HORMONAL REGULATION OF TUMOR GROWTH

R. L. NOBLE

Collip Medical Research Laboratory, University of Western Ontario, London, Canada

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I. INTRODUCTION

A review on the hormonal regulation of tumor growth must not only consider hormonal action and endocrine relationships as they are related to carcinogenesis, but also refer to the therapeutic use of various hormone alterations in the treatment of cancer. The growth of many of the tumors of endocrine organs to be discussed apparently is controlled by the same hormonal influences that affect the tissues of their origin. To retain a conservatively sized bibliography references have been omitted to papers on hormone-induced carcinogenesis and to those concerned with generally accepted endocrine concepts. In many papers few or no observations have been made on hormonal influence on tumor growth but have been directed mainly towards the problem of carcinogenesis. As a result, a large volume of reports has accumulated on this subject and may be found in comprehensive reviews by Gardner (128, 129, 131) and others (175, 237, 253, 387a). In this paper, emphasis has been placed on the concept of hormone-dependent (conditioned, responsive) and independent (unresponsive, unconditioned, autonomous) tumors and the transition which takes place due to progression of certain characteristics of the tumor. The experimental evidence for this concept is first discussed as it pertains to primary tumors in animals and the influence on them of endogenous and exogenous hormones. The endogenous and exogenous effects of hormones on transplanted tumors are considered separately, since through progression even the initial transplant may show characteristics altered from those shown by the primary tumor. The effects of induced hormone-deficiency on tumor growth have been discussed separately. The adrenal steroids have been considered under a separate heading since, with the exception of the lymphoid tumors, they may affect various types of experimental cancer directly without any apparent endocrine rationale. In addition, they may affect certain functions of the host, giving rise indirectly to

an effect on tumor growth. The therapeutic use of adrenal steroids in human leukemia and lymphoid tumors is discussed. The remainder of the review considers the action of hormones and induced deficiencies on hormone-dependent tumors in humans. The responses have been compared with those in experimental animals, and a theoretical discussion on the mechanisms of action has been included to suggest possible implications and further lines of experimentation.

Concepts of carcinogenesis. An appreciation of the factors concerned with carcinogenesis and of the physiological action of hormones is essential in attempting to understand the influence of hormones on tumor growth, especially because many tumors go through various stages of responsiveness to hormones and respond like normal tissue at some stage in their history. The classical observations of Rous and his colleagues (358, 359) on the stages of carcinogenesis in rabbit skin following the application of tar, and of Berenblum and Shubik (19, 20, 21) and others (361, 390) on similar phases in mouse skin in response to carcinogenic hydrocarbons, have led to the concept of initiating agents and developing or promoting agents in carcinogenesis. Specific carcinogens initiate an irreversible change in cells, which determines the site and nature of the tumor, whereas developing or promoting agents, which by themselves may not cause tumors, determine the time of development and may be necessary for the continued growth of conditional tumors. The development of permanent, irreversible qualitative change in one or more of the characters of a tumor, or "tumor progression", has been emphasized in a review by Foulds (105). The different stages in tumors arising in endocrine organs or induced by hormones are not readily defined. The hormone may act both as the initiating and promoting agent, although in most cases the latter type of action seems predominant. Examples of a hormone acting as an initiating agent may be found in experiments where estrogen treatment of mice is followed by cancer of the breast or uterus months after injections have been stopped and after the initial organ hypertrophy has regressed. In many other examples, however, the hormone induces hypertrophy of the endorgan, which then undergoes tumorous growth during which time the hormone acts as the promoting agent. The ability of hormones to induce tumors is strongly conditioned by the genetic constitution of the animal. The genetic factor is so predominant in some strains of mice as to make them totally unresponsive to treatment which is followed by a high incidence of cancer in susceptible strains (see reviews 178a, 241). The nutritional status of the animal may also be influenced by hormones; this *per se* may be an important factor in altering some types of tumor growth (see review 414). The variations in the different characteristics which may be found in tumors of organs under the control of hormones make the use of the term malignant, in the clinical sense, of little value. Such a term, although of use in referring to certain associated clinical and pathological characteristics in human tumors, is too general in experimental tumor research (17a, 55). It is necessary to refer to the different characteristics of each tumor in order to assess its "malignancy". Certain tumors may grow rapidly, show invasion and metastases and a histological picture of high grade

malignancy, and yet their continued growth is conditional on a constant hormonal stimulus. Characteristics to indicate the stage of progression which must be noted in any tumor are the growth rate, its primary hormone-dependency and the transplantability into hormone-conditioned or unconditioned animals, and, to a lesser extent, its histological appearance and proneness to metastasize. The final stage in the progression of a tumor is shown by a continued growth independent of the initiating or promoting stimulus, a lack of influence by other hormones, and transplantability to unconditioned animals of the same strain and even to unrelated strains. This concept is of particular interest because it is probably applicable to the behavior of various tumors in animals and in man. It may be seen, therefore, that "malignancy" cannot be classed as a single character. The disproportionate or "out-of-step" development of the various characters which determine malignant behavior may account for many anomalies in the behavior of cancer in man, such as the "benign" tumors that metastasize and the "locally malignant" tumors that do not. Errors in prognosis of early tumors may be explained by the observations that progression is independent of the size or duration of a tumor and may occur in stationary tumors. A tumor may, therefore, be small in size and young in clinical duration, yet advanced in the progression of its aggressive characteristics. Progression in tumors when growth is inhibited by hormonal or other therapy could explain the ultimate failure of all therapeutic measures. A rational therapeutic approach in humans should include an attempt to determine such features even though such a differentiation cannot be accomplished by histological means. Only human tumors which are still in the conditioned stage of progression and are still susceptible to hormonal therapy offer any hope of being temporarily checked in growth by hormone administration or by the endocrine ablations which are practiced at present.

II. OBSERVATIONS ON ANIMALS

A. Endogenous hormonal action

1. On primary spontaneous tumors. Mammary tumors. A high incidence of tumors has been observed to occur spontaneously in the mammary glands and uterus of mice and rabbits of certain strains. The incidence showed a definite relationship to the sexual maturity or reproductive history of the animal, which has implicated sex hormones as the causative agents. In such cases, ablation experiments removing the source of the hormone, or the administration of antagonistic hormones, has reduced the frequency of tumor formation.

In early studies by Slye, Loeb, Baatz and others, stimulation or inhibition of tumor growth was noted to be associated with pregnancy (8a, 152a, 253a, 391a). More recently, the effects of repeated pregnancies on spontaneous mammary adenocarcinoma of mice have been closely observed by Foulds (104) in the development of his concept of progression of various characteristics of tumors. The behavior of the mammary tumors could be divided into two types: those "unresponsive tumors" which grew steadily without alteration by pregnancy and those "responsive tumors" which showed various effects. Some responsive

tumors reached a growth peak shortly before parturition and then regressed, but growth of the same magnitude recurred at the next and successive pregnancies. Others reached successively higher peaks at each pregnancy, the "intrinsic growth rate" remaining constant. Some tumors maintained the same type of behavior throughout the life span of the animal; others changed, often abruptly as a result of an irreversible qualitative change or "progression". Progression was noted to occur independently in different mammary tumors of the same animal, usually in only one tumor at a time irrespective of the size or duration of the tumor, and without apparent effect on the others. It occurred independently in different characteristics in the same tumor, so that responsiveness and intrinsic growth rate might not have changed simultaneously. Progression was independent of growth and could occur in latent tumor cells or in stationary tumors. Progression was continuous or discontinuous by gradual change or abrupt steps, and did not always reach its endpoint within the lifetime of the animal. Serial transplantation was necessary in such cases to extend the duration of observations, and it was suggested that ultimately every tumor would become unresponsive. In this concept of progression, pregnancy was not necessarily the sole or essential cause, as changes did take place during intermissions in breeding.

Foulds in his experiments was unable to detect any difference in the behavior of tumors in mice which were allowed to lactate from those in animals deprived of their young. Pseudo-pregnancy which followed mating with vasectomized males was not believed to induce quantitative changes in tumors comparable to those occurring during pregnancy. Similarly, as will be referred to later, replacement therapy with chorionic gonadotrophin or estrogens did not duplicate the effect of pregnancy. Gardner (129) has suggested that, since progesterone levels are high in the mouse during pregnancy, the effects on the tumors might be attributable to this hormone.

2. On primary tumors induced by hormone-imbalance. The artificial creation of an imbalance in hormone-equilibrium in animals has been accomplished by varied procedures. In most cases such hormonal alteration must be present until the time of origin of the tumor; correction of the imbalance by hormone injections may prevent tumor development and may be envisioned as a form of prophylaxis. Prolonged hormonal imbalance has been followed by various types of tumors in mice and rats, guinea-pigs and rabbits. These have developed in ovaries following transplantation to the spleen or mesentery, the ensuing steroid destruction by the liver resulting in excessive production of the appropriate pituitary gonadotrophin. Similarly, testes of rats when implanted to allow venous drainage into the portal system develop interstitial cell tumors. The development of adrenal cortical tumors in male and female mice of particular strains followed when gonadectomy was performed early in life. Such an operation resulted in aberrant estrogen or androgen production by the adrenal cortex and possibly an increased production of pituitary adrenocorticotrophin (ACTH).

Most of these studies have concerned the induction of certain types of tumors and few attempts have been made to determine whether the altered hormonal state was essential for the maintenance of growth of the primary tumors. Granulosa-cell tumors which developed in intrasplenic ovarian grafts in rats, however,

showed dependence on pituitary hormones for growth since regressive changes, but not complete disappearance, followed hypophysectomy (236a).

3. On transplanted tumors. a. Transplants from spontaneous tumors with a hormonal background. Many spontaneous or primary tumors which have been induced by a suitable hormonal environment have been transplanted and the effects of endogenous hormones noted on the growth of the transplants. In some cases the effect of pregnancy has been noted, but frequently the difference in susceptibility of males or females to successful transplantation has been used to demonstrate sex hormone dependency of a tumor. Although the characteristics of the transplant may initially reflect those of the parent tumor, the experimental procedure of transplantation may itself occasion a further progression of characteristics and so be misleading, as emphasized by Foulds (104). Certainly, in many cases serial transplantation has led to marked changes in character of the tumors, and ultimate hormonal independency.

Emge (84) has listed twenty-five papers published from 1894 to 1934 in which are discussed the effects of pregnancy on the growth of spontaneous or transplanted benign or malignant tumors in animals. In six reports growth was apparently stimulated, whereas in twelve it was inhibited, while in seven no change was observed.

Mammary adenocarcinoma. Foulds (102) transplanted spontaneous mammary adenocarcinoma of mice into genetically suited recipients and noted that these, like primary tumors, might show increased growth during pregnancy and partial regression after parturition. Progression after serial transplantation was also noted, so that a final hormone-unresponsive stage resulted. In general, it was noted (103) that on transplantation such tumors showed varied responses. Of 25 primary tumors, three did not take, seven grew in females or estrogenized males but not in normal males, fifteen grew with little difference in males or females, although four of these were slightly or inconstantly retarded in males. Repeated transfers often rapidly showed changes, so that an increased growth rate was recorded and the transplants took successfully in either sex. More detailed studies were reported later (104) when the characteristics, such as responsiveness to pregnancy, were obtained for the primary tumors before transplantation. From these experiments it was found that, in general, responsive tumors were transplantable only into female hosts, whereas unresponsive growth took place equally well in males or females, but the correlation was not perfect. Progression was noted in autotransplants, and became evident on serial transplantation.

Mammary fibroadenoma. Quite extensive studies have been reported on the growth-behavior of benign transplantable mammary adenomas and fibroadenomas in rats. Usually, these tumors arose spontaneously in female rats of one year or more in age, but the incidence was low (62, 348) except in special strains of animals (39). Associated signs of sex hormone-imbalance have implicated this as a possible causative factor (9, 39, 167, 278, 321, 360). Transplantation was usually accomplished quite readily, although latent periods from one month to one year before growth commenced have been reported. The percentage of successful takes from any tumor was variable and unpredictable. Heiman (164) observed some 3000 rats and found that the average number of takes was higher

in females (66%) than in males (33%). Grauer and Robinson (145) showed longer latent periods and a slower growth rate of transplanted tumors in male rats. Millar and Noble (272) found that transplantation in early generations could be accomplished only in female rats, but that this sex difference appeared to diminish in successive generations. It seems likely that, early in the life of such tumors, they are conditioned to the female sex hormone but rapidly become independent, the fibromas being less dependent than the fibroadenomas; so hormone-dependency may or may not be shown, depending on the stage of progression of the tumor (106). It is of considerable interest that such histologically benign tumors, composed chiefly of fibrous tissue, are under some hormonal control and show evidence of progression of certain characteristics.

As might be anticipated, the response of transplanted fibroadenomas to pregnancy was one of increased growth which ceased on parturition (but the variations in growth rate reported have been large) (84, 86, 89, 144, 169, 272). The stimulation of milk-production has been described (169), and in some cases no effects of pregnancy were noted (84). The response of earlier generations to pregnancy in contrast to later ones was suggestive of progression and loss of sensitivity to the hormones of pregnancy (272).

Eisen (82) has studied a transplantable mammary adenocarcinoma arising in the August strain of rats. Although this tumor was inhibited by administered estrogens, tumor growth and structure during pregnancy and lactation or after castration was unaffected.

b. Transplants from tumors of non-hormonal origin. Little pertinent data can be found where changes in endogenous hormone production have had direct effects on transplanted tumors from primary growths whose origin is not related to hormonal imbalance. There is suggestive evidence that pregnancy in experimental animals was reflected by a general slowing of tumor growth, but this may have been a reflection of a nutritional competition between the tumor and growing embryo, or possibly due to an increased secretion of adrenal steroids. Foulds has commented on this opposite effect of pregnancy on tumor growth in general, in contrast to his findings of growth-stimulation of mammary tumors during pregnancy. On the other hand, no effect on growth of the Walker tumor in rats was noted due to pregnancy, but postpartum growth was accelerated (443). Little effect of pregnancy has been observed in rats bearing a Murphy lymphosarcoma, a hepatoma, or the Walker tumor (324). Of three different sarcomas of rats two showed a significant retardation of growth during pregnancy, but only of the initial transplant, since the growth of recurring tumors was not affected (88). The Walker 256 tumor, when transplanted into an exteriorized uterine horn, did not grow as rapidly in sexually immature as in adult rats (186). Sarcoma 180, a tumor not influenced by cortisone, has been found, in albino Swiss mice, to show a high incidence of regression during pregnancy, and also following sterile mating (185).

B. Exogenous hormonal action

1. On primary spontaneous tumors. Because of the difficulty in obtaining adequate groups of animals bearing spontaneous tumors of comparable age and

size, little has been reported on the action of hormones on such tumors. Foulds (104), in his studies on progression in spontaneous mammary tumors in mice, attempted to duplicate by hormone injections the growth-stimulating action of pregnancy on individual tumors. Using regressed tumors, he was unable to induce a recurrence with chorionic gonadotrophin; he could detect only a doubtful action on incompletely regressed tumors. Similarly, treatment with estrone or stilbestrol pellets did not cause a growth effect comparable to that anticipated to occur with pregnancy. Neither progesterone alone or as combined therapy, nor anterior pituitary preparations were investigated. Haddow and Robinson observed slight inhibition with large doses, 8 mg daily, of estrone on the growth of a spontaneous mammary tumor (155).

Heiman (167) compared the actions of hormones on spontaneous fibroadenomas of the rat with auto- and homotransplants of the tumors. Although the effects on growth and morphology were essentially similar, in some cases the spontaneous tumors were less affected. Some transplants showed a stimulation in growth from the injection of 0.1–2.5 mg of estradiol benzoate, but large spontaneous tumors were not affected. Similarly, androgen treatment tended to slow the growth and affect particularly the epithelial elements of the tumor.

2. On primary tumors induced by hormone-imbalance. Pituitary. Chromaphobe adenomas of the anterior pituitary have been shown by various workers to develop as a result of prolonged estrogen stimulation. Nelson (313) noted in rats that such primary tumors regressed if the source of estrogen was removed, although in similar experiments in mice (127) the tumors were not found to regress. Deanesley (67) found in rats that, if estrogen therapy was stopped before adenoma-formation, tumors did not develop.

Primary pituitary adenomas may also be induced by radiothyroidectomy, or total or partial surgical thyroidectomy, or treatment with antithyroid drugs. Such tumors are held in check by the administration of desiccated thyroid, thyroxine or thyroid grafts, procedures which would all be expected to depress the excessive production of pituitary thyreotrophin occasioned by the induction process (114).

Thyroid. Adenoma of the thyroid follows treatment with antithyroid drugs, or prolonged iodine deficiency in rats and mice, both of which procedures cause thyroid hormone-deficiency and increased thyroid stimulating hormone (TSH) production by the anterior pituitary. Leblond *et al.* showed that of the two main types of tumors which developed in mice during iodine deficiency, most of the β type nodules regressed but did not disappear when iodine was administered; such treatment presumably permitted synthesis of the thyroid hormone and a resulting reduction in TSH output. Although the median volume decreased from 0.7 mm^3 in the group which were iodine-deficient for eighteen months to 0.08 mm^3 after iodine replacement, a few of the nodules were independent and showed no change in size or histological appearance. Another type, the α-nodules, also present in the thyroid, did not respond as did the β-nodules (8, 243). In some cases, tumors of the thyroid induced by the administration of antithyroid drugs showed partial regression after thyroid therapy or cessation of administration of

the goitrogen, but in other cases growth was unaffected, presumably because dependence on TSH had been lost (157, 343).

Mammary gland. The repeated injection or implantation of pellets of estrogens in female rats, particularly of some strains, has been followed by the appearance of multiple mammary tumors usually having the histological appearance of adenocarcinoma, although fibromata have also occurred. Metastases may occur, and autotransplantation has been demonstrated. In 1941, Noble and Collip reported that, when pellets of estrone were used to induce tumor-formation, the apparently malignant tumors, in each of four cases, completely regressed following surgical removal of the pellet. Similarly, in four animals, injections of 2.5 mg daily of progesterone caused a gradual regression in the tumor size (319). These observations were apparently the first direct demonstration of experimentally induced histologically malignant tumors which exhibited total hormonal dependence, so that disappearance of tumors followed removal of the hormone stimulus. In discussing these experiments it was stated: "These observations—that malignant changes may be induced by the stimulus of a chemically pure hormone, that a continuation of the stimulus is essential for the maintenance of these changes, and that tissue exhibiting malignant characteristics may readily return to normal—would appear to offer a wide field for speculation on the etiological factors suggested for malignant processes, and on some of the properties ascribed to malignant tissue."

Uterus. Uterine fibromyomas (the only type of uterine tumor showing hormonal influence) can be consistently produced in guinea-pigs following prolonged estrogen administration, or by estrogen implantation directly into the uterus. Lipschütz and collaborators, in extensive studies of such benign tumors, have found that the continued stimulus of the estrogen was essential for continued growth, and regression of the tumor followed cessation of treatment (250, 251). Pituitary gland secretion was not essential in the production of such tumors, since they could be induced in the hypophysectomized guinea-pig (434). Hormones antagonistic to estrogen readily affected such tumors. The most active compounds opposing the action of estrogen in producing or maintaining such tumors in decreasing order of activity were 19-norprogesterone, progesterone, desoxycorticosterone and testosterone (252, 265). Uterine fibromas occurred also in the hamster following combined treatment with stilbestrol and testosterone but not after either substance was given alone. Tumor regression rapidly followed cessation of treatment (229a).

Other organs. In the hamster, basal cell carcinoma occurred in the flank organs following androgen treatment. These tumors were hormone-dependent and growth stopped following cessation of therapy although viability remained (229a). Fibromas of the epididymis have also been produced in the hamster by continued treatment with estrogen plus androgen. Regression of the tumors followed withdrawal of therapy (229a).

3. On primary tumors induced by other means. Carcinogen-induced tumors. Few studies have been reported on the effects of hormones on the growth of primary tumors induced by carcinogens, and there is little published evidence of hormonal

dependency of such tumors. There are, however, a large number of reports of carcinogens inducing mammary tumors in mice and this action is apparently enhanced by estrogens (see 388a). Even the gastric instillation of methylcholanthrene in estrogen-treated mice resulted in mammary carcinoma and sarcoma (387). Similarly, carcinogens induced mammary tumors in mice in which the viral agent was absent, but the estrogen hormonal factor was necessary (71). Carcinogen pellets readily induced local mammary cancer in the IF strain of mice, but, following ovariectomy and replacement therapy with estrogens, no tumors could be produced (35). Additional therapy with progesterone, however, was followed by tumor-induction by the carcinogen (219). The ability of 9,10-dimethyl-1,2-benzanthracene to induce mammary carcinoma in rats was apparently abolished or delayed by hypophysectomy (323). Mammary adenocarcinoma in Sherman or Wistar rats was induced by 2-acetaminofluorene in hormone-treated animals. Although such tumors were not markedly responsive to estrogen, they showed a marked increase in growth rate and an increased incidence following progesterone treatment (0.5 mg three times a week) (46).

4. On transplanted tumors. a) Transplants from spontaneous tumors with a hormonal background. Mammary adenocarcinoma. Spontaneous mammary adenocarcinoma of mice of susceptible strains may be transplanted into genetically suited hosts and such transplants have been used to determine the effects of hormones. Initially, transplants were found to take only in female mice, and not at all or after a long latent period in males. In males treated with estrogen, transplants grew equally as well as in females. Such hormonal dependency was rapidly lost after one or two passages, and eventually an independent tumor was found (103). The final stage of hormonal independence was reached rapidly. Such transplants may be maintained and used for chemotherapeutic studies, *e.g.*, the RC carcinoma of DBA/2 mice (415).

Fibroadenoma. Spontaneous fibroadenomas of rats may readily be transplanted, and a number of workers have studied their response to hormones. Although most of the early reports were chiefly concerned with attempting to alter the morphology of these tumors by hormones, growth rates have also been noted. The effects described have varied and may have been influenced by a number of factors. The number of transplanted generations may modify the hormone-response, as may the age of the host and the morphological characteristics of the tumor. Estrogens have been found to shorten the latent period for growth in male and female rats and increase the number of takes in castrated males. Evidence of changes from fibromas to fibroadenomas or liposarcomas was noted by Heiman (165). The same author later demonstrated a marked growth stimulation by estradiol (0.1 to 2.5 mg estradiol benzoate daily) and also morphological changes in auto- and homotransplanted tumors (167). Growth stimulation has also been noted by other workers, particularly in early generations of a tumor line (279, 280, 451), in contrast to negative findings when older generations have been used (86, 87, 169, 300). Progesterone has been reported to exert an inhibiting action (only on the adenomatous portion of fibroadenomas) and this effect could be overcome by pregnancy or administration of estrogen (168)

(18 mg of progesterone inhibited the stimulation of 1 mg estradiol benzoate but not of 2.5 mg). Testosterone propionate was found by Heiman to reduce the growth rate of transplanted fibroadenomas and to increase the tendency towards the development of fibromas and sarcomas. Pregnancy or estrogen administration offset the inhibitory action of androgen (166, 167, 168). Mohs could not demonstrate an effect of testosterone on tumor growth rate in castrated male and female rats (279). Later, however, he reported changes in morphology (281). Extensive studies on a transplanted fibroadenoma have been reported by Millar and Noble. The transplants from an original spontaneous mammary tumor maintained the morphological picture of a fibroadenoma throughout some years of study. In agreement with similar reports, the tumors showed a slow growth rate, did not metastasize, and grew to an enormous size with little effect on the host. Of greater interest, however, was the response of the tumors to hormones and the altered response in growth through successive generations, but with little alteration in morphology. Nevertheless, under certain conditions, sarcomatous transformation occurred in a high percentage of cases (275, 385). Since transplantation initially was successful only in females, as might be anticipated, treatment with low doses of estrogens (stilbestrol 1 to 10 μg daily, or estradiol) allowed a normal growth-rate in male rats. In females, one third-generation transplant showed stimulation, but this effect was not apparent in later generations. Associated with increased growth was a shortened latent period. Larger doses of stilbestrol, 50–100 μg daily, administered orally or by injection from the time of implantation, resulted in an inhibition of tumor development in rats of both sexes. Similarly, when stilbestrol injections were initiated after tumor growth had commenced at a 200 μg dose level, tumor growth was arrested (273). A similar biphasic growth response has recently been noted by Huggins *et al.* (208a). Dietary restriction, sufficient to cause body growth depression in control animals equal to that caused by the estrogen, did not affect tumor growth (271, 275). Fibroadenomas which were inhibited by estrogen administration, or other procedures, showed a high incidence of malignant sarcomatous change. On the other hand, normal or accelerated growth rate of the fibroadenomas was always associated with benignancy. Progesterone, 5 mg daily, administered alone or with estrogen, did not affect tumor growth. Testosterone propionate, 1 mg daily, on prolonged administration showed some indication of an inhibitory action. Cortisone acetate, 5 mg daily, did not affect the growth or morphology of the transplanted fibroadenomatas. Various experiments were also conducted using pituitary preparations. Stimulation of tumor growth was noted in males, females, and ovariectomized females after injections of saline suspensions of beef anterior pituitary lobes (100 mg equivalent daily). This growth-action was not increased by stilbestrol. This extract contained growth hormone and prolactin, but little gonadotrophin. A preparation of prolactin from sheep pituitaries, with little or no growth hormone, stimulated tumor growth. Purified growth hormone (Armour Laboratories), 0.5 mg daily, did not increase tumor growth (273). An extension of the above studies was made on sarcomas originating from the benign tumors. Such sarcomas could be transplanted readily, showed rapid growth and metastasized. Of the hormones tested on the tumors, only the larger dose of

stilbestrol showed a significant growth-depressing action (in two of three tumor lines), but this was slight and was demonstrated only in early generations. (Dietary restriction caused no tumor growth retardation.) Anterior pituitary extracts had no effect on the fibrosarcomas. Apparently, with the altered growth characteristics associated with the transformation to a sarcoma, the hormonal susceptibilities of the original fibroadenomas were largely or completely lost (274, 280).

Eisen (82) has studied the action of estrogen on a transplanted mammary adenocarcinoma (R2426) in the August strain of rats. The tumor arose spontaneously and could be readily transplanted, but only into rats of the same strain. Tumor growth was slow and metastases occurred. There was no indication of dependency on sex hormones. However, the injection of 0.166 mg of estradiol benzoate twice weekly was followed by an inhibition but not total suppression of tumor growth. The inhibitory effect was shown in both male and female rats. Caloric restriction to control the slow body growth rate of the estrogenized animals also caused a marked slowing of tumor growth rate, but a direct effect of the estrogen could not be excluded. In other control experiments with more rapidly growing sarcomas, estrogen injections had no effect on tumor growth, although body weight was affected. Testosterone propionate injected at a dose level of 2 mg twice weekly did not affect growth or morphology of the transplanted adenocarcinoma.

b. Transplants of tumors induced by hormone-imbalance. A very extensive list is now available of tumors which have been induced by various means in organs under endocrine control. In most cases the hormonal change must be continued to allow the appearance and development of the neoplasm. In many instances the effects of hormonal lack or injections have been ascertained on the growth of the tumor (see 108, 129).

Pituitary tumors. Prolonged estrogenic stimulation has been followed in mice, rats, and hamsters with the development of chromaphobe adenomas, usually of the anterior lobe, except in the hamster where the intermediate lobe was consistently involved. Marked differences in susceptibility were found in certain strains of mice and rats. In mice, the adenomas were transplantable initially only into animals of the same strain which had received estrogen treatment, and grew after prolonged latent periods. Once they had become established they lost their hormonal dependency and could be transplanted into untreated animals (128, 129). In rats, similar findings have been reported but transplantation was accomplished only in estrogenized recipients (79). Spontaneous adenomas which developed in aged Yale strain rats could only be transplanted intraocularly and appeared to grow better in male rats, but the effect of estrogen was not determined (128). Chromaphobe adenomas induced by estrogen, when assayed for hormone-content in hypophysectomized mice (128) or rats (320), appeared to be essentially devoid of hormones normally present in the anterior pituitary, although these earlier assays would not have shown luteotrophin activity. Recent findings have indicated that luteotrophin may be produced by such adenomas (269a).

The most recent paper by Furth and collaborators (113) postulating that

estrogen-induced pituitary adenomas in rats are comparable to those which they induced in mice by body irradiation is of interest, as are many of the suggested endocrine implications. The primary rat tumors were transplantable, and grew after a prolonged latent period in estrogenized recipients, although occasional growth in normal hosts was encountered. Metastases were not found. In successive generations a decreasing latent period was found and autonomous sublines developed which were transplantable into normal female rats. These tumor transplants caused stimulation of mammary tissue and were termed mammotrophic tumors—this apparently occurred as well with the autonomous transplants where no exogenous hormone was administered, but in such cases the ovaries were stimulated. The dependent and autonomous tumors had distinct and different morphological features. Estrogen-dependent transplants were believed to produce growth hormone (GH) as well as mammotrophin. This observation is curious in view of assays on primary pituitary adenomas, previously referred to, which did not show activity, nor was there a suggestion of released GH as indicated by body weight changes (320, 321). Although the alterations which occurred in such transplanted pituitary adenomas could be interpreted as progression and loss of hormonal dependency, the authors believed that mutation-like changes caused the autonomous variants, and have suggested that human neoplasms may be similarly constituted.

Adenomas of the pituitary have also been produced in mice by procedures which induced a diminution of thyroid hormone, especially following destructive doses of I^{131}, after thyroidectomy, and occasionally after thiouracil treatment and thyroidectomy. Certain strains were more susceptible to adenoma formation. The C57 strain was particularly susceptible to this procedure and also to the effects of estrogen. The pituitary tumors could be grafted, but initially only into mice with decreased thyroid function, such as those which had received I^{131} (68, 111, 115); they usually metastasized. It is of interest that an apparent quantitative relationship existed between thyroid-depression and the growth of grafted pituitary tumors. The transplanted tumors did not grow in normal mice or in those treated with 25 μc of I^{131}. When moderate depression of thyroid function was induced by 75 μc of I^{131} the transplants grew after a prolonged latent period and at a slow rate. With complete destruction of the thyroid by 200 μc, growth was rapid (112). Conditioning of the recipient was also accomplished by thyroidectomy or antithyroid drug administration (69). The primary tumors and transplants produced readily demonstrable amounts of thyrotrophin (TSH) and probably gonadotrophin. Some sublines were established which became independent of hormonal influence and could therefore be transplanted into normal animals. Takes occurred, but after a prolonged latent period (115). It would seem likely that the continued growth of the dependent transplants was, like the induction of the primary tumor, dependent on a reduction of thyroid hormone and an increased production of TSH by the pituitary. Gasden and Furth (120) have actually shown that the administration of thyroid hormone prevented the growth of dependent tumors in radiothyroidectomized hosts but accelerated the growth of autonomous pituitary

tumors. The interesting synergistic effects of body irradiation and TSH in resistant strains of mice, and the possibility of involvement of pituitary ACTH as well as TSH in pituitary tumor-induction and growth, have been reviewed by Gorbman (140). However, Furth and collaborators (69) believed that disruption of the thyroid-pituitary feed-back mechanism was all that was required to initiate pituitary tumors.

Thyroid. Tumors of the thyroid have followed the prolonged administration of antithyroid drugs in rats and mice, and although such tumors showed only low grade histological evidence of malignancy, they have metastasized to the lung. The appearance of thyroid tumors was related to an increased production of TSH; grafted pituitary tumors producing excessive amounts of TSH have likewise caused thyroid tumors. Successful grafting of thyroid tumors could be accomplished initially only in animals whose thyroid function was blocked by antithyroid drugs or in thyroidectomized rats. After successive transplants, however, the tumors in mice lost their hormonal dependence and grew in normal animals (294, 295, 450). Transplanted thyroid tumors produced demonstrable thyroid hormone-production in their dependent and independent stages. Studies of I^{131} pickup showed that this was variable but was never equal to that of normal thyroid tissue (295, 450, see also 293). Apparently most thyroid tumors, like pituitary tumors, showed a progressive loss of hormonal dependency and when first transplanted into normal hosts grew slowly after long latent periods. Progression occurred after successive transplantations until rapid growth was manifest. Transplanted thyroid tumors, in the rat, also showed dependence on high TSH levels for continuous growth (24). The development of a subline of a rapidly growing tumor not dependent on TSH was believed by Purves *et al.* (344) to represent a mutation and a natural selection of faster growing cell-types which eventually replaced the benign type of cell, rather than a progression of characteristics. Apparently the primary thyroid tumors of the rat tended to remain hormone-dependent and only one of one hundred showed the described anaplastic transformation.

Ovarian tumors. Ovarian tumors have been produced in rats and mice (and guinea-pigs and rabbits) in approximately five to seven months, as the result of hormonal imbalance induced by transplantation of the ovary into tissue from which the venous return entered into the portal system. The liver consequently inactivated the estrogenic hormones. It was essential to use castrated animals so that tumor formation was related to an increased pituitary gonadotrophin, probably follicle-stimulating hormone (FSH). However, treatment with chorionic gonadotrophin, prolactin, or pregnant mare serum gonadotrophin (PMS) has been stated to increase the speed of tumor formation. Granulosa cell tumors and luteomas have followed ovarian transplantation. In mice, the tumors were transplantable into intact or castrate male or female hosts and have metastasized. They were predominantly hormone-independent, although transplantation became progressively more successful with succeeding generations. Transplanted tumors produced the various sex hormones (119, 129, 130, 147). In the rat, however, castration was necessary to allow successful trans-

plantation of granulosa cell tumors, or alternatively, transplantation into the spleen of castrated animals to allow inactivation by the liver of tumor-produced estrogens (337, 455). Although no clear-cut hormonal dependency of such tumors in mice has been demonstrated, in the rat estrogen-inactivation with presumably increased pituitary gonadotrophin was necessary for transplantation, and exogenous gonadotrophin injections facilitated growth (455). Transplantation into hypophysectomized animals, a situation where a direct dependency might be demonstrated, has not been described. Transplantation of granulosa cell tumors, occurring spontaneously in the AXC inbred strain of rats, has been accomplished in males and females. In gonadectomized animals of either sex, however, tumor growth was retarded. Replacement therapy with estradiol, progesterone, pregnandione, or testosterone caused an increased growth-rate (210). The behaviour of this spontaneous type of ovarian tumor appeared to differ markedly from those referred to above, which were induced by ovarian transplantation.

Uterine cervical tumors. Adenocarcinomas of the cervix have been induced by prolonged estrogen treatment in mice of most strains, and occasionally in other species (129). Such tumors showed no evidence of hormonal dependency.

Testicular tumors. Interstitial cell testicular tumors have followed prolonged estrogenic stimulation in certain strains of mice, and similar tumors have been induced in grafts of testicle made into the spleen of castrated rats (33, 36, 187, 388). These tumors metastasized and pituitary gonadotrophin, probably LH, was implicated in their origin. They have been found to secrete appreciable quantities of androgenic hormone (129). Transplantation of most tumors was initially successful in estrogenized hosts of the same strain or F1 hybrids (126), although one case has been reported where hormone treatment of the host was unnecessary (34). Although transplants into untreated hosts did not grow, they apparently remained dormant for prolonged periods and then could be activated by estrogen treatment (126). Gardner has also observed that, although estrogen treatment was necessary to initiate growth of the transplant, it could then be discontinued and still be followed by growth or persistence of the tumor, so that some hormonal dependence was apparently rapidly lost by the tumor cells. Transplanted tumors have been found not to regress following hypophysectomy (126). Jull (218) has described a testicular tumor, in which, after twenty-five generations, the latent period after transplantation was increased by estradiol and stilbestrol, but not by triphenylethylene or other artificial estrogens. The tumor showed a progression of characteristics in over two years of observation, becoming less susceptible to hormones.

Adrenal cortical tumors. Adrenal tumors have developed, following gonadectomy early in life, in certain strains of mice, rats, guinea-pigs and hamsters. Adenomas and carcinomas have been described in mice and could be transplanted, but were apparently not dependent growth (129). Some tumors produced estrogens or androgens. Although testosterone treatment prevented the occurrence of adrenal adenomas, cortisone in doses sufficient to suppress pituitary ACTH did not prevent the induction of adenomas following castration

(283). In the rat, some effects of pituitary inhibition were reflected by tumor growth retardation (191).

Kidney tumors. The production of malignant tumors of the kidney, in the male hamster following prolonged estrogenic stimulation, has been studied extensively by Horning and Kirkman. These tumors metastasized and have been transplanted in estrogenized hosts. Hormonal dependency has persisted for over three years in Horning's experiments, although a steadily decreasing latent period suggestive of tumor progression has been noted (180, 190). Kirkman, however, has obtained autonomous transplants after fourteen estrogen-dependent generations. He has also induced kidney tumors in castrated females or in intact females when treatment was started before sexual maturity. Progesterone was antagonistic to tumor induction and growth (229a, 230).

c. Transplants from tumors induced by other means. Observations on the induction of tumors of endocrine organs by methods other than those directly affecting the secretion of hormones, which are pertinent to the previous discussions, include the application of radiation and carcinogens.

Pituitary. The extensive studies of Furth and collaborators have produced a wealth of information concerning the secretion of hormones and tumor induction. Following total body ionizing irradiation, pituitary tumors secreting TSH, ACTH, growth hormone (GH), and mammotrophic hormone (MH) have been produced and the effects of transplantation described. Evidence of hormonal dependency, although not marked, has been noted in these studies, but it must be pointed out that the endocrine patterns involved in some cases were obviously complex and not readily explained on simple endocrine interrelationships (109, 110, 117). Transplanted mammotrophic tumors showed some hormonal dependency in that they exhibited a faster growth rate in normal females than in males, and this preferential growth continued in successive generations even though the latent period became shorter. Conversely, ovariectomy greatly reduced the tumor growth rate and treatment with estrogen then caused marked acceleration. Growth was retarded also in hypophysectomized animals.

Ovary. An impressive array of ovarian tumors has also been described by Furth and collaborators to follow relatively small doses of body irradiation in mice. Most of these different types of tumors have been transplanted and have produced various sex hormones. Although in some cases transplantation was more readily affected in male rats, there seemed little evidence of a hormonal factor influencing the growth of transplants of any of these tumors (11, 118).

Prostate. Glandular prostatic carcinomas in mice have been produced and studied extensively by Horning (188). Implantation of prostatic tissue impregnated with carcinogen resulted, within two to three months, in tumors in the implant. Transplants of the induced carcinomas in 20 male mice castrated before puberty grew initially, but then growth was affected in 13 animals. Of these, four completely regressed and nine showed a marked inhibition of growth. However, four of six affected tumors resumed growth when testosterone propionate (1 mg daily) was injected into the host. Conversely, the growth of transplanted squamous cell carcinoma (which also was induced) was not affected

by androgen. Stilbestrol pellets of 1 mg were implanted every two weeks in 50 mice bearing transplanted glandular carcinomas. Of these, 15 showed definite retardation of tumor growth and 23 a slight arrest in growth. The remainder were unaffected. There were no regressions. Squamous cell carcinoma transplants were only slightly affected (15 of 50 animals) by stilbestrol, and then after a delay of some weeks. Adenocarcinomas of the rat prostate have also been induced by implantation of carcinogen-crystals directly into the prostate gland; some of the tumors showed hormonal dependency (277).

d. Transplanted tumors. General. The response to hormones of many transplantable tumors has been reported. Such tumors have originated from various sources and in many different tissues. Those originating from endocrine organs have been maintained for such long periods by transplantation that hormonal dependency would hardly be expected to be present. Although various hormones have from time to time been reported to have some effect on certain transplanted tumors, there is little acceptable evidence of reproducible specific action of any hormone, with the exception of adrenal steroids, on tumors in general. Such literature will not be reviewed, but Dyer in 1949 listed some 270 references on this subject in compiling an index of tumor chemotherapy (80), and Sugiura and Benedict have also published an extensive survey (410). However, since some of the effects of sex and pituitary hormones are so striking on certain tumors in humans, as will be summarized later, it is perhaps pertinent, in contrast, to note some negative results in animals.

Mammary tumors. Estrogens. Negative findings were reported for stilbestrol treatment (pellets of 1.5 to 6.0 mg) on the growth of transplanted tumors in 163 mice (81 controls) of 4 strains by Ludford and Dmochowski. Using transplants, usually many generations removed from the original spontaneous tumor, of mammary carcinomas and sarcomas, no effect of the estrogen was noted on tumor growth, except a non-specific action when near-toxic doses caused undue body weight loss (258).

Androgens. Negative findings for testosterone (1.0 to 2.5 mg in oil daily) were reported on transplanted mammary carcinomas in mice by Nathanson and Andervont. No influence on tumor growth in a group of 20 animals was noted (20 controls) (308). Others have also reported negative findings (217a, 344a).

Pituitary hormones. Neither luteotrophin (LTH) nor growth hormone (GH) was found to have a direct action on transplanted mammary adenocarcinoma in C3H mice, although GH treatment prevented the weight loss and tumor inhibition caused by cortisol (400). In other experiments, prolonged administration of GH for 50 days after an initial stimulation caused some retardation of tumor growth (394), but LTH did not affect the growth of transplants (391). In early reports, gonadotrophin preparations were found to inhibit the growth of transplanted Ehrlich adenocarcinoma of the breast in mice (456).

Other tumors. Only occasional evidence for effects of the above hormones on transplanted tumors of non-mammary origin has been presented. Nathanson *et al.*, however, did show an inhibiting effect of estrone on transplanted sarcoma

180. This effect was found only in the C57 black strain of mice and was not apparent in the Bagg albino strain A (312, 362). In a recent paper Hamburger *et al.* (186), using sarcoma 180, have compared subcutaneous or intraperitoneal transplants with those placed in an exteriorized subcutaneous uterine horn of the same animal. In Swiss mice, it was found that the uterine tumors grow more rapidly than subcutaneous ones. Castration caused a moderate decrease in tumor size in the uterus, whereas progesterone or estradiol treatment caused increased tumor growth. The subcutaneous transplants, on the other hand, showed an inhibition of growth associated with castration, or treatment with 5 μg every second day of estradiol or progesterone, the latter substance being particularly effective. The interesting observation was also made that hormone therapy apparently protected the uterine wall from tumor infiltration, whereas castration made it more susceptible.

Reference has been made previously to fibrosarcomas which arise from benign mammary fibroadenomas in rats. Although the benign tumor may exhibit marked hormone dependency the sarcomas have been shown to be either not affected by hormones or to exhibit only slight growth inhibition following estrogen treatment (274, 280). The growth of the Walker tumor in the rat was found to be moderately affected by a synthetic artificial estrogen in experiments by Haddow and Robinson (154).

Growth hormone has not been found to affect the growth of induced lung metastases of a sarcoma in mice, although effects on the host were produced (445). Pituitary gonadotrophic hormone was not found to affect mouse sarcoma 180 (30, 235).

C. Effects of induced hormonal deficiency on tumor growth

The effects of hormone deficiency on tumor growth have been investigated under several different sets of circumstances, which result in different types of effects. In experiments where tumor dependence on certain endogenous hormones was manifested directly, removal of organs producing the involved hormone resulted in a failure or reduction of tumor growth. In other types of experiments, removal of endocrine organs resulted in a hormone-imbalance with a net increase in other hormones, particularly those of the pituitary gland and adrenals. Under such circumstances organ ablation, although removing the source of one hormone, paradoxically manifested itself in a stimulation of a dependent tumor, because of an indirectly increased hormone production. Finally, removal of the pituitary gland has been studied, not only from the point of view of causing secondary atrophy of endocrine organs, but also because of the possibility of removing a hormone acting directly on tumor growth, such as growth hormone. These three different types of response to the removal of hormonal influence will be discussed in more detail.

1. Induced primary hormonal deficiency. Direct hormonal dependence of a tumor implies its growth only in the presence of the hormone derived from exogenous or endogenous sources. In the previous parts of this review, examples of hormone-dependent tumors have been given and will not be recorded again

in detail. It may be noted that, as in the case of mammary adenocarcinomas in mice, the induction of such tumors was dependent on ovarian secretion, and ovariectomy abolished or greatly reduced the incidence of tumors. However, once the tumor was manifest, in most cases, it had developed independence and was not influenced by ovariectomy. The best examples of gonadectomy retarding the growth of tumors dependent on sex hormones have been studies using estrogen-dependent rat mammary fibroadenomas, and experimental prostatic adenocarcinomas dependent on androgens. A relative hormone-deficiency has also been produced by withdrawal of an administered hormone, on which the tumor was dependent, or by tumor transplantation into castrated hormone-deficient hosts. Such examples, previously described, included estrogen-induced pituitary adenomas in rats and mice, estrogen-induced uterine fibroids in the guinea-pig, and kidney tumors in the hamster. The induction of dependent rat mammary adenocarcinomas by implantation of estrone pellets was previously noted (319). Although these histologically malignant tumors occasionally metastasized and could be autotransplanted, they were entirely hormone-dependent. Following surgical removal of the pellet, the tumors rapidly regressed. Reinsertion of pellets was followed by a recommencement of the tumor growth in the same areas of the mammary glands..

2. Induced hormonal deficiency—secondary hormonal stimulation. Tumors which were hormone-dependent but were stimulated by hormone removal through a secondary stimulation of a different hormone have been best exemplified by transplanted thyroid tumors. These tumors were apparently dependent on an increased secretion of pituitary TSH for growth. Such conditions were accomplished experimentally by stimulating the production of the pituitary hormone by thyroid gland ablation or the administration of antithyroid drugs. A rather similar type of reaction has followed ovariectomy of mice of certain strains at a very young age. Instead of a lowered incidence of mammary tumor development in such animals, the paradoxical finding of an increased incidence was encountered. Excessive estrogen production by the adrenal cortex was associated with gonad-removal in such cases, and under these conditions actual tumor formation in the adrenal cortex has occurred.

A somewhat more complicated situation was present in experiments where castration was essential to allow tumor formation to take place in ovaries grafted into the spleen, or in testicular interstitial cells similarly grafted. In such cases tumor dependency, when present, was most probably related to an increased production of pituitary gonadotrophin. The presence of the normal sex hormone secretion by the gonads was sufficient to prevent the usual response of the pituitary, an increased secretion of gonadotrophin, to sex hormone deficiency.

3. Hypophysectomy. The effects of hypophysectomy, as a procedure to remove hormones on which a tumor shows simple dependency, have not been studied extensively. Of considerable interest, particularly from the point of view of the use of hypophysectomy as a therapeutic procedure in humans, is the effect on mammary tumors. Tumor formation in the mammary glands of mice of susceptible strains was prevented by early hypophysectomy, but then could not be

stimulated by hormonal therapy (234). This lack of effect, however, was not conclusive, since normal mammary development is a complex phenomenon controlled by pituitary secretion as well as steroid hormones (52, 316). The localized nodules of mammary tissue which appeared early in such strains of mice, however, did persist or in some cases grew after hypophysectomy (125). In rats with transplantable mammary fibroadenomas, studied by Huggins *et al.*, hypophysectomy allowed a slow but progressive growth. Estrone and progesterone combination therapy caused a moderate acceleration in growth rate, but with the additional treatment of growth hormone the growth rate was restored to normal. Luteotrophic hormone (prolactin) could not be substituted for growth hormone and none of the mentioned four hormones alone had any effect on tumor growth (208).

Effects of hypophysectomy include a cessation of body growth in older animals, a reduced food intake, and a lowering of metabolic processes. These general effects may influence the growth of tumors transplanted to hypophysectomized animals, but may be similar to the inhibiting action of simple caloric restriction (414). In earlier papers the inhibitory effect of hypophysectomy on the growth of transplanted tumors originating from non-endocrine organs was noted (12, 14, 255, 268, 352). Many have commented on the fact that some tumor growth progressed despite a decreasing body weight (107). McEuen and Thomson (268), in dietary controlled observations, believed such effects of hypophysectomy might be non-specific but the interpretation of their results has been questioned (13). However, more recent observations on force-fed hypophysectomized rats showed a reduction in growth of the Walker 256 to about 46% of the size of controls (413). The inhibitory effect of hypophysectomy on the growth of transplanted Walker rat tumor or sarcoma was not prevented by GH, PMS, or FSH, (85, 107, 269). However, in one report ACTH, TSH, and LTH were all believed to increase tumor growth rate (107). More recent interest in tumor growth in the hypophysectomized animal has followed the observation that tumor induction by methylcholanthrene was inhibited by hypophysectomy in rats (285, 286), and replacement therapy by crude pituitary extract or GH (but not by ACTH) allowed normal tumor growth (284). In addition, a series of reports from the same laboratory showed that prolonged treatment of rats with pituitary growth hormone gave rise to tumors in various organs (287, 289), but this did not occur in hypophysectomized animals (290). In comparable experiments in mice of strains A, C3H, and C57 black, growth hormone did not induce tumors (291). Although hypophysectomy in the rat, as shown by Griffin and collaborators (150), inhibited the appearance of tumors induced by acetylaminofluorene and aminofluorene, this result might have been related to effects on the metabolism of the dye. Administration of GH or ACTH partially restored the rate of carcinogenic action. No effect of pituitary removal was seen on established hepatomas (356). In the case of carcinogenic hydrocarbons the delay in the appearance of tumors after hypophysectomy represented a quantitative alteration in growth rate rather than any qualitative difference in response to carcinogens in the absence of pituitary hormones (4, 13, 136, 233, 284, 285, 323).

The transplantation experiments described in mice (116), where pituitary adenomas grew slowly in hypophysectomized recipients, probably represented a non-specific effect rather than the dependency of such tumors on pituitary hormones. The effects of GH and adrenal steroids on tumor growth and metabolism have been reviewed by Reid (351).

Effects of growth hormone. The observations on the carcinogenic action of prolonged treatment with growth hormone are of considerable interest, and it is possibly of significance from an endocrine point of view that mammary tumors were a frequent consequence. Unfortunately, these experiments did not include attempts to demonstrate whether the continued growth of the primary tumors or transplants was dependent on growth hormone administration. Although a highly purified growth hormone preparation was used in these experiments, the effects of trace impurities of other pituitary hormones and the development of antihormones must at least be considered as possible contributory factors to the tumorigenic action. Such effects have been demonstrated in rats but not in mice.

4. Adrenalectomy. The effects of adrenalectomy on tumors of lymphoid tissue will be discussed later. Removal of the adrenal glands has been reported to affect transplanted tumors, not of lymphoid tissue origin, in much the same fashion as does removal of the pituitary (217, 357, 443). Although several workers had noted a reduced growth rate of transplanted sarcomas and carcinomas in mice and rats concurrent with alteration in body growth following adrenalectomy (73, 107), Ingle and Baker (212) found a significant retardation of the growth rate of transplanted Walker 256 tumor even in force-fed adrenalectomized rats. The same effect was found by others in experiments where body growth was carefully controlled, the adrenalectomized animals having tumors 57% of the size of those found in control animals. Small replacement doses of cortisone or adrenal extract allowed an improved tumor growth to about 30% of the size of controls. A similar effect was noted in hypophysectomized rats (413).

Combined adrenalectomy and hypophysectomy had a greater restraining effect on tumor growth (30–50% of control size) than either operation alone; the total effects apparently were additive (413).

5. Tumor growth in diabetic animals. The reduced growth of transplanted tumors in animals with untreated diabetes (induced by alloxan or pancreatectomy) has been described, although whether such an effect was related to the lack of insulin or to secondary metabolic changes was not determined. Goranson has noted that rat sarcomas, transplanted (48) or induced (78) were not affected by alloxan diabetes. On the other hand, the growth of hepatomas in rats (138, 139, 363), or of Ehrlich ascites carcinoma in C57BL mice (216) was inhibited in animals made diabetic by alloxan, as was the growth of the Walker 256 carcinoma in rats following pancreatectomy (211), or after alloxan (107). Complete regression of established tumors was noted in 7 of 8 animals when alloxan was administered (138). This differential response of the growth of sarcomas and carcinomas in the diabetic animal, if substantiated, might suggest that different metabolic pathways occur in the two types of tumors.

III. EFFECT OF ADRENAL STEROIDS ON TUMOR GROWTH AND LEUKEMIA

1. In animals. The effects on tumor growth of endogenously stimulated or exogenously administered adrenal steroids have been considered under a separate heading since the actions appeared to be of a different category than those previously considered. In most cases, with the exception of lymphoid tumors, there is little evidence to suggest that excess or lack of adrenal steroids is directly implicated in experimental tumorigenesis, and there are no cases reported of tumors dependent on adrenal steroids. (Sex hormone production by the adrenal cortex will be discussed subsequently.) Nevertheless, the growth of many tumors can be inhibited by adrenal steroids. The possible mechanism of action of adrenal steroids is complex and cannot be discussed here (317). The steroids effective against against the growth of tumors and leukemia contain oxygen at C_{11}, and cortisone and cortisol have been extensively studied. Such compounds are secreted by the adrenal cortex after ACTH therapy. These hormones also represent the steroids which affect carbohydrate and protein metabolism and have an active anti-inflammatory action, and are used in the treatment of collagen diseases in humans. Other properties, which possibly may be associated with their effect on tumors, are inhibition of hyaluronidase activity, destructive effects on some blood cellular components, and suppression of antibody formation. The latter effect will be considered in connection with the use of cortisone to allow heterologous transplantation of tumors.

a. Thymus and lymphoid tumors. The thymus and lymph nodes appear to be under some physiological control of the adrenal cortex, adrenal insufficiency causing hypertrophy and excessive hormone secretion being followed by atrophy. The circulating blood lymphocytes and eosinophiles also are affected, a drop in the blood counts being caused by adrenal steroids. It was logical, therefore, to study the effects of adrenal steroids on tumors related to lymphoid tissue and white blood cells, such as lymphomas, lymphosarcomas, and lymphatic leukemia. Detailed studies have been recorded on many aspects of this problem and the interpretations are complex (see 222, 224). Some indications have suggested that adrenal hormones have an influence on tumor growth but are not of major importance from an etiological viewpoint. A few more direct findings may be summarized. Increased incidence was noted of lymphoid tumors arising in the thymus in certain strains of mice following estrogen treatment or irradiation, and the incidence of leukemia was likewise increased. Such tumors were transplantable. The incidence in some strains was considerably higher in females than in males, and exogenous estrogen treatment of males reduced the incidence as did testosterone in females. Androgens inhibited the lymphomagenic action of X-rays. Since both estrogens and irradiation caused thymus atrophy by an action through the adrenal cortex, this organ was implicated. Adrenalectomy increased the number of takes of transplanted lymphoid tumors (leukemia) in rats (408b) and was followed by an increased incidence of tumors in the C58 strain of mice (240), and also in irradiated C57 mice (223). Conversely, adrenal extract or cortisone was found to decrease the number of takes or incidence of lymphoid tumors (163, 223, 299, 448). Hypophysectomy did not inhibit the

induction of lymphomas by irradiation (302). A transplantable lymphoid tumor in chickens showed transitory growth inhibition after treatment with ACTH, or cortisol (239).

b. Experimental leukemia. Adrenal cortical extract, cortisone, and other adrenal steroids have been found to prolong the life of high leukemic AKR mice (242, 449), and of animals bearing transplantable leukemia (447). In some cases, survival was not influenced but a lowering of white blood cell counts was noted (43, 242). Mouse leukemia, resistant to aminopterin treatment, has been shown to respond to cortisone therapy (44).

c. Experimental tumors. General. The effects of ACTH and adrenal steroids on many types of spontaneous or transplanted tumors in mice, rats, and other species have been reported. Usually, large doses have been used and tumor growth inhibition has been observed. The effect of body weight loss, which occurs from the administration of adrenal steroids, has seldom been considered as a non-specific factor influencing tumor growth, since in most cases a direct action seems apparent. In mice, the growth of sarcoma 37 (70, 411), osteogenic sarcoma (404, 411), Crocker's sarcoma (76), lymphosarcoma (404, 411), rhabdomyosarcoma (179, 180), and spontaneous or transplanted mammary carcinoma (17, 142, 267, 400) was usually inhibited. Carcinogen-induced skin papillomas in mice regressed following the local injection of cortisone (90, 452). Other tumors were sometimes affected (404). Ehrlich's ascites tumor also responded to cortisone, or cortisol (409). Little or no effect has been reported on the growth of sarcoma 180, adenocarcinoma EO771, or Harding-Passey melanoma (411), and an ascites producing sarcoma (142). In rats, inhibition of growth of sarcoma R-39 (411), and lymphosarcoma (213) has been noted. Conflicting reports have appeared on Walker 256 (214, 411), and no effects were found on Flexner-Jobling carcinoma (411) or on the growth rate of the Novikoff hepatoma (181). A transplantable osteosarcoma responded to cortisol in adrenalectomized rats but not in intact animals (386). Negative effects on a mammary fibroadenoma have been referred to previously (273). A sarcoma in the hamster (59, 247) and malignant mast cell tumors in dogs (31, 38) have been reported as inhibited by cortisone. Experiments comparing the activity of various adrenal steroids may be found in the review by Stock (405).

d. Cortisone and metastases. Cortisone treatment of mice bearing mammary adenocarcinomas or sarcomas has been followed by the appearance of multiple metastases, an event not found in untreated controls. The primary tumor under these circumstances showed either growth inhibition (5, 282) or was not affected (17, 340). The metastases, on transplantation, were still retarded in growth by cortisone (5). These experiments could not be confirmed by others (221). It has been reported that cortisone inhibited the spontaneous production of lung metastases from a transplantable mammary adenocarcinoma in ZBC mice (266).

Recently, it has been found in mice (446) that under experimental conditions where cortisone and other adrenal steroids (and also growth hormone) increased the number of lung metastases from the intravenous injection of tumor cells, that this effect could be abolished by treatment with heparin or dicumarol.

Metastases from subcutaneous tumors in cortisol-treated animals were also reduced by heparin treatment. These results, which have important implications, would suggest that the action of adrenal steroids on the dissemination of metastases may be on the blood clotting mechanism rather than directly on tumor cells.

e. Cortisone and heterologous transplantation. Large doses of cortisone, or total body irradiation, is followed by a breakdown in immunity reactions, so that under favourable circumstances heterologous transplantation of some tumors may be accomplished. Human tumors have been successfully transplanted to rats and other species under such circumstances by Toolan and others (172, 182, 325, 424, 425). Heterologous transplantation of tumors from other species has also been reported (32, 146). Similarly, the resistance of alien strains of mice to certain tumors of mice of different strains has been markedly decreased by cortisone, which allowed successful transplantation and tumor growth (100, 192). This effect, however, was restricted to certain tumors and certain strains of mice, and was, therefore, not believed to be necessarily related to a general breakdown of natural barriers to tumor transplantation (99).

2. In humans. a. Lymphoid tumors and leukemia. The regressive changes in lymphoid tumors observed in animals suggested that when ACTH and cortisone became available for clinical study, the effects should be determined on tumors and leukemia of humans. In the original reports by Pearson and associates and Farber and collaborators, the striking regressions or remissions of acute leukemia, chronic lymphatic leukemia, and lymphosarcoma were emphasized (91, 92, 328, 330, 331, 401). In 51 of the initial cases of acute leukemia, discussed by Burchenal (40), there were 18 good responses in 35 children to ACTH or cortisone therapy, but only 5 of 16 adults responded. The remissions consisted in a return of the peripheral blood picture and marrow to approximately normal, and a return of liver and spleen and nodes to normal size. The remissions lasted for one to twelve weeks. In some cases the patient continued to feel well for some weeks after the bone marrow showed a relapse. Remissions to a second course of therapy occurred in 6 children, but larger doses of ACTH or cortisone were required. Occasionally, a third remission could be induced in children. In the adult, a second remission was rarely induced by therapy. The initial doses used were ACTH, 50–100 mg, four times daily, with double the dose for adults, although even larger doses have been used. Cortisone was given at a daily dose of 50–200 mg to children, and 200–400 mg to adults. Patients who become refractory to adrenal steroids were found to respond to other chemotherapeutic agents (229).

It now appears that in acute leukemia initial remissions have been reported in 70–75% of cases in children with acute granulocytic or acute lymphocytic leukemia. No response has been found with monocytic leukemia, and cortisone therapy may even be contraindicated (444). Remissions have lasted for three weeks to three months. The literature on 425 cases of acute leukemia has been reviewed (98) and other reviews may be noted (22, 42, 364), as well as confirmatory reports of the original observations (25, 245, 367, 396, 403).

Chronic lymphatic leukemia. Subjective and objective improvement has frequently been noted in patients with chronic lymphatic leukemia after cortisone therapy. Cases which showed an associated thrombopenia or hemolytic anaemia were particularly benefitted. Although total remissions were not encountered, palliation of the disease continued for two weeks to three months. Refractiveness did not occur as rapidly as was found in acute leukemia, so that effective responses could be elicited after three or more courses of treatment (41, 328, 330, 419).

Plasma cell myeloma. In some cases this condition has responded to cortisone therapy and was temporarily held in check by the administration of 50 mg daily (41, 328).

Lymphosarcoma. A shrinkage of tumor masses and general clinical improvement has been found to occur in many cases of lymphosarcoma after ACTH or cortisone therapy. Patients in the terminal stages of the disease, however, may die even when the objective signs of their disease may be improving. In some cases, apparently complete regression of tumor masses has been seen after 18 days of treatment, and remissions have continued for some months after cessation of therapy. In some cases, three or more courses of treatment have given satisfactory remissions (328, 419).

Hodgkin's disease. Cortisone, although resulting in subjective improvement in the treatment of Hodgkin's disease, has not been shown to be a reliable agent in inducing remissions (408). When these occurred their duration was very brief (246, 419).

b. Effects on other tumors. No measurable effect was observed during the administration of ACTH or cortisone to patients with chronic myelogenous leukemia or acute monocytic leukemia. Although some shrinkage of enlarged lymph glands sometimes occurred, no effect was found on the altered blood picture or other manifestations of the disease. The treatment did not alter the course of the disease process. Ewing's tumor, neuroblastoma, malignant melanoma, osteogenic sarcoma, rhabdomyosarcoma, synovial sarcoma, squamous cell carcinoma, and carcinoma of lung, pancreas, adrenal and liver likewise have not shown beneficial objective improvement, although striking subjective changes have been noted (198, 328, 329, 419). Nine patients with advanced cancer of various parts of the digestive tract were not benefitted by ACTH or cortisone, and they did not show any subjective improvement (341).

c. Side effects. Numerous side effects of prolonged ACTH or cortisone therapy have been described and in some cases these have been so serious as to necessitate cessation of therapy. These have been observed in cancer patients and have been summarized by Pearson and Eliel and others (328).

IV. HORMONAL ACTION ON TUMOR GROWTH IN HUMANS

Following a consideration of the effects of hormones on tumor growth in animals it is of interest to compare the results described with those obtained with tumors of humans. The behaviour of human tumors is also fundamentally important to the cancer investigator, since clear-cut examples of hormonal dependent tumors occur. Observations on humans have been divided into the

effects of endogenous hormones on tumor growth, the action of exogenously administered hormones which may exert an antagonistic hormonal action, and the effect of hormonal lack occasioned by removal of the hormone source. The literature on the beneficial actions of hormones, gonadectomy and adrenalectomy for mammary and prostatic cancer, has now reached considerable proportions. No attempt has been made to review it in *extenso*, but reference has been made to some of the earlier contributions and to later ones emphasizing certain aspects pertinent to this review. The value of hypophysectomy has been studied more recently, as has the use of certain hormone substitutes, so that only preliminary results have been reported.

It is curious that observations on the influence of hormones on human cancer preceded by many years any directly related experimental studies. Galton has made extensive reference to early clinical contributions on cancer affected by hormones (123), and some of his findings are of historical interest. White, in 1893, described ablation operations and observed regression of uterine fibroids after ovariectomy. During the next two years he, and also Hayden, observed relief of symptoms of prostatic hypertrophy in the male after castration. Beatson, in 1896, described beneficial effects in two cases of mammary cancer following ovariectomy, although Schinzinger, in 1889, had apparently suggested that such a procedure might be beneficial. A series of reports up to 1905 confirmed Beatson; they included quite extensive series of ovariectomized cancer patients, *e.g.*, Boyd 1900—54 cases; Thomson 1902—80 cases; Lett 1905—99 cases. At about this time the use of X-ray to induce an artificial menopause was utilized for the treatment of cancer of the breast. Finally, Huggins and his collaborators emphasized the value of castration for cancer of the prostate, and focussed serious attention on the treatment of hormone-dependent tumors in humans.

Of primary concern to this review are the effects of hormones on tumor growth. The types of tumors which are emphasized, therefore, are those showing a dependence on hormones for growth. It should be understood, however, that only some tumors show any alterations in growth attributable to hormone manipulation. The others, which cannot be differentiated by microscopic examination, apparently represent autonomous tumors. Whether they have passed through a dependent phase is speculative. In animals, small tumors as soon as discernable may already be unresponsive to hormones. It should be appreciated also that regression of the primary growth, or metastases of hormone-dependent tumors produced by hormone manipulation, is a transitory phenomenon. Ultimately, a state of autonomy is reached. During the course of the disease, additional forms of treatment, usually the removal of other sources of hormone production, may again be followed by a temporary remission, yet all such treatments remain only palliative, and cures are not accomplished (318).

A. Endogenous hormonal action

The effects of pregnancy on the growth of many forms of cancer in humans have been repeatedly noted. In a consideration of these reports it should be appreciated that age of the patients may be an important factor leading to

erroneous impressions. For example, tumors occurring during pregnancy are of necessity in a relatively young age group where malignant processes tend to be rapidly progressive. Comparison with a control group of an older age having tumors in the same organ would not be an adequate control. The increase in the growth of tumors of endocrine organs normally stimulated during pregnancy may be related primarily to the increased vascularity of the organ rather than to a specific hormonal action. Conversely, the increase in adrenal steroids in pregnancy may have a direct action on the tumor. The rapid growth and spread of a tumor following pregnancy may be related to the mechanical effects of surgical intervention rather than to a sudden drop in hormone production following parturition. From reviews of this field (84, 244) and published papers, the following data have been summarized.

Breast. The controversial problem of whether breast tumors in humans are found in association with a disturbed hormonal environment has been reviewed by Nathanson (305) and Shimkin (387b) and is beyond the scope of this paper. Most authors, however, have noted that both benign and malignant tumors of the breast showed an accelerated growth during pregnancy and that the effects were generally unfavourable to the survival of the patient (51, 393, 427, 436, 441, 442). Tumor growths were also accelerated after parturition (383, 417). Some fibroadenomas of the human breast showed a hormonal dependency. Changes in size and in histological appearance of such tumors have been noted during the menstrual cycle (215), and increased growth was encountered during pregnancy and lactation. Tumors have been found to recede following parturition but then may be stimulated by succeeding pregnancies (84, 135, 215, 228, 244, 292). These changes seemed comparable to those occurring in the surrounding normal breast tissue, although most authors believed that the tumor was more sensitive to hormones (135).

Uterus and cervix. Less agreement was found on the effects of pregnancy on cancer of the cervix. Earlier authors considered that pregnancy was detrimental to the patient and influenced cancer unfavourably. Later papers, however, presented more clear-cut evidence that there was no accelerated growth of the lesion which could be attributed to the hormonal changes in pregnancy. Actually, some authors were impressed with an apparently beneficial effect of pregnancy, particularly as it affected the results of surgery or radiation. A rapid increase of tumor growth has occurred following parturition (63, 84, 193, 393).

Uterine fibroids. Definite evidence has been presented that in some cases fibroid tumors of the uterus or mesentery enlarged rapidly during pregnancy and in many instances growth occurred. In such cases a rapid regression of the tumor took place during the period of involution of the uterus and sometimes was followed by its complete disappearance. During subsequent pregnancies tumor enlargement did or did not take place. Morphological changes due to pregnancy were not found (84). Some fibroids regressed at the menopause but in those cases with vascular adhesions to extrapelvic organs growth continued even though ovarian and uterine atrophy was present. This observation has suggested that the primary factor controlling the growth of this tumor may be vascular rather than hormonal (418).

Other tumors of the uterus. Only occasional reference has been found to the effects of pregnancy on sarcoma of the uterus, cancer of the vagina and chorion-epithelioma. These tumors were aggravated or activated (84).

Ovaries. Reports on cystomas, dermoid and Krukenberg tumors of the ovary have not indicated a specific influence of pregnancy on tumor growth. The occasional rapid increase in size encountered was probably due to mechanical factors (84).

Tumors of other organs. From only a few cases reported it has been suggested that pregnancy accelerated cancer of the gastro-intestinal tract, urethra and bladder, and pituitary tumors. No effect was noted on respiratory tract or brain tumors (84). No conclusive effect on 93 reported cases of Hodgkin's disease was observed (50, 160), and pregnancy was not found to exacerbate the disease (209). Pregnancy, apparently, did not consistently alter the course of some cases of acute or chronic leukemias, although acute exacerbation has been reported of chronic leukemia (6, 133, 389).

B. Exogenous hormonal action

Estrogens, androgens, and occasionally progesterone, have been used extensively in the therapy of human neoplasms. Such studies have also included various synthetic substances related to the natural hormone but with or without hormonal activity.

1. Cancer of the breast. a. Estrogens. Although from an endocrine viewpoint the use of estrogens to inhibit the growth of cancer of the mammary gland might appear paradoxical, the value of such treatment has been well established since the initial extensive report by Haddow *et al.* (156), and others (353). Of particular significance was the observation that such therapy was effective almost exclusively in the post-menopausal patient. In earlier papers, treatment with stilbestrol and other synthetic estrogens was followed by significant retardation of tumor growth in 30–40% of cases (27, 56, 81, 156), and more recent papers have indicated that such treatment was of particular value in post-menopausal patients with soft tissue lesions, or, rarely, with osseous lesions (304). In post-menopausal patients 60% showed subjective improvement and approximately 50% showed regression of the primary tumor; 40–45% exhibited regression of soft tissue metastases, and 33–40% of pulmonary lesions, but only 23–28% of osseous metastases were improved (2, 57, 310, 350, 406, 407, 422). The average duration of remissions was about eight months, and survival of nine to sixteenth months for many patients could be anticipated (307, 453). The effects of treatment in some cases was of shorter duration (174, 310, 372), and the age of the patient seemed an important factor. The longer the time which had elapsed since the menopause the more favourable was the response. All types of estrogen were active (375). The doses recommended by the Therapeutic Trials Committee (57) were as follows: diethylstilbestrol 15 mg daily; ethinyl estradiol 3 mg daily; premarin 30 mg daily; estradiol dipropionate 5 mg twice weekly; dienestrol 15 mg daily; diethylstilbestrol-dimethyl ether 30 mg daily. The results were better in patients who had received a total dose of 2.0 g or more. Smaller doses were partially effective (74). (For a review of the literature see 364.) The evidence has

suggested that estrogens in such cases were acting through an inhibitory action on the pituitary gland, which prevented the anticipated direct stimulatory effect on mammary tissue. Apparently, breast tumors in post-menopausal women were less sensitive to estrogen stimulation than those in younger women. The dose of estrogen employed was usually sufficient to affect pituitary function and to cause a decreased excretion of urinary gonadotrophin. Patients who showed a low gonadotrophic hormone excretion prior to treatment (pseudohypophysectomy type), showed a poor response to estrogen therapy (375). Views have been expressed on the values of massive estrogen doses, but these have been seldom used routinely (177, 178). An occasional patient who failed to respond to small doses has been found to react favourably to more massive ones.

Women of the pre-menopausal age group frequently showed an acceleration of tumor growth in response to estrogen administration. Kennedy and associates (307, 327), however, have found regression in this age group of patients who would tolerate massive, up to 1 g daily, doses of stilbestrol. It was suggested that with such doses one passed through the stimulatory phase, and eventually a failure of anterior pituitary function was produced. Such an inhibitory effect by estrogen on mammary tissue has been shown in animals by Gardner (124). The regression of cancer lesions following the cessation of estrogen therapy (or androgen therapy) has been noted frequently (74, 93, 375).

Male breast cancer. Mammary cancer in the male has also responded to estrogen therapy. Primary and secondary lesions of three cases of breast cancer in the male were reported to regress following treatment with 1 mg daily of ethinyl estradiol (303).

b. Androgens. In contrast to estrogens, androgens, since they were first used by Ulrich (431) and Loeser (256), have proven to be most useful as a form of therapy in breast cancer present in the pre-menopausal patient with osseous metastases. Soft tissue lesions have also responded. In this age group, tumors and metastases may be stimulated by estrogens and be dependent on them for continuous growth. Androgens might, because of their antagonistic action on estrogens, reduce estrogen activity. In addition, they would cause depression of the pituitary with a resulting fall in urinary FSH and LH, and an increased 17-ketosteroid secretion, as well as an increased excretion of prolactin (95, 310, 365, 372).

In general, following androgen therapy, some 15–30% of all patients showed objective improvement of primary lesions, although 80% experienced relief of pain. Regression of bone metastases occurred in 25% or more, but soft tissue lesions responded less frequently. Lung lesions regressed only in about 5% of cases. The duration of remissions averaged seven to eight months and lasted maximally one and one-half to two years (1, 2, 56, 57, 74, 96, 123, 173, 257, 306, 350, 378, 406, 422). Subjective improvement was often striking despite progressing lesions. A particular side effect associated with this form of therapy was hypercalcemia, which occurred in 10% of cases (149, 227, 301, 335). The healing of osteolytic lesions has been noted to take place at the same time as new osseous lesions appeared (374). Androgens have caused exacerbations of the disease in

some patients (332). Active compounds were virilizing; and virilization has become so marked that therapy has had to be discontinued (371). In studies of the effects of testosterone propionate, in doses from 25 mg to 200 mg three times weekly, little difference in effectiveness was noted (57). It was recommended that the dose should not exceed 150 to 300 mg a week, but the response was improved when the total dose was 3 g or more. Various related compounds have been examined by Segaloff and associates and others for their effectiveness on breast cancer. These have included dihydrotestosterone (androstanolone or stanolone) (134, 226, 382), androstanedion (376), androstenediol (383), methyltestosterone (381), vinyltestosterone (377) and methylandrostenediol (225, 379). The effects of these and other derivatives have been discussed in a recent review by Segaloff (372). The adrenal androgen, dehydroepiandrosterone, was not active. Active compounds were androgenic and virilizing and also caused a reduction of urinary gonadotrophin. Urinary prolactin, as well as 17-ketosteroids, were increased. The long-acting esters of testosterone did not show any superiority as therapeutic agents and had the disadvantage that it was not possible to terminate their action rapidly, in cases where this was desirable. The halogenated androgen fluoxymesterone (Halotestin) has been found to be at least as active therapeutically in cancer of the breast as testosterone when administered orally at a dose of 20 mg daily; it was also virilizing (226a).

In attempting to explain the mechanism of action of testosterone, it is of interest to note that ovariectomy is of benefit only to some 10 % of post-menopausal women with mammary cancer, so that an anti-estrogen action of androgens would not explain the number of such cases which benefit from androgen therapy, unless estrogens are produced by extra-ovarian sources. The conversion of androgen to estrogen in the body has been suggested to explain the exacerbations noted at times with androgen therapy, and possibly the occasional favourable response of soft tissue lesions (161, 307, 309, 310, 332, 422). It has been noted in this connection that in four patients both estrogens and androgens were found to cause an exacerbation and that in two ovariectomized, adrenalectomized patients estrogens were isolated from the urine after androgen administration (301). The observation that testosterone has induced a remission of breast cancer in the ovariectomized, adrenalectomized patient has suggested that in such a case inhibition of pituitary function was produced (see 350).

c. Progesterone. Progesterone therapy has been found to be of less value than that with other steroids. In one report only 2 of 20 cases of breast cancer were favourably influenced. The regressions were relatively minor and of short duration. Severe local reaction occurred with the doses used. One of the two cases had previously responded to testosterone (141). Others reported either no effect or a response in 3 of 13 patients treated with 100–300 mg three times a week, and some regressions lasted 2 to 6 months (350), (discussed by Escher 421). Urinary gonadotrophins were reduced (141).

d. Adrenal steroids. The possible mode of action of adrenal steroids on cases of breast cancer is complex. In experimental animals it has been shown that ACTH treatment led to an increase in progestogen in the adrenal gland (263), and also

in the blood of the ovariectomized rat (454). Stimulation of androgen production has also been described. Cortisone, by its depressing action on ACTH production, might be expected therefore to depress the secretion by the adrenal of sex steroids. It has been reported that therapeutic doses of cortisone in the ovariectomized patient reduced the level of urinary estrogen, presumably by suppressing the secretion of estrogen by the adrenals as a result of a reduced ACTH production (395). Conversely, ACTH has been found to augment the growth of breast tumors in three of four patients (419). Variable results, however, have been found in the treatment of breast cancer with cortisone. Some authors have used therapeutic doses—up to 75 mg daily—but others used 100–200 mg daily. It is possible that larger doses may act either directly on the tumor or by being converted into sex hormones. In more than half of 16 patients Meyer (270) obtained objective improvement, which lasted up to two years in some cases, and nearly all cases were benefitted subjectively even though low doses of cortisone were used. Lemon (246) also found 6 of 12 cases to benefit, but he used 100 mg daily as a maintenance dose. West *et al.* (440) found objective remissions in 9 of 21 women, but large doses of cortisone (300 mg orally) were required both to induce and to maintain the remission. Responses were obtained in estrogen-dependent or independent tumors, before or after ovariectomy and after adrenalectomy. The longest remission observed was three months. Others have obtained some objective improvement with cortisone but this was not as marked as that obtained by subsequent adrenalectomy (420). Segaloff *et al.* and other workers have failed to observe objective regressions, although striking subjective improvement was encountered (159, 373). Cortisone has been frequently used to alleviate undesirable subjective symptoms in the terminal stages of cancer. Synthetic compounds, such as prednisone (Meticorten) or prednisolone (Meticortelone), which have been stated to possess a similar and possibly superior ability to depress ACTH secretion, but to exert less effect on salt metabolism than cortisone, have been used by a number of workers in the treatment of breast cancer. Evidence of objective regression was encountered in some cases with 50 to 100 mg of prednisolone daily (232).

2. Prostatic cancer. a. Estrogens. Shortly after castration was found to be an effective treatment for cancer of the prostate and with the ready availability of orally acting, highly potent artificial synthetic estrogens (72), it was reported that estrogens would also alleviate the symptoms associated with prostatic cancer.

In 1941, Herrold reported results on twelve cases treated with stilbestrol (at a dose level of approximately 70 mg a month), in which regression or stabilization of the condition was associated with a dramatic and prompt relief of symptoms (see 297). Other similar findings were reported at this time, or shortly after (53, 54, 66, 77, 162, 220, 437). The associated changes in acid phosphatase of the blood serum (151) served as an important indication of therapeutic effectiveness (203, 305, 437). The dosage of the various estrogens used in the successful treatment of prostatic cancer is sufficient to depress the pituitary secretion of gonadotrophins. Stilbestrol also caused a fall in the urinary metabolites of both gonadal and adrenal origin in intact and castrated patients, presumably through a de-

pression of pituitary gonadotrophin and ACTH production (66, 370a). Daily dose levels of 10 mg stilbestrol or of 45 mg dienestrol gave similar results on prostatic cancer (355). The estrogen tri-p-anisylchloroethylene (TACE) has been reported effective in prostatic cancer even in patients resistant to other estrogens (49). No increased beneficial results have been noted when an estrogen-phosphate compound (ST 52-ASTA) was used in an attempt to allow acid phosphatase to free the estrogen directly in prostatic tissue (368), although others thought the compound was superior to other estrogens (47). An occasional case of prostatic cancer has been found to show an apparent exacerbation of tumor growth from estrogens (428).

b. Androgens. Since the normal function of androgens is to maintain growth and function of the secondary sex organs in the male, it might be expected that administered androgens would exacerbate dependent prostatic cancer. Huggins has reported that such activation occurred in a small number of cases tested (195, 203). In more recent studies on this problem it has been found that not all cases of prostatic tumor growth were affected by exogenous androgens, even though the levels of acid phosphatase in serum increased. In one report, only 5 of 22 patients showed increased symptoms following testosterone injections, although a rise in acid phosphatase occurred in nine (37, 350, 428). In some cases androgens actually caused a regression of the tumor and raised the interesting possibility that they were undergoing conversion to an estrogen (37, 326, 428).

c. Progesterone. On the basis of clinical and experimental observations that progesterone depressed the secretion of luteinizing hormone of the pituitary (7, 141), which in turn was responsible for maintaining androgen secretion by the testes, progesterone has been administered to patients with prostatic cancer. Of nine previously untreated cases, eight responded to doses of progesterone of 25 to 300 mg daily; one case refractory to treatment did not react favourably to subsequent castration. Of ten patients in relapse after castration or estrogen therapy, seven showed some improvement. Some of the cases were treated orally with anhydrohydroxyprogesterone (pregneninolone). In six cases pain was made worse by therapy, indicating that a critical dose-level was necessary for maximum effectiveness. Intolerance to repeated dosage was found (428, 429).

d. Adrenal steroids. Cortisone has been used to treat patients with cancer of the prostate when activation was believed to be due to the secretion of androgen by the adrenals. Although large doses of cortisone (300 mg) have resulted in an increased excretion of 17-ketosteroids in the urine (397), and conversion to androgens has occurred, as will be discussed later, daily doses of 50 to 75 mg caused a disappearance of androgen activity in the urine (28, 370a). Stimulation of pituitary gonadotrophin secretion, however, with small dose levels of cortisone does occur (276, 373, reviewed 322). Cortisone therefore has been used in the castrated patient to prevent androgen secretion by the adrenals. In five of twelve cases refractory to estrogen and castration, treatment with cortisone caused objective improvement (432, 433). Others reported that six of ten cases showed objective improvement but this lasted only an average of eighty-two days (276). Some observers have not noted improvement other than in subjective symptoms

in small numbers of cases (159, 198). Cases which showed improvement with this therapy might be expected to benefit from adrenalectomy (370a).

3. Tumors of other endocrine organs. a. Estrogens. Cervical carcinoma. Massive doses—200 to 500 mg daily—of stilbestrol were given to 27 cases of cancer of the cervix. Only subjective improvement and haemostasis with epithelialization of lesions was observed (315).

Chorionepithelioma. In one report estrogen was believed to have caused regressive changes in metastases associated with decreased urinary gonadotrophin (183).

Testicular tumors. Tumor growth was not found to be influenced by estrogen therapy (430).

Non-endocrine organ tumors. A wide variety of tumors of non-endocrine organs in thirty patients were not favourably affected by estrogen therapy although a bladder carcinoma showed some regression in size (156).

b. Androgens. Uterine fibroids. Greenblatt (148) observed objective improvement in five of seven women with large uterine fibroids following implantation of 100 mg pellets of testosterone propionate.

Ovarian, cervical, uterine, or vaginal cancer. A number of workers treated malignancy of the female reproductive organs by androgen therapy. Although an increase in body weight and subjective improvement were sometimes striking there were only occasional signs which suggested objective improvement of the cancerous process (152, 423, 435).

c. Progesterone. Uterine fibroids have been reported by Goodman (137) to show regressive changes following progesterone injections, 10 mg three times weekly, but these data have been criticized as not being based on objective measurements. Daily injections of 20 mg of progesterone did not produce any change in measured size of uterine fibromyomas in three cases (384).

Cervical carcinoma. Alterations in cancer of the cervix were noted after the injection of 250 mg of progesterone daily in 11 of 17 patients (176), but these changes were not considered to be significantly different from the normal variation (175a). Others (16) could not detect objective changes after intravenous injections of progesterone.

d. Thyroid carcinoma. Balme (15) reported a case of well differentiated carcinoma of the thyroid with pulmonary metastases which did not respond to treatment with radioiodine. However, treatment with thyroxine was followed by improvement. Lung metastases did not take up tracer doses of I^{131} following thyroxine treatment, suggesting that this tumor was TSH-dependent. Crile (60) also reported regression of metastatic thyroid cancer following treatment with dessicated thyroid, although the anaplastic highly malignant type of tumor did not respond.

C. Effects of induced hormonal deficiency

1. Gonadectomy. a. Prostatic cancer. Although the dependence of the human prostate on testicular function had been recognized for many years, and castration had been practised for prostatic hypertrophy or inflammation (reviewed by

Haddow 153), Huggins and collaborators first made extensive use of the operation for prostatic cancer. In the initial group of 45 cases, 31 showed a prolonged inhibition of the cancerous process lasting at least thirty months, 9 cases showed temporary improvement, and only 5 were unaffected (205, 206). Similar results were published shortly thereafter (412) and these observations were typical of the many confirmatory reports which followed (53, 184, 195, 196, 238, 346, 349, 354, 392). Successfully treated patients showed a rapid relief from pain, regression and healing of the primary and secondary lesions, and lowering of serum acid phosphatase; approximately 26 % of these patients survived five years, and up to 10 % continued for ten years (196, 203, 314). In many cases it took several years before growth of the tumor was renewed. Preliminary castration or hormone therapy was believed to give a better opportunity for surgical prostatectomy (370). Associated with castration an increased excretion of pituitary FSH was found but estrogen and androgen excretion diminished. The level of urinary 17-ketosteroids fell initially but then gradually rose to above pre-operative levels, which indicated an increased production of androgens, presumably by the adrenal cortex. Apparently, after castration, an enhanced adrenal response to ACTH was found, with an increased androgen production, so that stress might be considered as a possible factor causing reactivation of prostatic carcinoma (302, 305, 370a). Patients who responded initially to estrogens but then became refractory were again improved by castration. Various workers have believed that castration alone, estrogen alone, or a combined form of therapy was the most efficacious type of treatment of prostatic cancer. An analysis of cases from fourteen centres would appear relevant to this controversy. Of 115 patients treated with stilbestrol 18.3 % survived five years; of 359 castrated patients 26 % survived for the same period. The combined therapy for 113 cases resulted in 36.3 % survival. Of 504 untreated control cases, recorded up to 1940, only 9 % survived five years (314). Some centres have reported better survival figures, *e.g.*, 56 % of patients surviving five years, and 20 % ten years, after androgen-control therapy. The comparable control figures given for untreated cases were 11 % and 3 % respectively (402). From the survey of 1818 cases of prostatic cancer controlled by endocrine therapy, it was concluded that combined castration and estrogen therapy offered the best control in cases free of metastases. When metastases were present castration alone was significantly more effective than stilbestrol treatment, and the addition of estrogen to the treatment of this group of patients did not offer any advantage (314).

b. Breast cancer. After Beatson (18), in 1896, had observed beneficial effects of ovariectomy in 2 cases of breast cancer, Lett (248), in 1905, reported on 99 cases of inoperable breast cancer treated by ovariectomy. He found that of 75 premenopausal cases 41 % showed improvement and in 5 cases this was sustained for at least four years. Little effect, however, was noted in women past the age of 50. Despite such earlier observations, thirty years elapsed before serious attempts were again made to treat this form of cancer by removal of the ovaries, or by attempting to destroy their function by X-ray. It may be noted that irradiation of the ovaries in humans, as in animals, although preventing ovula-

tion and menstruation, may not suppress estrogen secretion comparable to ovariectomy (270, 311, 395). Dresser (75), in 1938, found that ovarian irradiation was beneficial in 30% of 57 patients with breast cancer. Others have found fewer cases to benefit (3, 93, 94, 366, 380, 416, review 123).

More recent observations have shown that ovariectomy in 77 pre-menopausal women with breast cancer was followed in 44% by objective remissions, whereas of 21 women past the menopause only 2 were improved (332, 350). The beneficial effects of ovariectomy, therefore, essentially concern the pre-menopausal patient. The most optimistic reports showed only 10 to 25% of post-menopausal cases to be favourably affected. It may be noted that, since estrogen may still be excreted well beyond the cessation of menstruation in the natural menopause, it is difficult to divide groups of patients accurately. Usually, five years of amenorrhoea has been considered necessary before placing a patient in the post-menopausal group, although some writers have preferred to set the age at sixty years. Segaloff *et al.* (380) reported 50% regressions in pre-menopause cases, and both the primary lesion and metastases were favourable affected by ovariectomy. Apparently there was no predilection for regression of soft tissues or osseous metastases. Radiation of the ovaries was found to be somewhat less effective on breast cancer, although such a procedure was followed by amenorrhea and an increase in urinary gonadotrophins, and an immediate decrease in urinary estrogens. Detectable estrogen, however, was present after ovariectomy (372) and has been found in above normal amounts in the urine of patients with breast cancer, after the menopause (395). The recent detection of, and observations on, a new estrogenic urinary metabolite have an important bearing on quantitative estrogen determinations (265a). The duration of regressions induced by ovariectomy was frequently prolonged, averaging nine months (332) and may extend to two years. Estrogenic hormone-dependence of breast cancers seems a major factor in successful treatment, since approximately 50% of such cases showed a renewed growth of the tumor after provocative treatment with estrogens. Progesterone was without effect. Reactivation of tumor growth, caused by the administration of small doses of estrogen, was not prevented by the simultaneous injection of large doses of testosterone (350, discussed by Pearson). Calcium excretion studies of pre-menopausal breast cancer patients suggested that the hormone-dependent patients who responded to ovariectomy exhibited a different pattern from those who did not respond to such an operation (335).

Male breast cancer. Castration for the treatment of cancer of the breast in the male has been followed in most cases, and particularly in older individuals, by a regression of the primary tumor and osseous metastases (3, 93, 94, 207, 426). These reports would suggest that cancer of the male breast was more frequently hormone-dependent than that of the female, and the response to hormone-deprivation was often more dramatic and prolonged.

2. Adrenalectomy. The eventual relapse after gonadectomy as a therapeutic procedure in the treatment of hormonal dependent prostatic and breast cancers, when considered with the increasing evidence that the adrenal cortex could produce both androgens and estrogens, suggested that the exacerbation might be

related to the liberation of steroid sex hormones from the adrenal. It seemed logical and justifiable, therefore, to study the effects of the additional operation of adrenalectomy in such patients. Huggins and Scott first made such studies and observed some benefit from adrenalectomy. However, total hormone-maintenance of the adrenalectomized patient was not practical until the advent of cortisone, so that extensive observations were not made until 1951. The possible occurrence of accessory adrenal tissue in 32% of individuals and the difficulty of complete removal during surgical adrenalectomy has been reported (143), and may account for failure of this form of therapy in some individuals. Another operative procedure has been attempted as an alternative to adrenalectomy. Following removal of one adrenal the venous drainage of the other was shunted through the portal circulation, or the adrenal was transplanted into the spleen. As a result, the liver destroyed both estrogens and androgens, causing a fall in urinary 17-ketosteroid and estrogen secretion. With such a procedure no supportive adrenal steroid therapy was necessary, and objective tumor regressions have been reported (45, 122).

a. Prostatic cancer. Huggins and Scott, in 1945, reported regressions of prostatic cancer following adrenalectomy in a patient during the period when life was maintained by desoxycorticosterone (204). Two years later, Cox also observed a temporary remission (58). In 1952, Huggins and Bergenstal published observations on seven patients in whom prostatic cancer had become refractory to antiandrogenic treatment. The patients were then adrenalectomized and maintained on cortisone. Two of these patients had a remission from their disease of six to twelve months, whereas 2 had no subjective or objective improvement (197, 198, 199). West and collaborators, in eleven similarly treated patients, observed transient subjective improvement in ten, but objective changes in the primary tumor were seen in only two cases (439). It would now appear that 20 to 30% of patients have shown objective improvement after bilateral adrenalectomy, and probably twice that number showed amelioration of pain (10, 159, 347, 420). The urinary 17-ketosteroids, although already at a low level due to castration, showed a further drop, and androgen levels were also reduced. Cortisone, but not glycyrhizin, when used as maintenance therapy, increased 17-ketosteroid excretion (194). Small amounts of estrogen and androgen, however, have continued to be excreted after adrenalectomy (158, 204, 298), although some workers reported a disappearance of androgen (28). The seriousness of the operation of adrenalectomy and the difficulty of subsequent maintenance (199), the number of patients showing improvement and the transitory nature of subjective and objective improvement, should be carefully considered before undertaking this form of therapy for the cancer patient. Primary adrenalectomy is not adequate to depress androgen production and will not affect prostatic cancer. In one case described by Huggins and collaborators, adrenalectomy did not affect the prostatic tumor, but when castration was performed one month later a typical remission was noted.

Which of the adrenal androgens may be implicated in hormonally dependent prostatic tumors is of considerable endocrinological interest. Since, as previously

noted, less than half of the number of patients who responded to castration showed an exacerbation following injections of testosterone, it is possible that some adrenal androgen is particularly active in reactivating tumor growth. It is of possible significance that both Nathanson and Bergenstal have mentioned a case of a castrated and adrenalectomized patient in whom the prostatic tumor was activated by injections of 100 mg daily of dehydroepiandrosterone (199, see discussion). Curiously enough, however, it has been shown that this substance may be converted to estrogens in the body, estrone and estriol having been identified (307).

b. Breast cancer. As in cancer of the prostate, adrenalectomy has been performed for breast cancer which escaped from treatment following ovariectomy or hormone administration. Again, the objective has been to remove production of steroid sex hormones by the adrenal cortex—in this case estrogens. In their initial report, Huggins and Bergenstal observed the effects of adrenalectomy on 6 patients with breast cancer. Of these, two were not improved, but three showed objective improvement lasting in two cases for more than thirteen months (198, 199). In a larger series of cases, Huggins and Dao noted major regression in 10 of 25 cases who were not menstruating and also in 10 of 25 pre-menopausal cases. In ten cases, urinary estrogens disappeared after adrenalectomy. In two male patients previously castrated, but with progressive breast and metastatic lesions, regression occurred in one case, while the other showed regression of a pulmonary lesion although a cerebral metastases progressed in growth (64, 200). Brain or liver metastases usually have indicated an unfavourable prognosis.

It would now appear that 40 to 45% of cases have shown objective improvement after adrenalectomy (26, 61, 64, 83, 121, 122, 170, 171, 335, 345, 420); the average duration of remission was nine months, but may continue up to three years. In a series of 136 patients, Cade (452) found excellent or good subjective improvement in 58%, and objective changes in 48% of cases. The important observation has been made that adrenalectomy was effective only in cases that had previously had objective regression following ovariectomy; 45% of 39 oöphorectomized cases had lesions which remained dependent on hormones formed in the adrenal and regressed following their removal (335, 350). Similarly, patients who responded to androgens also did so to adrenalectomy (122). However, these correlations were not always perfect (420); Huggins has commented on a case made worse by testosterone but which then responded favourably to adrenalectomy (199, see discussion). In post-menopausal women, however, where a poor response to ovariectomy is to be expected, combined ovariectomy and adrenalectomy, in 25 cases, was followed by remission in 16 cases, averaging in excess of eight months' duration (332). Such a procedure has been advocated in the older age group where adrenal estrogens presumably predominate and may be expected to yield objective remissions in 50% of cases (336). Estrogen excretion in the urine has been stated to be approximately double in ovariectomized women who showed a favourable response to adrenalectomy when compared with those who were non-responsive (201). Dao has noted the disappearance of estrogen after adrenalectomy (64). Huggins and Dao have commented on their observa-

tions that few women under forty years of age responded to adrenalectomy, and the most favourable results occurred in women between forty and sixty-five. Better results were obtained with slower growing tumors where the interval between mastectomy and recurrence was as long as five years. Certain morphological types of cancer were never found to respond to adrenalectomy (201). Following exacerbations after adrenalectomy, steroid therapy has been reinstituted but the effects, when present, were of brief duration. In some cases estrogens have precipitated marked hypercalcemia (420).

Male breast cancer. Cancer of the male breast recurring after castration, and estrogen therapy showed a prolonged regression after adrenalectomy (45a, 65, 200).

c. Cancer at other sites. Although there are only a few observations on the effects of adrenalectomy on cancer of organs not directly influenced by the endocrine system, there is little evidence to recommend it as a therapeutic procedure. Huggins and collaborators, in early studies, removed the adrenals from one case each of chorionic epithelioma, squamous carcinoma, melanosarcoma, gastric carcinoma, and lung carcinoma. Although survival was from one to two months postoperative, there was no indication that the tumors or metastases were influenced (198, 199). In two cases of ovarian cancer with widespread peritoneal metastases a marked remission followed adrenalectomy, but lasted for only three months (199, see discussion), while in another case the disease progressed (420). One case of melanosarcoma was unaffected by adrenalectomy (236).

d. Cortisone replacement therapy after adrenalectomy. Conversion to androgen. The maintenance of the adrenalectomized (or hypophysectomized) patient has necessitated the use of cortisone or other adrenal steroids as a form of replacement therapy, usually at a dose level of 25 to 60 mg daily. Although an increase of 17-ketosteroids has been found in the urine, it seemed of importance to determine whether there was an associated increase in androgen in the body which might exert a stimulating effect *per se* on androgen-dependent tumors. The report of Munson and associates (298) has a direct bearing on this question. In castrated adrenalectomized men who showed a very low (equivalent to 1 international unit daily) but constant urinary androgen level, the daily oral administration of 25 to 50 mg of cortisone did not cause any increased excretion. At a level of 100 mg daily some increase occurred, while with 300 mg the excretion of androgen amounted to 5 I.U. daily. Hydrocortisone at a dose level of 300 mg was followed by the excretion of 20 I.U. of androgen daily, but corticosterone had very little effect (297). It would appear from these observations that the usual maintenance dose of cortisone did not appreciably contribute to androgen production, and, in fact, Dorfman has been impressed by the absence of androgenic property of the metabolites recovered after cortisone or hydrocortisone administration (29, and 199, see discussion). It is of interest in the experiments of Munson *et al.* that hydrocortisone caused almost double the urinary 17-ketosteroid excretion as compared with cortisone, whereas corticosterone had much less effect (298).

e. Androgen conversion to estrogen. The possibility has been referred to previously

that the activation of breast cancer, when encountered following androgen treatment, may be due to an estrogen formed from the androgen. Also, it has been suggested that such a phenomenon might explain the occasional benefit derived from androgen therapy in post-menopausal patients with soft tissue lesions (309, 310). Recently, observations were made on two patients, previously ovariectomized and adrenalectomized, who did not excrete estrogens in the urine. Following treatment with testosterone propionate, however, estrone and estradiol were identified in the urine (301, 438).

3. Hypophysectomy. As the ultimate ablation procedure in the sequence of gonadectomy and adrenalectomy, hypophysectomy has been performed on cancer patients where the tumor has become reactivated despite other forms of therapy. From an endocrinological viewpoint complete hypophysectomy would insure a minimal secretion of sex hormones from normal gonads or adrenals or from aberrant tissue left after their surgical removal. In addition, hypophysectomy would remove hormones which may have a direct action on breast and prostate, and on tissue growth in general. Such treatment, therefore, might result in a deficiency of a different type of hormone on which the tumor was dependent for growth. It is not possible, at present, to state which hormones are involved, but there is ample evidence that hypophysectomy has resulted in remission of primary tumors and metastases, even though refractiveness had developed to all other forms of therapy. The operation from the patient's point of view, has been stated to be usually less distressing than adrenalectomy, and the postoperative hormonal maintenance has been found to be less critical. The major difficulty has been to ensure complete removal of the anterior lobe without inflicting damage to the optic nerves. The onset of diabetes insipidus has not been a serious complication, and could be minimized by not cauterizing or clipping the pituitary stalk at operation. The implantation of radioactive material, such as radon or yttrium 90, into the pituitary fossa has been attempted by several investigators (101, 327), but nerve damage has followed such a procedure. Interruption of the pituitary portal system by suturing a plastic film over the sella has been suggested as a method to prevent revascularization of pituitary remnants (327, see Matson and Hume). The pituitary gland has been found to be resistant to destruction by general radiation even when rotational cobalt-beam therapy has been used (74, 339). With special techniques such as cyclotron radiation, however, it has been possible to induce functional impairment of the gland, which has been followed by remission of hormone-dependent tumors (242a, 327).

a. Prostatic cancer. A favourable response to hypophysectomy by patients with prostatic cancer, who no longer benefitted from androgen depletion following castration or adrenalectomy, would indicate a direct dependency of tumor growth on pituitary hormones. Hypophysectomy would not be expected to reduce androgens under such conditions unless aberrant adrenal tissue had been left at surgery. The evidence of a direct action of pituitary hormones—luteotrophin, and possibly growth hormone—on the prostate, has been suggested in a few experimental studies. Prolactin labeled with I^{131} was found to be concen-

trated in the prostate of the rat (398, 399). Androgen stimulation of the prostate in the hypophysectomized rat was not of the same magnitude as was found in the castrated animal. A pituitary factor, probably luteotrophin, which augmented androgen action has been postulated (369, 383a, see also 199 discussion).

Hypophysectomy of patients with prostatic cancer has been reported to give effective results in a few cases. In these instances tumor growth had recommenced following castration. Of four patients one showed a remission lasting 15 months (259, 333, 334). At present it has been reported that 50% of the collected 16 cases have obtained objective improvement (261a). These results obtained on castrated, adrenalectomized patients would suggest a direct participation of pituitary hormones in the maintenance of growth of the prostate in humans.

b. Breast cancer. The rationale of hypophysectomy for dependent mammary carcinoma has been based on sound but complex experimental observations. As a definite over-simplification it may be stated that the growth of mammary tissue, in certain species at least, is controlled by the action of estrogen and progesterone. These hormones may fail to act in the absence of pituitary hormones, luteotrophin being necessary for some trophic action, but the addition of growth hormone is required for complete action. Adrenal secretion may participate in lieu of gonadal hormones (97, 316). Huggins and Dao have demonstrated luteotrophin action in cancer patients, and injections have been followed by milk secretion in elderly women despite an earlier ovariectomy. This was found in cases of mammary adenocarcinoma, but not in cases with undifferentiated breast tumors. Milk secretion was also observed in males following estrogen pretreatment and luteotrophin injections (202). Hypophysectomy might be expected to act on mammary tissue by three possible routes: (i) to reduce the output of sex steroids to a minimum, (ii) to remove two pituitary hormones which may affect the breast directly, and (iii) to render the breast tissue unresponsive to any sex hormone influence. It would seem, from the results to be discussed, that the first and second may be accomplished, although it is doubtful whether the last effect occurs in the human.

Although a few patients had been subjected to hypophysectomy for cancer or other diseases previously (333, review), Luft and Olivecrona, in 1953, reported detailed studies on cases of cancer of the breast. Since these patients were not previously adrenalectomized and some had intact ovaries, the mechanism of the response could not be analysed. However, remissions of the cancer process were induced in some cases (259–262). Pearson *et al.* observed tumor regression in two cases that had shown a reactivation of tumor growth after having previously responded to ovariectomy and adrenalectomy, so that a dependent action on pituitary hormones was suggested (334). To date, fifteen such cases have been studied and four or five have shown a remission (261a, 327a). In one patient in whom the tumor regressed after hypophysectomy, injections of pituitary growth hormone were followed by a negative calcium balance which increased until cessation of treatment. No exacerbation of symptoms was noted but it was believed that the results obtained indicated a stimulation of metastases (333). Recent studies have indicated that hypophysectomy resulted in as high as 50 to

60% remissions in cases of mammary cancer, possibly a greater number than has been found to benefit by ovariectomy alone. Many patients had not previously been subjected to ablation surgery, so the result of hypophysectomy reflected the effect of both a direct and an indirect removal of hormones. It has not yet been established whether hypophysectomy offers an improved prognosis and longer survival if performed initially, or in sequence to ovariectomy (and possibly adrenalectomy), but remissions have averaged about nine to fifteen months, and some cases have continued well for two years (23, 253, 327, 333). The results of hypophysectomy in 109 cases of female breast carcinoma have been the largest single study of this form of treatment reported, and may be summarized (327). About 50% of the suitable cases showed objective remission or arrest of the disease. Three of 6 pre-menopausal untreated patients showed an objective remission after hypophysectomy; of 16 patients previously ovariectomized 8 showed remission; of 11 patients previously ovariectomized and adrenalectomized 4 showed remission; of 34 post-menopausal patients 62% showed remission. In 36 cases with remission survival averaged 9.3 months with 21 still living, whereas of 31 cases with no remission survival was 4.4 months with 7 still living. To date, of 197 collected cases 56% have shown objective remissions (261a). Mammary cancer in a male, that had failed to respond to estrogens, castration, X-ray, or cortisone, showed a remission of 12 months after hypophysectomy. In this case growth hormone did not reactivate the tumor, but ACTH caused a transient stimulation of the tumor (333). Other cases in males which had shown a response to castration responded favourably to hypophysectomy, surviving over two years (261a, 327).

Any method to predict the response of a tumor to pituitary removal would be of extreme importance. It would appear, at present, that a previous remission following ovariectomy has indicated the cases which proved the most favourable for hypophysectomy. Four pre-menopausal women who failed to respond to ovariectomy also failed to respond to hypophysectomy (333). Estrogen treatment followed by exacerbation, or favourable response to androgen therapy has also indicated those cases which have responded to hypophysectomy. In the post-menopausal group of cases, even though there was only a low percentage who responded to ovariectomy, as many as 60% were favourably influenced by hypophysectomy. In such cases, the desirability of preliminary ovariectomy has been questioned (327). Certain morphological types of tumors have been suggested as not being amenable to treatment by hypophysectomy, and the presence of liver and brain metastases has been associated with poor survival. Similarly, patients over sixty-five years of age have not responded well (261a, 327). Detailed hormonal excretion studies on hypophysectomized patients have recently been published (148a). It has been found that small amounts of estrogen in some cases continued to be excreted in the urine. Since tumor reactivation may depend on such an estrogen, it would be of importance to determine its source. In the advent of persistent urinary estrogen in the ovariectomized-adrenalectomized (39a, 408a), and hypophysectomized individual, its origin is somewhat uncertain. However, it has been suggested that cortisone or other adrenal steroids, used as maintenance

therapy after hypophysectomy, may be in part converted in the body to an estrogen, although direct evidence is lacking (327). The suggestion that cortisone may stimulate pituitary remnants has also been made (338). There are sporadic reports that mammary tissue or tumors may themselves produce an estrogen (249, 342). Also, a possible dietary intake of estrogen should be considered, in view of the widespread distribution of estrogenic substances in nature, and in view of the general use of orally active estrogens in treating and preparing livestock and fowl for market. Estrogen activity in commercial rat food has been encountered experimentally (132).

c. Cancer at other sites. In a pateint where widespread metastases occurred after removal of an adrenal carcinoma, hypophysectomy failed to cause any remission of the disease. There was no depression of 17-ketosteroid output by cortisone before removal of the tumor, nor was the level altered by hypophysectomy (231). Since such adrenal tumors are not responsive to ACTH reduction induced by cortisone (in contra-distinction to adrenal hyperplasia), it is unlikely that they would be influenced by removal of the pituitary. Hypophysectomy has also been performed on six cases of choriocarcinoma (two of females), seven cases of malignant melanoma, one of thyroid carcinoma, one of reticulum cell sarcoma, and cases of ovarian carcinoma and hypernephroma. Where the results could be evaluated, no beneficial effect on tumor growth was noted (327, 333).

d. Reactivation of tumors by pituitary hormones. Studies on the experimental reactivation of tumors, in patients who have shown a beneficial response to hypophysectomy, are of considerable importance in determining on which hormones such tumors are dependent. Although results from such studies are still very preliminary and require confirmation on a larger number of cases, the following resume of the discussion at the recent symposium on hypophysectomy may be of interest. The best evidence concerned the treatment of a few cases of breast or prostatic cancer with pituitary growth hormone (GH). In some instances subjective signs of exacerbation of the disease and changes in calcium excretion usually associated with progression of tumor growth were noted. This was not found in gonadectomized patients and in one gonadectomized-adrenalectomized patient. The action of GH, therefore, appeared to be directly on the tumor rather than through a secondary action due to trophic stimulation from possible impurities. It is possible that a spontaneous exacerbation might have occurred at the time of treatment, but, in most cases, the subjective symptoms decreased on cessation of GH treatment. ACTH injections caused an exacerbation in one of two cases which had been castrated and hypophysectomized, but the liberation of sex hormones from the adrenal might be expected. Luteotrophin has been stated to have caused a possible reactivation in one hypophysectomized patient (327). Further experiments of this type on castrated, adrenalectomized, hypophysectomized patients may determine which pituitary hormones are directly implicated in breast and prostatic cancer, although the completeness of hypophysectomy and adrenalectomy in the cases studied should be verified at autopsy.

e. Order of therapy for cancer of the prostate or breast. Since many of the procedures which have been discussed cause temporary remissions of prostatic and

breast cancer, it is important to determine the best sequence of therapeutic procedures, although full discussion is beyond the scope of this review. Papers by Segaloff and Pearson *et al.* concerning breast cancer (332, 372) have indicated that there is not yet an accepted order of therapy. It should be appreciated that, since all the methods discussed are only palliative and their effect is transient, standard surgical and radiation therapy should be fully utilized initially in the hope of curing the disease. Further observations are required to determine the procedure best suited to produce the longest total duration of regression and health for the patient.

Prophylactic therapy. The so-called prophylactic use of steroids or organ removal at the time of surgical removal of the primary tumor has been defended by some workers but opposed by others (270, 372). The objective of such a procedure has been to delay the appearance of metastatic growths rather than to affect their growth once it had commenced. More extensive records of survival times are required to determine if this form of therapy has any merit over the application of hormone treatment commencing when secondary lesions appear.

Terminal therapy. Steroid hormone therapy has again been attempted when tumor regrowth occurred in the final stage of the disease, but any effects described have been of short duration. It is of some interest that no cases have yet been reported to respond to estrogen, but a number have shown brief regressions due to androgen therapy. Cortisone (or cortisol or Meticorten) must be used in the maintanance of hypophysectomized patients and, in addition, thyroid hormone has usually been given as replacement therapy. Terminally, however, subjective improvement may be effected by massive doses of cortisone.

V. GENERAL DISCUSSION

From a consideration of the response of hormone-dependent tumors in experimental animals and those in humans, it seems highly probable that some common underlying process exists. In animals, the hormonal pattern associated with tumor growth can be more readily ascertained and the influence appears simpler than in humans. It is useful to attempt to detect a reasonable hormonal basis for the behaviour of dependent tumors in humans in order to compare them with those in animals. Although endogenous hormone fluctuations, as they occur in pregnancy or at the menopause, may affect the growth of certain tumors, more exact data have been obtained from procedures where exogenous hormones were administered, or where endogenous hormone production was decreased by various surgical operations. It seems clear that gonadectomy in both sexes is usually followed by a reduction in the respective sex hormones, and that tumors dependent on these show an initial regression in growth. The pre-menopausal case might be expected to be more affected than the post-menopausal patient in which estrogen production is low. It is also apparent that the adrenal cortex produces both types of sex steroids, probably more in the post- than in the pre-menopausal woman, and that this adrenal activity is increased following gonadectomy. In view of the secondary production of sex steroids, the response to adrenalectomy can be attributed to a reduction in sex hormones. Observations on

steroid excretion in the urine, before and after the operative procedures described, have been compatible with the results observed on tumor growth. Hypophysectomy, when used as a primary operation, would reduce the sex hormone output of the gonads and adrenals to low levels and, in this way, would indirectly influence hormone-dependent tumors. In addition, the removal of pituitary hormones having a direct effect on tumor growth is apparent in cases which respond to hypophysectomy after previous gonadectomy and adrenalectomy. The possibility must be considered, however, that such cases may have aberrant adrenal tissue which is affected by pituitary removal. Tumor growth may be slowed due to the general systemic effects of hypophysectomy, as has been demonstrated in animals. However, little evidence has been presented in humans that tumors of organs other than the breast and prostate have responded to hypophysectomy. The recurrence of tumor growth after hypophysectomy may be related to various causes. Pituitary remnants may have been left at operation. Estrogens, from unknown endogenous or exogenous sources, have been shown to be present, or the tumor may have lost its dependency on sex or pituitary hormones. The sequence of responses shown by many tumors to a series of ablation procedures removing sources of hormones points strongly to hormonal participation in the growth of such tumors. When it has been attempted to reduce the function of endocrine organs, such as the ovaries or pituitary, by radiation therapy, the results have not been as satisfactory as following surgical removal of the organ.

The response of some tumors to hormonal therapy may also be rationalized. The regression of prostatic cancer after estrogen therapy results from a suppression of pituitary gonadotrophin and secondary depression of androgen production by the testes. Possibly a direct hormone antagonism may occur (since combined estrogen-castration therapy is more successful than castration alone, in some cases). The response of post-menopausal patients with cancer of the breast to estrogens can also be explained on the basis of a suppression of pituitary hormones, provided such tumors are more responsive to pituitary hormones than they are to estrogens. Conversely, in the pre-menopausal group, breast tumors appear more sensitive to estrogens and may be stimulated by therapeutic doses. There is some indication, however, in those patients that massive doses of estrogen may inhibit tumor growth, presumably related to pituitary inhibition. Recent interest in the actions of estrogens has concerned their possible direct action on cellular mitosis (194a), their direct effects on cellular enzymes (296), and their competitive antagonistic action to other hormones (435a). Androgen treatment of pre-menopausal cases might act by antagonizing estrogen action successfully, as well as by reducing pituitary gonadotrophin. The results would indicate that androgen therapy has been most effective in the pre-menopausal patient. The predilection of certain hormones to affect metastases, of either the osseous or soft tissues, is not readily explicable. The paradoxical occurrence of exacerbation instead of inhibition, or the regression of soft tissue lesions after androgens may be explained by the conversion of appreciable amounts of androgen to

estrogen in some individuals. The results obtained from cortisone treatment of cancer of the prostate and breast may be related to a number of actions. Cortisone in therapeutic doses has been shown to reduce estrogen and androgen production by the adrenal; it causes a reduction in ACTH secretion by the pituitary which, through its action on the adrenal cortex, may stimulate the release of androgens and progesterone; it may affect tumors in animals directly. Cortisone in larger doses has been found to be converted in the body to androgen, which may, in turn, possibly end as an estrogen. The effects of cortisone, therefore, are related to the dosage employed. Its use as maintenance therapy after adrenalectomy or hypophysectomy is probably not associated with an appreciable conversion to sex steroids. Progesterone therapy has been shown to be of little value although it may cause some depression of pituitary function, and objective changes in a small percentage of tumors. Injection may be followed by severe local reactions.

Studies on the exacerbations of tumor growth which may be provoked by hormone administration are not numerous, but are important in attempting to determine hormone dependency, and, possibly, for selecting cases for ablation operations. If the injection of a hormone induces an exacerbation, it is strongly suggestive that removal of the endogenous source of the same hormone will be followed by tumor regression. Similarly, a tumor which has shown hormone dependence and which has responded to an initial ablation operation, or has shown a good response to an antagonistic hormone, has usually been found to respond to a subsequent ablation procedure. However, the rather unexpected findings have been reported that exacerbations cannot be induced by estrogen or androgen in all patients who have hormonally dependent breast or prostatic tumors. The explanation of this observation is not apparent, unless the dosage or duration of treatment were at fault, or unless some tumors show a stage in progression where, even though they are hormone-dependent, hormone stimulation becomes ineffective. It would be of interest to know whether, at the time when tumor regrowth occurred in cases which did not show a stimulation by hormones the tumor was still dependent for growth on sex hormones, as indicated by a second ablation procedure. The question may be raised of whether or not a tumor could be stimulated by only a particular androgen. Most evidence has ndicated that the effects of any compound have been related to its physiological activity rather than to its chemical structure, but more studies of this nature are required. That dehydroepiandrosterone treatment may aggravate prostatic cancer and, yet, not be effective in mammary cancer has been noted. The experimental transplanted testicular tumor described by Jull, which was inhibited by treatment with estradiol and stilbestrol, but not be triphenylethylene, is of interest in view of the clinical report that TACE may induce remissions in prostatic cancer which is resistant to other synthetic estrogens. The preliminary findings, that breast tumors in hypophysectomized patients will respond to pituitary growth hormone, strongly suggest that such tumors may be dependent not only on sex hormones, but also on pituitary secretion. Frequent observations, that tumor regression may occur after the termination of steroid therapy,

suggest that such lesions were dependent on the particular hormone during injections. On the cessation of treatment, a relative hormone-deficiency follows and caused tumor regression. The occasional example of a human thyroid tumor regressing in response to thyroid administration is suggestive that such tumors showed a dependency on pituitary thyrotrophic hormone, as has been noted in experimental thyroid tumors. Tumors of other organs, such as the uterus and gonads, which, on the basis of the accepted endocrine control of the tissue counterparts, might be expected to exhibit hormonal dependency, have unfortunately rarely shown any favourable influence due to hormone manipulation.

The response of human tumors described above can be most logically explained by the concept of initial hormone dependence, and progression to an ultimately unresponsive growth. Even the unusual, apparently paradoxical, clinical findings may be explained on a fairly rational endocrinological basis, although one must assume in some cases chemical conversion of hormones and indirect actions on the anterior pituitary. Such assumptions, however, seem reasonable on the basis of observations in animals and humans, even though they are not proven. In addition, the studies in experimental animals, which have been reviewed, indicate clearly that both spontaneous and transplanted tumors may exhibit marked hormonal dependency, and in certain cases a striking parallelism exists with corresponding tumors of humans. Primary mammary tumors occurring spontaneously in mice, or those induced by estrogen in rats, show typical sex hormone dependence for continued growth, whether the hormone be secreted during pregnancy or come from an exogenous source. The mouse tumors observed by Foulds showed progression through all stages of hormonal dependency. Induced prostatic carcinoma in mice also showed a characteristic growth pattern affected by sex hormones in a way corresponding closely to the progress of the disease in humans. Similarly, tumors of the pituitary, thyroid, or gonads showed hormonal dependency, but this was frequently followed by a rapid progression to autonomous growths. On the other hand, in contrast to human tumors, some growths in animals may continue to remain entirely hormone-dependent, such as rat mammary carcinoma, or tumors of the hamster kidney. Factors which influence the rate of progression of such tumors are of great practical importance, but are little understood. If tumors remained hormone-responsive, as they may during the life span of an experimental animal, a cure following complete hormone removal might then be expected. Unfortunately, in the human, all tumors apparently show progression to an ultimate autonomous stage, and little has been accomplished in studying means of preventing or even reversing such progression. It is of interest, however, that metastases of thyroid carcinoma in man that do not pick up I^{131} can by suitable treatment in some cases be made functional so that they actively take up iodine. Such an example suggests that progression in the metastases can be made to revert, so that a hormone-forming tumor ensues. A more complete understanding of the process of progression is essential before any further major progress can be made in cancer therapy by hormone manipulation. The development of tumor refractiveness to hormonal therapy is curiously reminiscent of the resistance which develops in leukaemic cells to chemothera-

peutic agents, and in bacteria to antibiotics. In tumors, hormone responsiveness may be lost gradually or occur suddenly, as exhibited by mammary carcinoma in mice, by thyroid adenoma in rats, and by pituitary tumors. Various workers share the view that, in such cases, a mutation results in autonomous tumor cells with a more rapid growth rate, so that these cells develop preferentially. On the other hand, many animal tumors show a very slow and gradual progression to hormone independency, and it is difficult to envision them initially composed of a mixed population of cells with different growth potentials. In humans, it might be argued that, if tumor cells are originally either hormone-sensitive or hormone-insensitive, one would not expect the rather constant finding that approximately half of all breast cases when first treated will not respond to hormones, whereas in prostatic tumors almost 90% are responsive. Furthermore, since some tumors, when initially examined are composed entirely of non-responsive cells, it might be anticipated that some tumors would also be encountered of entirely responsive cells. In the latter case cures by hormonal manipulation would be expected and should have been reported. Many writers have envisioned some cellular adaptive mechanism to take place rather than actual mutation. In such a cirsumstance endocrine organ tumor-cells are initially envisioned as requiring, like the tissue of their origin, a particular hormone for growth. Under hormone stimulation, however, they exhibit an increased growth over their normal-cell counterparts. Following a regression due to removal of the hormone, not all cells die but some may alter their metabolic requirement so that growth can eventually proceed without the hormones. Similarly, even with progressive growth certain cells may develop an altered metabolic pathway so that a hormone is not essential for growth. Local cellular regression or atrophy preceding the development of malignancy has been referred to frequently in the literature, and gross or microscopic atrophy of a tumor or cells may be a preliminary step to the development of a cancerous growth. Such changes have been particularly emphasized in studies of the prostate of humans, the mammary glands of mice, and mammary tumors in rats. In the last case it was observed that, provided the growth of a fibroadenoma of the breast was maintained by suitable hormonal therapy, it assured benignancy, but any procedure which checked tumor growth was followed by progression, so that sarcomatous transformations took place.

From the therapeutic point of view there can be no question of the place of gonadectomy and hormonal therapy in the treatment of cancer of the breast and the prostate. The use of adrenalectomy and hypophysectomy, although allowing a further respite for the patient, should at present be confined to large institutions where these forms of therapy can be studied. Much information may still be obtained from patients treated in such a manner, so that, ultimately, the most beneficial therapeutic rationale can be established. The use of adrenal steroids in certain forms of leukemia is well established in the clinic and is in harmony with observations in animals. Again, the development of refractoriness to treatment limits the value of this therapy. Whether such ultimate resistance to treatment occurs from a progression of characteristics of the tumor cell or is related to some other mechanism remains to be solved. The information now available from all

the observations which have been reviewed indicates that the influence of hormones on tumor growth offers as challenging a field to the investigator, and one with as much hope of reward as any other in cancer research.

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