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Endocrine-induced regression of cancers

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The natural course can be utterly different in various sorts of malignant disease. Some tumors grow without any apparent restraint whatever. When man harbors a neoplasm of this kind, an increase in the size of the cancer is readily evident from day to day and death ensues in, say, six weeks. Conversely, some malignant growths disappear spontaneously. Both of these antipodal effects are rare. Mostly, man with cancer lives 1 year or a little longer after the neoplasm becomes manifest, and it would appear that some inhibition of growth of the tumor takes place to produce this protracted course.

The net increment of mass of a cancer is a function of the interaction of the tumor and its soil. Self-control of cancers results from a highly advantageous competition of host with his tumor. There are multiple factors which restrain cancer - enzymatic, nutritional, immunologic, the genotype and others. Prominent among them is the endocrine status, both of tumor and host - the subjects of this discourse.

In hormone-responsive cancers, appropriate endocrine modification results in catastrophic effects on cancers of several kinds (Table 1) in man and animals, even in those in the terminal stages of the disease. Of course, there ensues *pari passu* improvement in the host's condition. The results are often spectacular. The benefit can be evident within a few hours after the interven-

Table 1

Eight hormone-responsive cancers of man and animals

Type of cancer	*Species*
Carcinoma of breast	Human: female (17), male (18). Rat (44)
Carcinoma of prostate	Human (12)
Carcinoma of thyroid	Human (52)
Lymphosarcoma, leukemia	Mouse (48). Human (50)
Carcinoma of kidney	Hamster (53). Human (54)
Carcinoma of endometrium	Human (55)
Carcinoma of seminal vesicle	Human (56)
Carcinoma of scent-glands	Hamster (57). Dog (58)

tion. The improvement can persist throughout the remainder of the life of the organism; in man regressions lasting more than a decade are not uncommon. There can be complete disappearance of the lesions. But worthwhile benefit ensues only when all or much of the cancer is hormone-responsive and only a small proportion of cancers possess this functional characteristic in a pronounced degree.

The therapeutic system of endocrine-restraint of cancer came from the efforts of many workers. I was never alone in my studies in which one or two students always participated as colleagues. It is a privilege to thank the scores of young men and women who sustained our work.

Lacassagne[1] was the first to indicate that a correlation probably exists between hormones and the *development* of cancer since injections of estrone evoked mammary cancer in each of three males of a special strain of mice; carcinoma of the breast had never been observed previously in animals in this category. The proof that hormones can influence the *growth* of cancer was derived from tumors of the prostate of the dog and, later, of man.

The second quarter of our century found the biological sciences much preoccupied with two noble topics : *(i)* chemistry and physiology of steroids and *(ii)* biochemistry of organo-phosphorus compounds. The key to the puzzle of the steroid hormones in cancer was the isolation of crystalline estrone by Doisy *et al.*[2] from extracts of urine of pregnant women. In the phosphorus field there were magnificent findings of hexose phosphates, nucleotides, coenzymes and high-energy phosphate intermediates. These wonderful discoveries provided the Zeitgeist for our work.

Through the portal of phosphorus metabolism we entered on a series of interconnected observations in steroid endocrinology. A program was not prepared in advance for this basic physiologic study. The work was fascinating and informative so that it provided its own momentum and served as an end in itself. There were blind alleys but eventually the labyrinth of the experimental series was traversed and we were somewhat amazed to find ourselves studying the effects of hormonal status on advanced cancers of people.

Phosphorus metabolism in genital tract

The fluid of spermatocele contains spermatozoa which become motile upon exposure to air. It was observed[3] that, remarkably, spermatocele fluid is devoid of acid-soluble phosphorus and free hexoses, whereas human semen

contains very large amounts of inorganic phosphorus and a monosaccharide identified as fructose by Mann [4]. At the time of ejaculation in the human male, the environment of spermatozoa is altered by a sharp rise in its content of fructose and acid-soluble phosphorus. We found that the seminal vesicle in man is the chief source of these components in semen.

It was somewhat difficult to obtain unmixed secretions from the various accessory sex glands of man, so a simple technique [5] was devised to collect the prostatic secretion (Fig. 1) of dogs quantitatively at frequent intervals for years. Often the prostatic fluid of normal adult dogs is secreted for many months with little variation in its quantity or chemical characteristics. This steady state is noteworthy since secretion of the prostate is the end product of a chain of antecedent events involving synthesis of steroids and protein hormones.

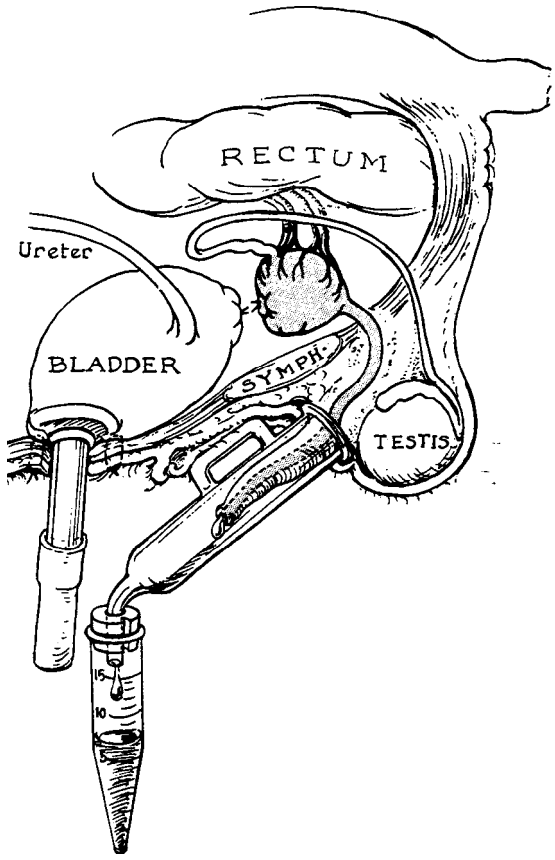

Fig. 1. The prostatic isolation operation.

Following orchiectomy, the prostate shrinks, the oxidative phase of carbohydrate metabolism declines [6], and secretion stops. Testosterone corrects these defects. The cycle of growth and atrophy created by alternately providing and then withholding testosterone was induced repeatedly in the course of the life of the castrate dog. The prostatic cell does not die in the absence of testosterone, it merely shrivels. But the hormone-dependent cancer cell is entirely different. It grows in the presence of supporting hormones but it dies in their absence and for this reason it cannot participate in growth cycles.

A remarkable effect of testosterone is the promotion of growth of its target cells during complete deprival of food. Androstane derivatives conferred on the prostate of puppies a selective nutritional advantage [7] during starvation of 3 weeks whereby abundant growth of this gland occurred while there was serious cell breakdown in most of the tissues of the body. It is useless growth since it does not mitigate the ordeal of starvation. It is reminiscent of a nutritional advantage for growth which some malignant tumors possess in undernourished hosts.

Hormonal control of prostate cancer

It was good fortune that some of our metabolic experiments had been carried out on dogs since this is the only species of laboratory animal in which tumors of the prostate occur. As in man, it is very common to find spontaneous neoplasms of prostate in aged dogs. Among the signs of great age in this species are cataracts and worn teeth. When testes are present in dogs with these stigmata a prostatic tumor is likely; if, in addition, the dog had an interstitial cell tumor of the testis (this was common) a prostatic neoplasm was always found. Most of the canine prostatic tumors are benign growths with much hyperplasia of epithelium and many cysts; carcinoma is usually detected only by histological examination.

At first it was vexatious to encounter a dog with a prostatic tumor during a metabolic study but before long such dogs were sought. It was soon observed [8] that orchiectomy or the administration of restricted amounts of phenolic estrogens caused a rapid shrinkage of canine prostatic tumors.

The experiments on canine neoplasia proved relevant to human prostate cancer; there had been no earlier reports indicating any relationship of hormones to this malignant growth.

Measurement of phosphatases in blood serum furnished the proof that can-

cer of the prostate in man is hormone-responsive. The methodology is simple and the results are unequivocal. Kutscher and Wolbergs [9] discovered that acid phosphatase is rich in concentration in the prostate of adult human males. Gutman and Gutman [10] found that many patients with metastatic prostate cancer have significant increases of acid phosphatase in their blood serum. Cancer of the prostate frequently metastasizes to bone where it flourishes and usually evokes proliferation of osteoblasts. In the school of Robert Robison, Kay [11] found that brisk osteoblastic activity gives rise to increased alkaline phosphatase levels in serum.

Human prostate cancer which had metastasized to bone was studied at first. The activities of acid and alkaline phosphatases in the blood were measured concurrently at frequent intervals. The methods are reproducible and not costly in time or materials; both enzymes were measured in duplicate in a small quantity (0.5 ml) of serum. The level of acid phosphatase indicated activity of the disseminated cancer cells in all metastatic loci. The titer of alkaline phosphatase revealed the function of the osteoblasts as influenced by the presence of the prostatic cancer cells that were their near neighbors. By periodic measurement of the two enzymes one obtains a view of overall activity of the cancer and the reaction of non-malignant cells of the host to the presence of that cancer. Thereby the great but opposing influences of, respectively, the administration or deprival of androgenic hormones upon prostate cancer cells were revealed with precision and simplicity. Orchiectomy or the administration of phenolic estrogens resulted in regression of cancer of the human prostate[12] whereas, in untreated cases, testosterone enhanced the rate of growth of the neoplasm.

Results consistent with the foregoing were obtained by studying another enzyme of the prostate, fibrinolysin, in blood of patients with disseminated prostate cancer. In our metabolic studies it had been found that human prostatic fluid contained large amounts of many proteolytic enzymes [13] and especially one which was highly active against fibrin as a substrate. Prostatic fibrinolysin differs from plasmin and trypsin.

Subsequently Tagnon *et al.*[14] observed that the blood of some patients who have metastases of cancer of the prostate becomes incoagulable because of its concentration of prostatic fibrinolysin. The content of this proteolytic enzyme in serum is reduced or eliminated by the administration of estrogenic substances or by gonadectomy; orchiectomy is hazardous when the blood is incoagulable but, fortunately, the pills of diethylstilbestrol are effective therapy. Testosterone causes fibrinolysin to reappear in such patients. The entry of pros-

tatic fibrinolysin into the blood is similar to that of acid phosphatase; each enzyme enters the plasma, but only from metastasis and not from the primary neoplasm. The antiandrogenic measures restore the coagulability of the blood.

The control of activity of cancer by excision of endocrine glands is physiologic surgery wherein removal of a normal structure can cause healing of distant disease. Stilbestrol, which had been discovered in 1938 by E. C. Dodds *et al.* [15], was the first synthetic substance to control cancer; hence the study of the prostate cancers was the start of chemotherapy of malignant disease.

The first series of patients with prostatic cancer treated by orchiectomy [16] comprised 21 patients with far advanced metastases; only 4 of them survived for more than 12 years. Despite regressions of great magnitude, it is obvious that there were many failures of endocrine therapy to control the disease but; on the whole, the life span had been extended by the novel treatments and there had been a decrease of man-pain hours.

Clinical mammary cancer

The first indication that advanced cancer can be induced to regress was the beneficial effect of oöphorectomy on cancer of the breast of two women. This empirical observation [17] of Beatson in 1896 was remarkable since it was made before the concept of hormones had been developed. The beneficial action of removal of ovaries was not understood until steroid hormones had been isolated 4 decades later.

But why does breast cancer thrive in folks who do not possess ovarian function - in men, old women, and females who have had oöphorectomy? Farrow and Adair[18] observed that benefits of great magnitude frequently follow orchiectomy in mammary cancer in the human male. Thereby, they established that testis function can sustain mammary cancer.

A half century after the classic invention of Beatson it was found out that adrenal function can maintain and promote growth of human mammary cancer. The adrenal factor supporting growth of cancer was identified [19] when it was shown that bilateral adrenalectomy (with glucocorticoids as substitution therapy) can result in profound and prolonged regression of mammary carcinoma in men and women who do not possess gonadal function. In developing the idea of adrenalectomy for treatment of advanced cancer in man we were considerably influenced by the discovery of Woolley *et al.* [20] that adrenals can evoke cancer of the breast in the mouse. Regression of great magni-

tude of human mammary cancer also can be brought about by hypophysectomy[21] as well as by adrenalectomy.

Haddow *et al.* [22] found that phenolic estrogens can have an ameliorative effect in human mammary cancer. A paradox seemed to be involved since, in some circumstances, estrogenic compounds are activating agents for cancer of the breast. In one room the surgeons were removing sources of estrogenic hormones, while nearby the physicians were prescribing estrogens for mammary cancer; both groups were achieving therapeutic triumphs in some cases. Emerson said, "The ambitious soul sits down before each refractory fact. " The vexatious paradox was resolved by experimental studies.

Experimental mammary cancer

Many of the early investigations in this area were carried out on mice and admirable discoveries had been made; chiefly, these concerned the etiology of mammary cancer. But there was a serious disadvantage in use of the mouse - mammary cancers in this species are seldom hormone-responsive. True, in some strains breast cancer diminished somewhat during lactationas and increased in size during pregnancy. But Mühlbock [24] found that in most strains of mice mammary cancers are hormone-independent when the tumors have reached palpable size. Yet the thing about cancers is to cure them.

Studies of the rat altered the course of research on breast cancer because this species has a remarkable propensity to develop mammary carcinoma after exposure to aromatics or, to a lesser extent, irradiation. Further, many of the cancers of rat evoked by these methods are completely hormone-dependent and so can be extinguished by endocrine methods.

Compared with mouse and other rodents, rat is extremely vulnerable [25] to polynuclear aromatic hydrocarbons. In the rat, small amounts of carcinogenic aromatics exert the following effects: *(i)* profound depression of incorporation[25] of thymidine in DNA ; *(ii)* augmented p roduction of messenger RNA[26] *(iii)* induction of synthesis of a soluble enzyme, menadione reductase[27] and of microsome-bound enzymes and other protein [28]; *(iv)* cause cancer or kill the recipient [29].

Maisin and Coolen[30] repeatedly painted mice with 3 -methylcholanthrene (3-MC) andobserved that, in addition to cancer of the skin, mammary cancer developed in a small but significant percentage of the animals after seven months. Shay[31] fed rats a small dose of 3-MC each day for many months and

observed a high incidence of mammary cancer; the tumors were first detected after 4 months. We found that, under conditions which are highly restricted but easily satisfied, a single massive but tolerable dose of any of a large number[32] of polynuclear aromatic hydrocarbons or aromatic amines rapidly and selectively induced breast cancers which were palpable within one month. It is a method of extreme simplicity. Two carcinogenic aromatics, 7,8,12-trimethyl- and 7,12-dimethyl-benz(a)anthracene (7,12-DMBA), are more efficient than all others by 10 times.

Whereas a single feeding of a solution of 7,12-DMBA always induces breast tumors[33], intravenous injection of a concentrated lipide emulsion [34] of the aromatic is more efficacious and has an additional advantage - it introduces the compounds suddenly into the blood as a pulse-dose. When 3 pulse-doses of 7,12-DMBA were given to Sprague-Dawley female rats, at age 50, 53 and 56 days, mammary tumors were evoked in all animals and large numbers of breast cancers [35] were palpable within 4 weeks. The superficial location of rat's mammary glands readily permits detection of the cancers by palpation and the end point is sharp because the cancers are firm in consistency and discrete. A tumor weighing 8 to 10 mg can be detected with ease. The earliest mammary cancer was found by histological search on day 11 and by palpation on day 20 after the pulse- dose. This is somewhat comparable to a famous experiment of Rous [36] who injected a cell-free filtrate of chicken sarcoma I into other fowls and observed the first palpable tumor 10 to 21 days thereafter. In contradistinction to the Rous virus, aromatic hydrocarbons elicit benign tumors of the breast in addition to the cancers.

The mammary cancers of the rat seldom metastasize but kill the host by attaining great size and invading adjacent tissues. Metastases can be produced readily; in the experiments of Dao [37] injection of mammary cancer cells in portal vein caused multiple cancers in the liver. The respiration values [38] of the mammary cancers are similar to those of normal lactating mammary gland. The high rate of glycolysis, which Warburg [30] found to be distinctive of the metabolism of cancer, prevailed in the induced carcinomas.

Rats are also rather susceptible to the development of mammary cancer after exposure to a big dose of ionizing radiation[40]. 7,12 -D M BA[41] and radia - tion[42] possess in common the ability to inflict selective lesions of identical sort in rat's testis. With both agents the prime targets are those germinal cells which multiply by mitosis and hence synthesize DNA; in contrast those cells of testis which proliferate by meiosis and do not synthesize DNA are spared from injury by 7,12-DIMBA.

Hormone-deprival in control of cancer

Mammary cancers induced in the male rat by aromatics were not influenced by orchiectomy and hypophysectomy [43]; by definition, these neoplasms are hormone-independent. In contrast to male rat, most mammary cancers of men wither impressively after deprival of supporting hormones.

The hormone-responsiveness of established mammary cancers induced in female rat by aromatics [44] or ionizing radiation [45] is identical; it was a newly recognized property of experimental breast cancers. Prior to this finding, clinical study of patients with mammary cancer was the only material available for investigation of hormonal-restraint of neoplasms of the breast.

In female rat, growth of the mammary cancers wasaccelerated in pregnancy and by progestational compounds [46]. We have not found any dosage of estradiol-17*B* which markedly enhanced the growth of these tumors.

In female rat, many but far from all of the induced mammary cancers vanished after removal of ovaries or the pituitary. In our experiments hypophysectomy was the most efficient of all methods to cure rat's mammary cancer. Malignant cells which succumb to hormone-deprival, by definition, are hormone-dependent. The quality of hormone-dependence resides in the tumor cells whereas their growth is determined by the host's endocrine status. Both man and the animals can have some of their cancer cells which are hormone-dependent while other neoplastic cells in the same organism are not endocrine-responsive.

The cure of a cancer after hormone-deprival results from death of the cancer cells whereas their normal analogues in the same animal shrivel but survive. It is a basic proposition in endocrine-restraint of malignant disease that cancer cells can differ in a crucial way from ancestral normal cells in response to modification of the hormonal *milieu intérieur* of the body.

Hormone-interference in cancer control

It was unexpected to find that mammary cancers can be extinguished by providing excessive amounts of ovarian steroids; this effect is cancer control by hormone-interference.

We induced mammary carcinoma in rats which were then treated for a limited time with large amounts of estradiol *plus* progesterone [46]. This combination of hormones excited such exuberant growth of normal mammary

cells that the breasts resembled those of rats late in pregnancy. Nevertheless, many of the mammary cancers were completely eliminated and 52 percent of the rats were free from cancer [32] six months after steroids had been discontinued. These rats had been cured of cancer because the tumors did not reappear during subsequent pregnancy. The heavy hormonal burden of pregnancy upon mammary cancer had not reactivated dormant cancer cells if any had been present.

In patients, the combination of huge amounts of progesterone and of estradiol injected intramuscularly induced measurable and worthwhile improvement[47] in patients with far advanced disseminated mammary cancer, both in women and men. Moreover, benefit was obtained in patients in whom other forms of endocrine therapy such as adrenalectomy and oophorectomy had. previously promoted tumor regression followed by recrudescence.

In another type of hormone-interference, cancer cells are exterminated in parallel with normal cells of similar kind. Glucocorticoids will cause a remission of some lymphogenous tumors and leukemia. Heilman and Kendall administered large amounts of cortisone to mice bearing a transplanted lymphosarcoma - "Although dramatic and apparently complete cures are produced, they are only temporary in a majority of animal s[48]." In contrast to the beneficial effects of cortisone, adrenalectomy enhances growth of lymphomas i n mouse[4 9]. Pearson *et al.* [50] found that corticotropin (ACTH) or cortisone caused dramatic if temporary regression in certain cases of human leuke - mia and Hodgkin's disease.

Dougherty and White [51] found that administration of pituitary ACTH to the mouse causes a regression of lymph nodes and thymus. Regression of lymphomas brought about by glucocorticoids does not differ in principle from the effect of corticosteroids on. the lymphocytes of normal animals and man.

Conclusions

Cancer is not necessarily autonomous and intrinsically self-perpetuating. Its growth can be sustained and propagated by hormonal function in the host which is not unusual in kind or exaggerated in rate but which is operating at normal or even subnormal levels.

Hormones, or synthetic substances inducing physiologic effects similar thereto, are of crucial significance for survival of several kinds of hormone-

responsive cancers of man and animals. Opposite sorts of change of the hormonal status can induce regression and, in some instances, cure of such cancers. These modifications are deprivation of essential hormones, and hormone interference by giving large amounts of critical compounds.

The control of cancer by endocrine methods can be described in three propositions: *(1)* Some types of cancer cells differ in a cardinal way from the cells from which they arose in their response to change in their hormonal environment. *(2)* Certain cancers are hormone-dependent and these cells die when supporting hormones are eliminated. *(3)* Certain cancers succumb when large amounts of hormones are administered.

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