several strains (13). Interstitial cell tumors in estrogen-treated mice may appear in one testis or in both simultaneously. The testes bearing tumors are usually considerably enlarged, or even greatly enlarged, and yellowish or yellowish-brown in color. Metastatic growths are noted frequently in the iliac and in the perirenal nodes, less frequently in the lungs. Metastases occur only when the tumors become quite large.

The tumors produce androgen. The seminal vesicles of the host are often large and filled with secretion although the animals bearing them have received estrogen until the time of necropsy (19). In estrogen-treated mice without testicular tumors the seminal vesicles are usually small and atrophic as would be expected because the testes are small and atrophic and produce small or negligible amounts of androgen. (Estrogen does induce an increase in the fibromuscular tissue of the seminal vesicles and a squamous metaplasia of the epithelium of the coagulating gland and sometimes of the seminal vesicles.)

The tumors consist, for the greater part, of large cells not unlike normal Leydig cells (Fig. 6). These cells replace, with progressive development of the tumors, all of the normal constituents of the testes and extend through the tunica albuginea. In small areas of the tumors, or making up large proportions of the growths of a few tumors, are groups of small cells. Mitotic figures occur more frequently in the smaller and more hyperchromatic cells. Hooker and Pfeiffer (19) have studied this problem extensively, and consider that these cells are the primary hyperplastic elements of the tumor; that they differentiate in some tumors into typical large Leydig cells such as are found in most of the tumors.

The testes of estrogen-treated mice of those strains not susceptible to testicular tumors show marked atrophy of the seminiferous tubules; much as would occur subsequent to hypophysectomy (9). The Leydig cells are atrophic; the intertubular spaces are small and contain small groups of macrophages.

The damage to the seminiferous tubules in the estrogen-treated mice of the A strain is not as great as in mice of most strains (9). Estrogen has a qualitatively different effect upon the pituitaries of mice of this strain from that upon mice of strains in which testicular tumors do not appear. The inter-
Fig. 4.—Interpretative schema of hormonal and genetic influences in experimentally induced pituitary tumors. The tendency for chromophobe adenomas of the pituitary is transmitted by both male and female mice of the C57 strain to their F₁ offspring.
Fig. 5.—Interpretative schema of hormonal and genetic influences in experimentally induced tumors of testicular interstitial cells. It is assumed that estrogens cause greater production of gonadotrophin (luteinizing hormone) in animals of the A strain. (The possibility still exists, however, that the end organ, namely the testes, of the A strain may differ from those of other strains.) The tendency for these tumors is transmitted by both male and female mice of the A strain.
Interstitial cells of the testes of estrogen-treated mice first hypertrophy, are then depleted and are replaced by brown cells—macrophages. Subsequently local foci of hyperplasia of the interstitial elements occur, forming small, nodular tumors and finally the larger tumors. The sequences of progressive changes in interstitial elements of estrogen-treated mice of the A strain have been described in detail (19).

Not only is an altered balance of hormones necessary for the genesis of testicular tumors but it is also necessary for their growth subsequent to transplantation in a new host. The interstitial cell tumors of the testis grow when they are transplanted into mice of the same strain provided the hosts receive estrogen (15). They have not grown in untreated males and few will grow in untreated females. Fragments of the tissue may persist in the subcutaneous tissues for several months and can be found only upon the closest inspection. Histological study of these remnants reveal tissues that are scarcely identifiable and certainly not similar to that of the original grafts. If, however, after the transplant has remained dormant for a period of several months estrogen is administered, the grafts begin to grow. In fact, they grow as rapidly as does a second graft implanted into the same mouse at the time the administration of estrogen is begun. After the tumors have started to grow estrogen treatment may be discontinued and the tumors grow progressively (15).

If male or female mice of the A strain are hybridized with animals of strains not susceptible to testicular tumors, such tumors occur in the estrogen-treated hybrids. The tendency is transmitted by both males and females (Fig. 5).

If animals of the A strain are mated with animals of the C57 strain, the strain in which pituitary tumors develop, then both the pituitary tumors and testicular tumors may occur in the same animal (Fig. 7). They are not mutually incompatible.

How can these observations be explained? Do the estrogenic hormones act directly upon the testes as a carcinogenic hydrocarbon might act on skin, or is the tumorigenic action mediated indirectly? It is probable that the effects upon the testis are mediated through the pituitary (Figs. 5, 7). It has been known for several years that the injection of estrogenic hormone increases the production of luteinizing hormone (L.H.) in acute experiments—experiments of short duration (5, 22). It has been demonstrated that L.H. stimulates the interstitial cells of the testis and is identical to interstitial cell stimulating hormone. The interstitial cell tumors are assumed to arise in an environment of increased or continuous stimulation by intrinsic L.H., a stimulation induced in turn by prolonged exposure to estrogenic hormones, the latter, in these experiments of extrinsic origin. If this assumption is true it could be tested by subjecting susceptible animals to luteinizing hormone for prolonged periods. Such experiments have been undertaken but they are difficult to evaluate because the antigenic nature of most gonadotrophic preparations that have been used leads to the production of antihormones so that no more than indications of the correctness of this hypothesis can be obtained (30). The only known experimental means of inducing an animal to increase the production of its own luteinizing hormone is by the injection of estrogenic hormone and this quality may be particularly

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Fig. 6.—Photomicrograph of interstitial cell tumors of testis of a mouse of the A strain that had received 250 μgm. of stilbestrol weekly for 34 weeks, beginning at 36 days of age. This tumor consists of large and well differentiated cells. Similar tumors have appeared in mice of the A strain given equilin benzoate, estrone or estradiol and several esters of these substances, stilbestrol and triphenylethylene. Mag. X 220.
FIG. 7.—Interpretative schema of hormonal and genetic influences in hybrids obtained by crossing mice of the A and C57 strains.
pronounced in mice of the A strain. An endocrine environment of increased and prolonged exposure to L.H. is assumed to be responsible for testicular interstitial cell tumors in estrogen-treated mice of some strains. The possibility exists, however, that estrogens act directly upon the testis in inciting interstitial cell tumors.

Interstitial cell tumors rarely occur in man, but more frequently in horses and in dogs. It is of interest that the stallion excretes large amounts of estrogen.

Tumors of the adrenal cortex occur under conditions indicative of the etiological role of an endocrine imbalance. They were first described in castrated mice by Woolley (35), and in castrated guinea pigs by Spiegel (32). Mice castrated at birth, or in our experience up to two months of age (2), acquired, after many months, adrenal hyperplasias and, in mice of some strains, adrenal tumors. Dr. Woolley and his associates have shown that these tumors are prevented by the injection of gonadal hormones (38). In the absence of gonadal hormone the internal environment is proper for adrenal hyperplasia, and in some strains for the development of malignant growth in the adrenal cortex (Fig. 7). One might recall here the intimacy of the adrenal and gonadal tissues embryologically, their histogenic similarities and the chemical similarities of their secretions. It has been shown that some pituitary extracts induce the adrenals to produce the hormones that have androgenic activity (35). Although increases in adrenocorticotropic hormone subsequent to castration have not been demonstrated there may be more than one hypophyseal adrenocorticotropic substance. All that can be said for certain is that adrenal tumors occur in suitable mice in the absence of the usual source of gonadal hormones.

The adrenal cortical tumors differ histologically; some consist predominantly of small, hyperchromatic cells and others of cells with a more abundant cytoplasm that resemble the cells in the zona fasciculata of the normal gland. The tumors may become larger than the normal kidney, and metastatic growths have arisen from them (36, 37). Tumors of the adrenal cortex under such circum-

Fig. 8.—Schema of hormonal influences in the genesis of tumors of adrenal cortex (Wooley [35, 38]).
stances have grown subsequent to transplantation into other mice of the same strain.

The adrenal tumors in some animals produce estrogenic hormones. The mammary glands of the host, the vagina and uterus are stimulated (35). The tumors tend to replace the humoral deficiencies of the castrated host. Castrated animals with adrenal cortical tumors excrete in their urine and feces approximately four times as much estrogenic substance as do animals with intact ovaries (2). Woolley and his associates have found that adrenal cortical tumors in mice of some strains produced predominantly androgenic hormones, as judged by the effects upon accessory genital organs and other tissues of the host (37). Mice of some strains acquire adrenal cortical tumors more frequently than others subsequent to castration and the influences of genetic factors are being studied. A higher incidence of adrenal cortical tumors occurs in hybrid mice than in either of the parental stocks (31).

A marked hypertrophy of the adrenal gland also occurs in some mice receiving estrogenic hormones (17). The adrenal glands are enlarged 2 or 3 times, the cortex is disorganized, extends through the capsule and largely replaces the medulla. Excessive and continuous estrogen in the environment also is associated with abnormal proliferative changes of the adrenal glands.

Ovarian tumors have been associated recently with circumstances indicating the influence of hormonal imbalances on their origin. It has been known for many years that the pituitary glands of castrated male and female rats contain from three to six times as much gonadotropic activity as do the pituitaries of the intact rats (3, 4) (Fig. 9). In man prolact A increases subsequent to the menopause—a well known fact. The removal of the gonads increases the production of gonadotrophin, especially of follicle stimulating hormone (F.S.H.). In fact, prolact A (the gonadotropic substance in urine of post-menopausal women) has almost a specific follicle stimulating effect. From such data and from other experiments Moore and Price (26) based their theory of reciprocal gonad-hypophyseal relationship.

It has also been known for many years that estrogenic hormones administered intraperitoneally are less effective than when administered subcutaneously. Zondek (39) found that hepatic tissue of rodents could destroy estrogens in vitro. Others have found that, in rats, ovarian grafts placed in the mesentery do not stimulate the uterus and vagina of castrated hosts whereas the same ovaries removed and retransplanted subcutaneously induced vaginal cornification (18). Two years ago Biskind and Biskind (1) observed tumorous growths in intrasplenic grafts of ovarian tissue in three castrated rats and this problem has been studied extensively in mice (23, 24).

Many tumors of ovarian tissue—granulosa cell tumors and luteomas—have developed in intrasplenic transplants of ovaries in castrated male and female mice of all of the five strains that have been studied (24). In several instances these tumors metastasized to the liver and they have grown, subsequent to transplantation, in untreated hosts of the strain of origin in almost all instances in which attempts have been made to transplant them. They attain large size, over two centimeters in diameter, when they are permitted to grow (24). Many of the tumors produce estrogenic hormone because the uteri and mammary glands of their hosts are well developed and they show prolonged periods of vaginal epithelial cornification.

The tumors arising in the castrated male mice have been predominantly granulosa-cell tumors. The cells are small, arranged in follicular or trabecular patterns and only in a few instances have they shown a tendency to undergo luteinization. They are similar to the rare spontaneous granulosa cell tumors observed in mice and to the ovarian tumors that develop in x-rayed mice (6, 7). On
Fig. 10.—1 and 2: Interpretative schema of hormonal and metabolic influences on the genesis of granulosa cell tumors and luteomas in intrasplenic ovarian grafts. 3 and 4: In unilaterally gonadectomized males and females no tumors appear. In castrated males and females tumors appear.
the other hand, many of the tumors arising in the ovarian transplants in castrated female mice are either mixed granulosa-cell tumors and luteomas or luteomas. There is a sex difference in the predominant type of tumor arising under such conditions (23).

Intratesticular ovarian grafts in castrated mice and intrasplenic ovarian grafts into intact or unilaterally castrated mice failed to become tumors (Fig. 10). Only one of a large series of subcutaneous ovarian grafts in castrated hosts became tumors. Intrasplenic grafts with vascularized adhesions to the body wall did not become tumors and such animals did not become anestrous. Because the uteri and vaginas of mice with large tumors are not atrophic it is assumed that the liver is unable to destroy the hormones that the tumors produce or that the hormone produced is qualitatively of such a type as to be unchanged by the liver.

How can one account for these observations? It is thought that they afford an example of the tumorigenic action of specific pituitary growth-stimulating hormone, namely, the follicle-stimulating hormone. As mentioned previously the hormone content of the pituitary gland and the excreted gonadotropic hormones increase subsequent to castration, and the increase involves primarily the follicle-stimulating hormone. Ovaries transplanted into the spleen continually have their endocrine secretions inactivated by the liver before they reach the general circulation and, hence, before they reach the pituitary gland. The vaginal smears of such animals rarely show cornified cells characteristic of estrus. Under such circumstances the mouse has an ovary but at the same time it is physiologically castrated. The continuous stimulation of the ovary by an augmented and continuous follicle-stimulating-hormone leads to abnormal proliferation and neoplasia. Injections of estrogenic and androgenic hormones in mice bearing intrasplenic transplants both prevent ovarian tumorigenesis (24).

This is another excellent example of a tumor arising because of the creation of an abnormal endocrine environment. Furthermore it is possible that the same mechanism is effective in the genesis of ovarian tumors subsequent to x-irradiation. Under such circumstances the hormone-producing capacity of the ovary may be so impaired that the pituitary secretion cannot be kept under control. More experiments must be done before the various assumptions can be accepted as facts.

SUMMARY

Tumors of four endocrine glands arise under conditions of hormonal imbalances in experimental animals. The gonadotropic hormones of the pituitary, in part by experimentation and in part by assumption, have been associated with tumors of the testes and ovaries. Pituitary chromophobe adenomas develop in estrogen-treated mice of some strains but not in others and the tendency to acquire such tumors is transmitted by both male and female mice to their hybrid offspring. An environment deficient in gonadal hormones and high in gonadotropic hormone (F.S.H.) results in adrenal cortical tumors in mice of some strains and in hyperplastic growth of the adrenal cortex in mice of other strains.

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Hormonal Imbalances in Tumorigenesis

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