THE HORMONE-DEPENDENT CANCERS*

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THIS paper is a brief account of studies on cancer pursued by co-workers in the Laboratory and of some significant contributions by others in related areas. There were only a few young people participating in our work at any one time, because creative work requires rather serene surroundings. Both distraction and, equally, solitude are deterrents of imaginative efforts.

The work consisted of attempts to pose simple questions and to find methods to answer them, trying to elucidate the nature of cancer. It is difficult to control a disease which is not understood. Conversely, with understanding, alleviation often follows soon.

HORMONE-DEPENDENT CANCER

The concept of hormone dependence of cancers arose from experimental study of the activity of prostatic glands, of both the normal and the malignant kind. The question was: Does the cancer cell possess qualities of its normal progenitor? The answer was affirmative. Indeed, some cancers retain to a high degree characteristics of their normal antecedents. Among these properties is hormone responsiveness.

From our studies it emerged that there is a fundamental difference between normal and malignant target cells in their response to the withdrawal of supporting hormones.

In castrate, but otherwise normal, males and females (in those strains where prostate is present), the prostatic cell is small, has a low metabolic rate and does not secrete. When an appropriate steroid, testosterone or one of its congeners, is administered, the cell enlarges, its metabolism increases and the cell secretes. All of these processes regress when testosterone is withheld. But the cell does not die in the

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absence of testosterone, it merely shrivels. The cycle of growth and atrophy can be repeated scores of times in the life of the animal. The male sex hormones take part in the regulation of the oxidative phase of carbohydrate metabolism[1] of the normal prostatic epithelial cell, but are not critical in maintaining its life.

Hormone-dependent cancers do not possess the ability to participate in growth cycles, which is characteristic of the normal prostatic epithelial cells. Testosterone was administered to previously untreated patients with cancer of the prostate, and the activity of the neoplasm was greatly accelerated.[2] Conversely, when the natural source of testosterone was removed by bilateral orchiectomy, the cancers regressed; the hormone-dependent malignant cells did not survive. In hormone-dependent cancers of all sorts, prostatic and others, the supporting hormones are of cardinal importance in maintaining the life of the malignant cell and in their absence the cancer cell dies.

It was found[3] that the administration of appropriate amounts of estrogenic substances resulted in a profound decrease in size of prostatic tumors of dogs. Similarly, estrogens caused a regression of prostatic cancer in man.[2] In fact, stilbestrol synthesized by E. C. Dodds was the first synthetic compound which could control any sort of malignancy, and this observation was the beginning of chemotherapy of cancer.

It is now established that orchiectomy or the administration of estrogens will induce a significant regression of cancer of the prostate in nearly every patient with this disease. The remission can last from a few months to 15 years or longer. In many patients, orchiectomy furnishes more effective control than estrogenic compounds do. It would appear that stilbestrol has properties which are unsurpassed by any other estrogenic compound in the treatment of prostatic cancer.

Measurement of phosphatases in blood serum furnished the proof[2] that cancer of the prostate in man is hormone responsive. The methodology was simple and the results revealing.

Kutscher and Wolbergs[4] had discovered that acid phosphatase was rich in concentration in the prostate of adult human males. Gutman and Gutman[5] had found that many patients with metastatic prostatic cancer had significant increases of acid phosphatase in their blood serum. Now cancer of the prostate frequently metastasizes to bone where it flourishes and usually evokes proliferation of osteoblasts. And H. D.

Kay[6] of the school of Robert Robison found that brisk osteoblastic activity gives rise to increased alkaline phosphatase in serum.

At first, human prostatic cancer which had metastasized to bone was studied. 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. The level of acid phosphatase indicated activity of the disseminated cancer cells in all loci. The titer of alkaline phosphatase revealed the function of the osteoblasts as influenced by the presence of the prostatic cancer in bone. Both cancer activity and osteoblastic reaction were measured simultaneously with precision in small quantities (0.5 ml.) of serum. The great influences of endocrine modifications of the host upon his cancer cells and consequently upon osteoblasts which were their near neighbors, were revealed with simplicity and in mathematical terms.

The retention of normal characteristics by cancer cells has been utilized for therapeutic purposes in five human neoplasms. These are carcinoma of the prostate, the thyroid,[7] the endometrium,[8] the mammary gland, and also leukemia.[9]

Clinical Carcinoma of the Breast

In 1896, Beatson[10] made a highly important discovery when he found that removal of the ovaries caused regression of cancer of the breast in women. This classic work is especially noteworthy because it was done before the secretion of endocrine glands had been discovered and the observation of Dr. Beatson was empirical. Soon it was found that many but not all women with mammary cancer benefited from oophorectomy. Surprisingly, the use of this procedure declined and for three decades this simple operation was rarely employed as a therapeutic device in cancer of the breast. The virtual disappearance of a highly useful treatment of disseminated cancer can be attributed in large measure to the empirical nature of the discovery.

While engaged in a study of induced hormonal imbalance, in men with advanced mammary cancer, Farrow and Adair[11] observed that orchiectomy was followed by regression of the neoplasm. This procedure is frequently followed by spectacular regression of cancer of the breast in the human male.

It was well known that mammary cancer frequently flourished in women and men whose gonads had been removed, but there was no explanation for this interesting and distressing phenomenon. It

was learned[12] that the adrenals can support the growth of cancer of the breast in a considerable proportion of clinical patients, male and female, and in these patients regression, both profound and prolonged, follows bilateral adrenalectomy.

The basic consideration leading to total adrenalectomy[12] was that the steroids which promote growth of the secondary sex structures are elaborated by tumors and hyperplasias of the adrenal cortex in man. Our work was considerably influenced by the observations of Woolley, Fekete and Little[13] who had discovered that gonadectomy performed in mice at an early age led to hyperfunctioning adrenal glands which permitted development of the mammary glands and formation of mammary cancer.

It was necessary to devise techniques for bilateral adrenalectomy and for hormonal replacement.[14] These goals were not difficult to attain, particularly since cortisone was in abundant supply in 1950. Maintained adequately on a simple program of steroid substitution, the adrenalectomized men and women are not incapacitated and are able to engage in all their usual activities. Moreover, in well-selected cases, disseminated mammary cancer regresses profoundly and for long periods of time.

Subsequent to these developments, hypophysectomy was introduced as a therapeutic procedure for mammary cancer by Luft, Olivecrona and Sjögren.[15] The perspicacity, tenacity of purpose and the skill of the Stockholm workers are admirable, and their work is an outstanding contribution to clinical medicine. But it would appear that hypophysectomy is not superior to removal of functioning gonads and adrenals in the control of disseminated mammary cancer.

Experimental Mammary Cancer

We see that noble procedures which effectively modify the hormonal state have yielded worthwhile benefit to many, but far from all, patients with disseminated mammary cancer. Only a few of the patients have been cured by these procedures. In contrast to the developments in prostatic cancer which emerged from the laboratory, all of the therapeutic measures for mammary cancer were developed through clinical investigation.

The vast amount of work which has been done in the laboratory on mammary cancer has yielded little that has contributed to the relief of suffering and the prolongation of man's life. There are several rea-

sons for this failure. The mouse was the animal used in most of the experiments, and in this species mammary cancers arise in most instances after a very long interval and the tumors are usually hormone independent. Both difficulties have been circumvented by the induction of mammary cancer in the rat with the use of hydrocarbons.

In 1936, Maisin and Coolen[16] repeatedly painted the skin of mice with hydrocarbons and observed that, in addition to cancer of the skin, mammary cancer arose in a considerable number of the animals (18 per cent) after seven months.

It has been found[17] that a single feeding (or intravenous injection) of any one of a number of polycyclic aromatic hydrocarbons evokes tumors, predominantly of the breast, in the albino rat. The most potent of these compounds is 7, 12-dimethylbenz(a)anthracene. This is a spectacular phenomenon. Both cancer of the breast and fibroadenoma are induced. The malignant mammary tumors arise early, the benign tumors appear after many months. The induction of mammary cancer is selective, invariable and rapid. The technique is extreme in simplicity. Under conditions which are easily satisfied, every rat develops mammary cancer within five weeks after the administration of the hydrocarbon. A single meal, at least for the rat, was identified[17] as a cause of mammary cancer.

There are three molecular parameters[18] of critical significance determining carcinogenicity in polynuclear aromatic hydrocarbons: 1) The molecules are strong electron donors as Szent-Györgyi[19] first demonstrated; powerful electron acceptors can cause cancer but, it would appear, only after they have been converted to electron donors *in vivo*. 2) A geometric factor, since the configuration must resemble that of purines and pyrimidines in the base pairs of nucleic acids, and the molecules must be flat. 3) Molecular thickness: this must not exceed the thickness of the aromatic double bond (3.6 Å).

It is of importance that a single shot of polynuclear aromatic hydrocarbons exerts the same tumor-producing effect in the rat as total-body irradiation does. The mammary cancers induced by both modalities are similar in many ways.[20] Approximately one-half of the tumors induced by irradiation or by hydrocarbons are hormone dependent since they regress after ovariectomy.

Mammary cancers of the rat, soon after their induction by hydrocarbons, are highly hormone responsive. Pregnancy[18] always promotes

their growth. Likewise, administration of progesterone to animals possessing ovaries accelerates the appearance of cancers, increases their number and augments the growth rate of cancers induced by a single feeding of 7, 12-dimethylbenz(a)anthracene.

The removal of ovarian steroids, estradiol-17β and progesterone, by ovariectomy causes regression of many of the induced mammary cancers. But the administration of large quantities of estradiol-17β and progesterone also results in a conspicuous effect in that a large number of cancers are destroyed.[18] Estradiol-17β, in its biological action, converted progesterone from an enhancer to a suppressor of breast cancer.

In some patients in relapse after adrenalectomy or hypophysectomy, the administration of estradiol benzoate with progesterone has been found[21] to have a beneficial effect on disseminated mammary cancer. No toxic or adverse reactions have been observed. The clinical improvement was considerable in some of the cases, although the benefit secured by this treatment was sometimes brief. In other cases it was of many months' duration, and the results seem sufficiently encouraging to merit more extensive trials and the use of other combinations of steroids to control mammary cancer.

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