Prospects in Endocrinology for Chemotherapy

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We may assume, on the basis of considerable experimental evidence, that hormones are not carcinogens. They do not initiate the primary mutagenic event that results in neoplasia, but in many experimental situations they act as cocarcinogens orpromoters of carcinogenesis. The influence of estrogenic substances on the development of mammary tumors in mice has been reviewed (16), and it is apparent that, in general, estrogens are necessary for the mouse mammary tumor virus to induce tumors in susceptible strains but rarely produce tumors in the absence of virus. Similarly, induction of mammary tumors in rats by the carcinogen, dimethylbenzanthracene, requires the action of estrogen during induction (5). The cocarcinogen effect of prolactin in induction of mammary carcinoma was demonstrated clearly by Furth (8) (Table 1). Subthreshold doses of dimethylbenzanthracene, X-ray, and mammary tumor virus caused high incidences of tumors when the animal received high doses of prolactin. The prolactin itself was not carcinogenic. Similarly, Weisburger (25) has reported that pituitary hormones increase the incidence of hepatomas induced by fluorenylacetamide. In man, an early menopause pituitary hormones increase the incidence of hepatomas carcinogenic. Similarly, Weisburger (25) has reported that uterine endometrium are probable examples of this stimulation prior to development of adenocarcinoma of the gland and the probable necessity for prolonged estrogen and androgens in the development of carcinoma of the prostate suggesting the promoting effect of estrogens. The role of decreased the incidence of development of breast cancer (6) but, in fact, they have already assumed some importance. The cocarcinogenic activity in man. The efficacy of the therapeutic procedures, adrenalectomy and chemotherapy agents may not be immediately apparent during induction (5). The cocarcinogen effect of prolactin in induction of mammary carcinoma was demonstrated clearly by Furth (8) (Table 1). Subthreshold doses of hypophysectomy, has been correlated with the excretion of certain 17-ketosteroids derived from adrenal cortical secretions (2). Thus, patients whose breast cancers responded favorably to the ablative procedures can be distinguished statistically from those who derived no benefit. This may mean that the cancer cell in the responsive patient is biochemically different from the cell in the resistant patient. Once two types of cancer have been defined, it is appropriate to think of other therapies that may take advantage of the differences between cancers.

If the endocrine environment in which breast cancer develops differed significantly from that of normal women, then the dream of oncologists, the elimination of chemotherapy, would be closer to reality. Many studies of this type have been undertaken during the past twenty years, and I intend to point out only a few results that may hold promise. The efforts of Bulbrook's group in defining responsive and nonresponsive patients with metastatic breast cancer (2) may be related to the role of the adrenal cortex in estrogen production. Abnormalities of estrogen metabolism have been a persistent theme in breast cancer research, and Lemon et al. (14) described a reduction in urinary estriol in women with breast cancer. Zumoff et al. (26) showed clearly that the metabolism of estradiol was altered by breast cancer and not other cancers in men. Finally, the studies of Rose (22) of tryptophan metabolism show that the excretion of this amino acid is higher in women with breast cancer and suggest (23) that this is due to higher estrogen levels. Prospective studies using as many of these technics as possible are needed to identify women with a high risk of breast cancer in order first, to try to find the cancer earlier and second, to modify the endocrine milieu. The preliminary results of one prospective study (3) suggest that the endocrine abnormalities of women who subsequently develop breast cancer are nongenetic.

To pursue this point further we may consider the interaction of the endocrine system with the tumor in the light of recently accrued knowledge of solid tumor kinetics. From studies with several animal tumor systems (1) and work with human tumors (7), it seems probable that changes in the rate of growth of a tumor are not due to major variations in cell cycle time but rather must be the result of a changing fraction of cells entering the proliferative pool, an altered rate of loss, or some combination of these phenomena. The cell cycle time seems relatively stable, and it is unlikely that hormones greatly alter the cell cycle time. Further, the relationship of cell cycle time of a few days in breast cancer (V. T. DeVita, personal communication) to a doubling time of up to 200 days (21) means that the measurable growth of a tumor nodule will be affected very little by even large changes in cell cycle time. It seems more probable then that the hormonal environment of...
endocrine-sensitive tumors may critically determine the rate of entry of cells into the proliferative pool or the rate of loss of new cells. A consideration of the mechanism of hormone action may now permit an informed guess about possible hormonal effects in solid tumor kinetics.

The current hypothesis of the mode of action of the steroid hormones states that they act at the level of transcription (Chart 1). The hormone alters nuclear gene expression resulting in new information available to the cell for synthesis of specific proteins necessary for cell growth. If we can assume, as seems likely, that cell cycle time is relatively independent of hormonal or other stimuli, then the phenomenon of acceleration of tumor growth by hormones is most likely due to an increased fraction of cells entering the proliferative cell pool. Changes in thymidine labeling as a function of hormonal stimulation of tumor cell growth have not been performed to my knowledge.


mRNA, messenger RNA; tRNA, transfer RNA; rRNA, ribosomal RNA.

The classical clinical situation in which it may be possible to test the hypothesis, and a therapeutic approach deriving from it, is human breast cancer. In about 30 percent of premenopausal women with metastatic disease, oophorectomy produces regression of the disease. When this happens, treatment with estrogens can cause exacerbation of disease as measured by an increase in the rate of osteolysis (20). If estrogen is increasing the rate at which cells enter the proliferative pool, this should have two important consequences. First, a greater proportion of cells will be actively proliferating and, therefore, susceptible to cycle-dependent agents such as 5-fluorouracil or Methotrexate. Second, there may be a degree of synchronization of cell cycles during stimulation of tumor growth that would further increase the efficacy of cycle-dependent drugs. This approach has not been explored because of lack of confirmatory data. With greater knowledge of cell kinetics during estrogen stimulation, the hypothesis may warrant testing.

The application and withdrawal of hormonal stimuli, such as estrogens in breast cancer and androgens in prostate cancer, that result in stimulation and regression respectively of the cancers, can scarcely have the same explanation as the regressions of breast cancer seen with pharmacologic doses of many hormones. Varying rates of regression of human breast cancer have been obtained with androgens, estrogens, progestins, and corticoids. It is unlikely that all of these agents can alter nuclear gene transcription and thereby decrease the fraction of cells entering the proliferative cell pool. A more reasonable hypothesis is that high plasma and tissue levels of these hormones render the environment less favorable for survival of the cancer cells so that the rate of cell loss is increased. This need not be a single mechanism, and one could envision such explanations as stimulation of immune mechanisms, change in the quality of connective tissue response about the tumor, and direct metabolic effects on the tumor cell. In any case, cycle-dependent drugs could not be expected to synergize with hormones used in this way if the locus of their effect is as proposed. Rather, noncycle-dependent drugs such as the alkylating agents might be at least additive.

The possibility of hormones somehow affecting the rate of cell loss in a tumor may be approached somewhat more specifically. Kaplan (12), in a thoughtful review, pointed out that one of the many differences between normal and neoplastic cells is that the normal cell retains the capacity to differentiate and thereby loses the capacity to divide further. Thus, if the tumor cell could be induced to differentiate further, the rate of cell loss in the tumor should increase. Progesterone and progestational agents cause regression of metastatic carcinoma of the uterine endometrium in about one third of the women. Since the normal biologic effect of progesterone is to cause biochemical and morphologic differentiation of endometrial cells, it is suggested that progesterone increases the rate of tumor cell loss by virtue of its capacity to induce differentiation. In this case, the use of chemotherapeutic agents concurrently with progesterone could decrease its effectiveness. Again, appropriate clinical trials or studies have not been performed.

These hypotheses have been summarized in Chart 2. It should be emphasized that they are only hypotheses, but they are capable of critical examination.

There is another area of interaction of endocrinology with cancers that is potentially capable of exploitation. Almost ten years ago Jensen and Jacobson (11) showed that the target organs for estrogens, the uterus, vagina, and pituitary gland, had high binding affinities for estrogens. Subsequently it was found that estrogen receptors are also present in dimethyl-benzanthracene-induced rat mammary tumors (13). Of particular pertinence to this discussion was the demonstration by Mobbs (15) that those tumors which regressed in response to ovariectomy could concentrate estrogens, whereas autonomous tumors had seemingly lost this capacity. Jensen (personal communication) has devised methods for measuring the cytoplasmic estrogen receptor in human mammary adenocarcinoma and is presently engaged in a prospective study of the correlation of the presence of estrogen receptors with the clinical course of patients following mastectomy and with their response to such procedures as oophorectomy and adrenalectomy.

The binding of estrogen to its receptors has been studied intensively by Jensen et al. (10). This binding can be inhibited by several estrogen antagonists that act as competitive in-
inhibitors of estrogens with the receptors. The capacity of one of these inhibitors to prevent specific binding of estradiol to mammary tumor receptors and its lack of effect on the nonspecific binding of estradiol to diaphragm are shown in Chart 3. Since the available antagonists have some weak residual estrogenic activity, it is not possible at present to blockade completely the estrogen receptors. Such a goal may seem trivial if one equates removal of the gonads and adrenal glands with complete deprivation of estrogens. However, a variety of synthetic and plant estrogens find their way into the diet. Thus the proposal that total deprivation of estrogens would result in more frequent or longer remissions in breast cancer has not been tested adequately. There are ample reasons to believe that current research will make available nonestrogen substances with high binding affinities for the estrogen receptors. Such agents should be important therapeutic agents, per se, and would permit definitive physiologic studies in estrogen-responsive tumors.

The finding that only estrogen-responsive tissues contain receptors of high binding affinity does create several unique possibilities for chemotherapeutic approaches. For example, radioactive isotopes may be incorporated into the estrogen or chemotherapeutic agents attached to the steroid moiety. This latter approach has, in fact, been tried with the esterification of estradiol to an alkylating agent (M. E. Wall, G. S. Abernethy, F. I. Carroll, and D. J. Taylor, manuscript in preparation). Although this steroidal alkylating agent has been found to be effective in several rat mammary tumors, it has not yet been established whether the estrogen specificity confers an advantage to the compound.

The nature of the estrogen receptors has been examined, and they have been shown to be proteins (18, 24). There is an intensive effort in several laboratories to isolate these receptors. It should then become possible to produce antibodies that would selectively injure only those cells with estrogen receptors.

This focus on the estrogen receptors seems warranted because wherein lies one of the possibilities of uncovering features unique to tumor tissue. The fact that uterus, vagina, and pituitary also contain these receptors may have little importance in considering therapeutic maneuvers. The significant consideration is that such tissues as kidney, liver, and bone marrow do not contain these receptors.

It would not be appropriate to conclude this discussion without calling attention to the interaction of estrogens with prolactin in the experimental mammary tumor (9, 17). Considerable experimental evidence was adduced to support the suggestion that it was not the level of estrogen, per se, but rather its effect on prolactin release, that determined the course of the growth of the mammary tumor. With the recent availability of a radioimmunoassay for rat prolactin, it has been shown that low doses of estrogen cause marked increases in plasma prolactin levels, whereas oophorectomy produces a fall (4). The relevance to the human problem is apparent, and the further exploitation of the study of plasma prolactin levels in experimental rat mammary tumors (19) will be relevant. Thus, the search for human prolactin and the ability to measure it in blood remain important goals in the endocrine management of human breast cancer.

It is apparent from these remarks that the endocrinologist continues to have an important role in the therapy of many common cancers in man. Until the ideal chemotherapeutic agent becomes available, the chemotherapist should be aware of the interactions of hormones with cell growth since they could increase the efficacy of chemotherapy. Finally, a deeper understanding of the mechanisms by which hormones affect normal and neoplastic cell growth almost surely will lead to technics capable of controlling or modulating growth.
REFERENCES


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