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, say, 6 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 intervention. 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 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, spermatocoele 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 (3) 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.

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 deprivation of food. Androstane derivatives conferred on the prostate of puppies a selective nutritional advantage (7) during 3 weeks' starvation 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 malignant tumors possess in undernourished hosts. Starvation does not cure cancer.

**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 cancer 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

### TABLE 1

**Eight Hormone-responsive Cancers of Man and Animals**

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Species</th>
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<tbody>
<tr>
<td>Carcinoma of breast</td>
<td>Human: female (17), male (18); rat (44)</td>
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<tr>
<td>Carcinoma of prostate</td>
<td>Human (12)</td>
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<tr>
<td>Carcinoma of thyroid</td>
<td>Human (32)</td>
</tr>
<tr>
<td>Lymphosarcoma, leukemia</td>
<td>Mouse (48); human (50)</td>
</tr>
<tr>
<td>Carcinoma of kidney</td>
<td>Hamster (53); human (54)</td>
</tr>
<tr>
<td>Carcinoma of seminal vesicle</td>
<td>Human (55)</td>
</tr>
<tr>
<td>Carcinoma of scent-glands</td>
<td>Human (56)</td>
</tr>
<tr>
<td></td>
<td>Hamster (57); dog (58)</td>
</tr>
</tbody>
</table>
Clinical Mammary Cancer

The first indication that advanced cancer can be induced to regress was the beneficial effect of oophorectomy on cancer of the breast in 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 four 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 oophorectomy? 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 magnitude 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 in 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 lactation (23) 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 production of messenger RNA (26); (iii) induction of synthesis of a soluble enzyme, menadione reductase (27) and of microsome-bound enzymes and other proteins (28); (iv) cause cancer or death of the recipient (29). Maisin and Coolen (30) repeatedly painted mice with 3-methylcholanthrene and observed that, in addition to cancer of the skin, mammary cancer developed in a small but significant percentage of the animals after 7 months. Shay (31) fed rats a small dose of 3-methylcholanthrene 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 1 month. It is a method of extreme simplicity. Two carcinogenic aromatics, 7,8,12-trimethyl- and 7,12-dimethylbenz(a)anthracene are ten times more efficient than all others.

Whereas a single feeding of a solution of 7,12-dimethylbenz(a)anthracene always induces breast tumors (33), intravenous injection of a concentrated lipid emulsion (34) of the aromatic is equally efficacious and has an additional advantage—it introduces the compounds suddenly into the blood as a pulse-dose. When three pulse-doses of 7,12-dimethylbenz(a)anthracene 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 8 to 10 mg can be detected with ease. The earliest mammary cancers which were palpable within 1 month. It is a method of extreme simplicity. Two carcinogenic aromatics, 7,8,12-trimethyl- and 7,12-dimethylbenz(a)anthracene are ten times more efficient than all others.

Hormone-Deprival in Control of Cancer

Mammary cancers induced in the male rat by aromatics were not influenced by orchectomy and hypophysectomy (43); by definition, these neoplasms are hormone-independent. In contrast to male rat, most mammary cancers of men wither impressively after deprivation 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 avenue available for investigation of hormonal-restraint of neoplasms of the breast.

In female rat, growth of the mammary cancers was accelerated in pregnancy and by progesterational compounds (46). We have not found any dosage of estradiol-17β 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) 6 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 exter-
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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 in man and animals. Opposite sorts of change of the hormonal status can induce regression and, in some instances, cure 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: (i) 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. (ii) Certain cancers are hormone-dependent and these cells die when support hormones are eliminated. (iii) Certain cancers succumb when large amounts of hormones are administered.

REFERENCES AND NOTES

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