Control of Cancers of Man by Endocrinologic Methods

CHARLES HUGGINS

(Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Ill.)

In certain patients it is clinically possible to induce a profound regression of widely disseminated cancer even in the terminal stages of the disease by modification of the hormonal status of the host. These witherings of extensive cancer in multiple loci are accompanied *pari passu* by clinical improvement which lasts for more than a decade in favorable cases, the neoplasm remaining in an atrophic condition or having been destroyed—in whole or in part. Prolonged or worth-while relief has been rendered thereby to many people. It is now certain that steroid hormones are of great significance in the maintenance of three neoplasms. The problem is far from solved, however; many patients do not respond to attempts at hormonal control, and in others the relief is of short duration. It would appear that the control of cancer by steroid modifications is in its incipience—only a crack has developed in the façade of cancer.

The purposes of this communication are to present some of the methods of control and to indicate the theoretical considerations which led to the conception of these modes of treatment as indicated by the discoverers.

The control of cancers, to be designated, by hormonal means rests on two principles (15, 27) of medicine. (*a*) Cancer is not necessarily autonomous and intrinsically self-perpetuating. Some neoplasms retain sufficient characteristics of the normal cells from which they arose that the tumor cells function like the tissue of origin. When the original cells are dependent upon hormonal support for metabolic activity at a high rate, its cancers can be similarly dependent, and these atrophy when hormonal support is withdrawn by any of a number of means; these cancers are by definition dependent tumors. When normal cells concentrate chemical substances selectively, their neoplasms can have the same property; this explains the carcinocidal action of I^{131} on certain thyroid cancers. (*b*) The second principle is that disease (here cancer) can be sustained and propagated by hormonal function that is not abnormal in kind or exaggerated in rate but which is operating at normal or even subnormal levels. It is now appreciated that trace amounts of hormones can drive cancer to such exuberant growth that it causes the death of the host.

CANCER OF THE PROSTATE

Prostatic cancer is a common disease of the elderly human male; its natural course has been well established. In the study of Bumpus (3) there were 485 patients who received no form of treatment. The average duration of the disease from first symptoms to death was about 31 months; four patients lived more than 3 years, and two of them more than 10 years. When metastases had occurred at the time of examination, two-thirds of the patients were dead within 9 months. In the study of Nesbit and Plumb (40) there were 260 patients with metastasis at the time of diagnosis. The average survival following diagnosis in this untreated group was 16.9 months, while the median survival time was 9.6 months; the extremes were 1 month and 176 months.

The endocrine treatment of prostatic carcinoma consists of anti-androgenic measures. This idea arose from physiologic studies of the prostate.

The function of the prostatic glands is external secretion, and a method (23) was devised to obtain and to measure the output of the prostatic glands in dogs over a period of years. It was found that the secretion of the prostate of healthy dogs often remains relatively constant, varying only slightly in its amount over many months. This constancy indicated that during these periods the pituitary-testis-target complex remains in a steady chemical state. Orchiectomy abolishes the prostatic secretion; the prostate undergoes atrophy.

The prostatic secretion of dogs is eliminated also by the administration of phenolic estrogens (18); here, too, the prostate shrinks in size. The

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suppression of prostatic function is due to manifold actions of phenolic estrogens. Among these, estrogens cause metaplasia in the prostatic epithelial cells. Furthermore, the production of gonadotrophin is depressed. The simultaneous administration of gonadotrophin (13) and phenolic estrogens preserves the prostatic secretion, although the output is reduced in amount. In dogs in which the prostatic output has been abolished by orchiectomy or by the injection of estrogenic substances, the administration of testosterone or related compounds restores the secretion to normal, both in quantity and in quality.

The next observation in the development of therapy for human cancer was the effect of anti-androgenic measures on cystic hyperplasia of the canine prostate. In the dog, as in man, neoplasms of the prostate develop in senility with great frequency. These tumors were found (18) to shrink profoundly after orchiectomy or the administration of estrogenic substances, whereas testosterone restored their size and accelerated their growth.

These findings in the dog proved to be pertinent to the human. Translated to man with prostatic carcinoma, they turned out to be directly applicable *en bloc* and permitted the introduction of anti-androgenic therapy in clinical practice. The treatment was not empirical; it had an experimental basis. Both orchiectomy and phenolic estrogens (21, 27) were effective in controlling cancer of the prostate in certain cases, while, conversely, the administration of testosterone intensified the growth of the neoplasm. Historically, the synthetic compound diethylstilbestrol was the first agent of known chemical constitution, aside from radium, to ameliorate carcinomatosis. These observations happened to be the beginning of chemotherapy of cancer.

The method of proof of a proposition can be of greater interest than that which is proved. The effects of the administration or withdrawal of steroids on human prostatic cancer were first proved by a systematic study of enzymes in the serum of patients with advanced cancer of the prostate. The proof concerned acid and alkaline phosphatases. Cancer of the prostate metastasizes to bone marrow and lymph nodes *inter alia;* in the bone it commonly causes osteoblastic metastases. Kay (31) discovered that the alkaline phosphatase content of serum was increased in the presence of increased osteoblastic activity accompanying some metastatic neoplasms; this explains the increase of alkaline phosphatase in prostatic cancer which has invaded the skeleton. Kutscher and Wolbergs (32) discovered that acid phosphatase was present in human prostatic epithelium in large amounts; that finding was confirmed and extended to include prostatic cancer by Gutman, Sproul, and Gutman (8). Moreover, in the serum of patients with cancer of the prostate Gutman and Gutman (7) found that acid phosphatase was increased, but only when the neoplasm had metastasized. It was evident to Huggins and Hodges (21) that the simultaneous estimation of acid and alkaline phosphatases of the serum over many days could provide quantitative information concerning the metabolic activity of the prostatic neoplasm and also, when metastases were present in bone, the reactivity of the host to the presence of the neoplasm in the skeleton. It was convenient and informative to study in a single sample of serum both the activity of cancer and the corresponding response of normal cells to the presence of that cancer. The administration of testosterone or, conversely, the institution of anti-androgenic measures caused characteristic reflections of hormonal activity in the serum enzymes, and these provided simple mathematical proof of the stimulatory or the inhibitory action, respectively, of these modifications of the hormonal *milieu intérieur*.

These findings were confirmed through the study of another enzyme in the serum of patients with disseminated prostatic cancer; this enzyme was fibrinolysin. It had been discovered (24) earlier that human prostatic epithelium secretes large quantities of a proteolytic enzyme which is specially active against fibrin as a substrate. Human prostatic secretion contains several proteolytic enzymes, of which fibrinolysin is the most active; fibrin is digested far more rapidly by prostatic fluid than is fibrinogen or denatured hemoglobin.

Tagnon *et al.* (49) observed that the blood of some patients with metastasized cancer of the prostate becomes incoagulable because of its concentration of prostatic fibrinolysin; fibrinolysis, as defined by these workers, is the complete dissolution of the blood clot within 24 hours at 37° C. The content of fibrinolysin in serum is eliminated (48) by the administration of estrogenic substances or by orchiectomy; testosterone causes fibrinolysin to reappear in such patients. The entry of prostatic fibrinolysin into the blood is similar to that of acid phosphatase. The anti-androgenic measures restore the coagulability of the blood.

The first series of patients with prostatic cancer treated by orchiectomy (27) comprised twenty patients with wide-spread metastases; only four of them survived more than 12 years. Despite regressions of great magnitude, it is obvious that there were many failures of endocrine therapy to control the disease.

Nesbit and Baum (39) reviewed the effects of orchiectomy and estrogenic substances on 1,818 cases of prostatic cancer. They state: "The present survey has demonstrated conclusively that patients with prostatic cancer who respond favorably to castration and/or estrogen therapy live more comfortably and longer than patients not treated by these methods."

It was postulated by Huggins and Scott (26) that, in some of the "failure" cases, the adrenal glands were the source of growth-promoting steroids in sufficient amounts to maintain activity of prostatic cancer in the absence of the testes. Bilateral adrenalectomy was carried out, and one patient survived for 4 months. With the advent of cortisone in large amounts the problem was reinvestigated (16, 17). There was evidence of regression of prostatic cancer in four patients after adrenalectomy, and a complete remission has persisted for 5 years in one patient so treated. Remissions following adrenalectomy have been reported by others (52); it is now known that adrenalectomy benefits only a small percentage of patients with prostatic cancer in relapse after orchiectomy and the administration of estrogens.

A further advance was made in 1952 when it was shown (14) that the administration of cortisone to patients in relapse after conventional antiandrogenic measures can cause some regression of the disease; adrenalectomy was not performed in these men. Such relief of symptoms is brief, being measurable in a few months only.

The level of 17-ketosteroids (46) in the urine of patients with cancer of the prostate is well below that for normal males of a younger age. Castration causes a prompt decrease in the excretion of androgenic substances, as determined by biological methods (10), and an increase of urinary gonadotrophins (10, 46).

Birke, Franksson, and Plantin (2) studied the urinary excretion of steroids in cancer of the prostate in two patients prior to orchiectomy and in ten patients after this intervention. Oral administration of cortisone acetate produced diminution of the urinary excretion of androsterone and etiocholanolone in the patients with intact testes. Cortisone therapy after orchiectomy resulted in complete disappearance of these compounds from the urine in nine cases, while in a tenth case these metabolites persisted although in greatly decreased amount.

MAMMARY CANCER

Ovariectomy.—Beatson (1) discovered that mammary cancer can be forced to regress by excision of the ovaries. The working hypothesis arose from reflection on the mechanism of lactation in farm animals and the similarity between "fatty degeneration" in a tumor and the formation of milk by the mammary gland. Beatson stated, "We must look in the female to the ovaries as the seat of the existing cause of carcinoma, certainly of the mamma, in all probability of the female generative organs generally, and possibly of the rest of the body."

The regression of mammary cancer can be profound; remission occurs in approximately 20 per cent of mammary cancers.[1]

Orchiectomy.—While engaged in a study of induced hormonal imbalance on the course of advanced mammary cancer in clinical cases, Farrow and Adair (6) observed that orchiectomy was followed by regression of the neoplasm in a male, age 72 years. Beneficial results of great magnitude have followed orchiectomy (28, 50, 51).

Adrenalectomy.—The hypothesis leading to adrenalectomy in mammary cancer is that the human adrenal gland can secrete sufficient quantities of growth-promoting steroids to maintain dependent neoplasms. Here are the basic theoretical considerations which led to the introduction (16, 26) of adrenalectomy: (*a*) Steroids which promote growth of the secondary sex structures are elaborated by the adrenal cortex in patients with tumors or hyperplasias of this structure. (*b*) Steroids of this kind are produced in certain women after the menopause. (*c*) Orchiectomy, in patients with cancer of the prostate, generally induces a rise (46) in the amount of 17-ketosteroids excreted in the urine. (*d*) Woolley *et al.* (53) discovered that gonadectomy performed at an early age in susceptible strains of mice leads to hyperplasias and neoplasms of the adrenal cortex and that these lesions often secrete steroids which induce growth in the mammary gland. (*e*) In force-fed ovariectomized rats, adrenalectomy retards (30) the growth of Walker carcinoma 256.

Maintained adequately with steroid substitution therapy, the adrenalectomized patients have a healthy appearance, are not incapacitated, and are able to engage in all their usual activities. When the patient is on an adequate hormonal maintenance, the glucose tolerance test (17), insulin tolerance test, and water diuresis test are normal and similar to those in the pre-operative period. In postmenopausal women, adrenalectomy frequently is followed by the recrudescence of menopausal symptoms which had been dormant for some years; the hot flushes have persisted more

[1] The statistical effects of treatments of advanced mammary cancer have been presented elsewhere (15).

than 5 years in patients who originally had widespread active mammary cancer. In such patients after adrenalectomy there is a pronounced rise in titer of gonadotrophins in the urine above preadrenalectomy levels.

It is certain that bilateral adrenalectomy without the removal of the ovaries can induce profound and prolonged regression (12, 17, 19) of disseminated mammary cancer. The first woman to be subjected to this operation, a women in the terminal stage of mammary cancer, is in good health after 5 years. Cade (4) states: "In a proportion of cases both subjective and objective improvement has been achieved which has never been accomplished before by any other method of treatment." It cannot be denied that hormones from either the ovaries or the adrenals can sustain mammary cancer in the human. Adrenalectomy has also caused regression of cancer of the breast in the human male (17).

However, the combined removal of the ovaries and the adrenals does not always lead to the complete atrophy of the human mammary gland. The formation of milk, in any amount, by the breast is the criterion of functional maturity of mammary epithelium, and this can be tested in intact persons. The administration of lactogenic hormone for 7 days induced the secretion of milk in certain patients (20) with mammary cancer; the induction of lactation is especially impressive in aged nulliparous women, and indicates that a potential secretory capacity can be retained by the human mammary gland in senility. In some of these women lactation, so induced, ceased abruptly following removal of the ovaries and adrenals, while in others it persisted for many months despite these operations. It is apparent that the human mammary gland can remain in a mature functional state in the absence of the principal steroid-producing glands.

Hypophysectomy.—The pituitary gland was removed (47) from a man with malignant melanoma, but regression of the tumor did not occur.

Hypophysectomy was introduced as a therapeutic measure in mammary cancer by Luft, Olivecrona, and Sjögren (37). The perspicacity, tenacity of purpose, and the skill of the Stockholm workers are admirable in their approach to this problem. The rationale for this procedure in mammary cancer is the profound atrophy of the accessory sex structures which follows removal of the pituitary; in the rat (22) and dog (25) this atrophy is more profound than that following adrenalectomy and ovariectomy. These animals deprived of the pituitary require no substitution therapy. Hypophysectomized man develops adrenal insufficiency (43) unless treated with appropriate steroids, and myxedema usually appears in a few weeks after hypophysectomy.

It is certain that remission of mammary cancer follows hypophysectomy in some cases (36, 45). Hypophysectomy induced objective remissions in 21 of 41 patients with advanced cancer (43). Pearson *et al.* (43) have reported that certain women, who had undergone castration and adrenalectomy earlier, received additional objective improvement in the form of regression of the carcinoma from hypophysectomy which was performed later.

Pearson *et al.* (44) have presented evidence to indicate that beef pituitary growth hormone caused an increased excretion of calcium in the urine of an hypophysectomized woman with breast cancer; but it is not yet certain that breast cancers are directly dependent on protein hormones.

Lawrence and Tobias (33) have investigated the effects of external radiation (a beam of protons derived from the cyclotron) of the hypophysis in mammary cancer. While some decrease of function of the target organs was observed, the effects on cancer of the breast have not yet been fully evaluated.

Administration of phenolic estrogens.—There is evidence that phenolic estrogens have an ameliorative effect on certain patients with mammary cancer. A paradox is involved in the treatment of breast cancer with estrogens, since compounds in this class are believed to be activating agents in many cases of mammary cancer; indeed, one of the purposes of adrenalectomy and ovariectomy is the elimination of endogenous estrogens. The paradox may be explained on the basis of the quantities of the estrogenic phenols which are involved. It has been shown that phenolic estrogens have a biphasic effect (29) on the growth of mammary tumors in ovariectomized rats; small amounts of phenolic estrogens promote the growth of this benign tumor, while large quantities block its growth.

The administration of phenolic estrogens to women with mammary cancer was introduced by Haddow *et al.* (9). The rationale underlying the investigation was the fact that many carcinogenic polycyclic hydrocarbons possess the property of retarding the growth both of normal and malignant cells. It had also been established before this study that phenolic estrogens retard the growth of human prostatic carcinomas.

Administration of testosterone.—It is certain that treatment with certain members of the androstane series causes regression of the tumor in certain women with advanced mammary cancer.

In 1939 Loeser (34) presented evidence that testosterone *delayed* recurrence following radical mastectomy for cancer of the breast. In December, 1941, Loeser (35) confirmed his earlier impression and extended his observations to include temporary improvement in women with metastatic mammary cancer.

The mechanism of action of testosterone in causing regression of mammary cancer is unknown. Myers *et al.* (38) observed that testosterone caused exacerbation of metastatic mammary cancer in bone in certain women; this stimulatory effect was related to the conversion of testosterone to estrone and estradiol.

LEUKEMIA

It is known that cortisone and related steroids will cause a remission in acute leukemia and in certain chronic lymphogenous tumors.

Dougherty and White (5) had observed that increased adrenal cortical function resulted in involution of normal lymphoid tissues. Heilman and Kendall (11) discovered that cortisone caused a rapid, profound yet temporary regression of a transplanted lymphosarcoma in mice; furthermore, when injections of this steroid were begun soon after inoculation of the tumor, its growth was delayed as long as cortisone was administered. Pearson *et al.* (41) observed that ACTH or cortisone resulted in a temporary regression in the size of enlarged lymph nodes in chronic lymphatic leukemia and Hodgkin's disease. Likewise, these agents induce a profound remission (42) in about 50 per cent of children with acute leukemia. The remissions in acute leukemia, while impressive, last for a few weeks or months only.

COMMENT

The origin of treatment of cancers of man through changes in his steroid environment has been traced in this paper. The principal experimental pathways leading to these concepts have been the biochemistry and physiology of normal cells, while laboratory studies utilizing malignant cells as test objects have had only a small influence in this regard. Yet it cannot be doubted—indeed, it is self-evident—that the study of neoplastic cells is the central problem of cancer research. The development of laboratory methods to study the effect of hormones on neoplastic cells is a problem for the present. It may be pointed out that many hundreds of steroids have been synthesized but have never been examined for their effects on the promotion or restraint of growth.

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