Endocrinologic Factors in the Design of More Selective Antitumor Agents

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Summary
The effectiveness of hormonal agents against tumors of the secondary sex organs might be improved by other combinations with hormonal and nonhormonal agents. The endogenous production of hormones thought to be necessary for the maintenance of hormone-sensitive tumors might also be interfered with by immunologic means, end organ competition via antiestrogens or antiandrogens, and by techniques designed for medical or pharmacologic ablation of adrenal and pituitary function. New agents are needed with substituents that increase delivery to or activation at the local tumor cell. There is room for considerable fruitful exploration of the hormonal treatment of nonhormonal tumors and of the nonhormonal treatment of so-called endocrine neoplasms by single drugs or combinations.

Introduction
There is a substantial need for progress in the design of more effective antitumor agents against tumors of the secondary sex organs. The recent summary presented by Dr. Albert Segaloff (35) to the Breast Cancer Task Force indicated that, in some 50 androgens tried clinically and in animals over the last several years, there has been no substantial improvement over the effectiveness of testosterone propionate or diethylstilbesterol, both of which were available prior to the institution of massive clinical trials of new androgens against breast cancer. It is obvious that the empirical selection of new agents for clinical trial has not resulted in the discovery of a new agent with hidden effectiveness (17). Nor do we know much about possible mechanisms for the effectiveness of these agents, since they are not active against cancer in physiologic replacement doses, and there is only an incomplete correlation between androgenicity or metabolic effect and their capacity to induce responses (8). The few generalizations which might be drawn from the androgen studies cannot be carried over into the estrogens or adrenocorticoïds because in these instances, androgenicity and anabolic effects appear to be totally independent of antitumor effects (9, 19). Moreover, there are no suitable animal tumor models for the screening of new steroids. Along with an increasing realization of the need for more substantial understanding of the cellular pharmacology of tumors arising from the secondary sex organs is the increasing awareness that steroid therapy in human malignancy may result in more morbidity and, in some instances, an excess of mortality over no therapy. This arises from studies by Wolf et al. (43) in lung carcinoma and by the Veterans Cooperative Group (39) in prostatic carcinoma. The studies by Witts et al. (42), by the Veterans Group, and by Knospe and Conrad (25) have reported the undesirability of adding steroids to the management of acute myelogenous leukemia of adults. My approach to this problem will be to point out some of the possible areas in which leads have been developed or are being developed and where additional funds and research efforts might be eminently worthwhile.

Hormonal Stimulatory Action in Drug Combinations. It is now known that sex steroids stimulate growth (40) and division (28) in target cells including those with neoplastic potential (7). The studies of the Memorial Group (30) on the stimulation of prostatic carcinoma in vivo by androgen administration, the occasional observation of apparent stimulation of breast cancer in some women following the administration of estrogen (11), the elegant work of Turkington and Riddle (38), on breast cancer organ cultures, and the work on formate incorporation into DNA by Winzler et al. (41) indicate unequivocally that animal and human breast cancer can be stimulated to cell division by the sex steroids. This paradoxically desirable effect has been suggested as a mechanism for "setting the stage" for more effective use of the potent antitumor DNA agents such as 5-fluorouracil. Such simultaneous use of the sex steroids might selectively increase the antimetabolite sensitivity of the tumor as compared with bone marrow and gastrointestinal epithelium. A protocol has currently been introduced into the Eastern Cooperative Oncology Group Studies by Dr. Samuel G. Taylor (37) of Chicago which may shed light on this intriguing suggestion. Previous work has been done in prostatic cancer by the simultaneous use of androgen and $^{32}$P (12), and in the treatments of thyroid carcinoma by the use of thyroid stimulating hormone (TSH) and radioactive iodine (6). The use of androgen plus 5-fluorouracil (5-Fu) or a nonhormonal cytotoxic agent might also be considered in men whose prostatic carcinomas were not initially sensitive to the more conservative measures of castration and estrogen administration.

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Hormonal Repression in Drug Combinations. The opposite use of sex steroids has been also suggested, i.e., the use of their inhibitory action as one component of a drug combination therapy scheme. For example, Brennan (3) has reported findings indicative of subliminal beneficial effects in a large number of women on hormones. The addition of nonhormonal antimetabolites, alkylating agents, or natural products to hormones might result in additive effects which result in objective responses (11, 14, 15).

Steroid Hormones and Host Resistance. The addition of steroids might increase the host resistance either to the tumor or to the toxic effect of nonsteroidal drugs. In the first instance, etiocholanolone, a pyrogenic steroid, was introduced by Hellman et al. (20) for the treatment of lymphoma. It is possible that the effect here was an indirect one, mobilizing host inflammatory responses to aid in tumor control. It has also been suggested by Brodsky et al. (4) and others that androgens may stimulate the bone marrow and allow larger doses of myelosuppressive agents to be given. The effect of androgens in the elevation of hemoglobin seems to be more well documented than that on the white cell precursors.

The adrenal corticoids may induce a number of enzymes in the liver and other organs which may alter the metabolism of some of the nonsteroidal agents in a beneficial way. The induction of triptophanpyrrolase may be characteristic of a larger group of enzymes some of which might be involved in the activation of “bound” chemotherapeutic agents such as cyclophosphamide or in the metabolism of drugs such as 5-Fu to their phosphorylated derivatives or other active forms.

Effects of Hormonal Agents upon Hormonal Action

There is considerable evidence to indicate that in the treatment of tumors of the secondary sex organs, the hormonal steroids do not act as physiologic agents but as pharmacologic agents. There is reason to think, therefore, that in their pharmacologic roles they may alter the metabolism of the other compounds and increase or decrease their effectiveness. They might also have independent actions which could be additive.

In the former case, we have some evidence from a combined study of ethinylestradiol and fluoroxymesterone in women with breast cancer as compared with halotestin alone. The estrogen-containing combination gave rise to a significantly larger number of instances of hepatotoxicity which interfered with the capacity of the patient to tolerate the combination regime. This can be taken as a suggestion of drug interference.

On the other hand, the Columbia group (29) has reported that progestins can be added to other sex steroids in the treatment of breast cancer with an apparent higher response rate. This could be explained on the basis of additive effect which, however, was not seen for estrogens and androgens in a report by B. J. Kennedy (16).

Another type of hormonal interaction might be steroid displacement from binding sites or the blocking of physiologic actions by antistereoids. Such antiestrogens as Nafoxidine (U 11, 100 A) and CL 618 (obtained from Parke, Davis & Company, Detroit, Michigan) have the capacity to interfere with the binding of estradiol to its receptor protein in vitro in sex steroid sensitive breast cancers, as reported by Jensen et al. (24). It would be intriguing to know whether this capacity of antiestrogens would extend to endogenously produced estrogens from whatever source and hence result in clinical antitumor effect. The same is true potentially for antiandrogens which have been used and developed as antisterility compounds in the male.

Improvements in Hormonal Agents

There is substantial reason to believe that the results obtained with the current sex steroids might be improved if these could be altered in such a way as to facilitate their pharmacologic effectiveness. For example, transport in the form of gastrointestinal uptake, plasma protein binding, and membrane transport into cells might be improved by the addition of prosthetic groups to steroid molecules. The use of sugar moieties might be substitutions which would increase active transport and cellular drug uptake. This might be true of other substituents which would increase the hydrophilic and decrease the lipophilic characteristics of the steroid molecule. Substituents which would interfere with catabolic degradation might also prolong or intensify the activity of the steroid.

The molecule diethylstilbesterol diphosphate (Stilphosterol) represents an attempt to use the elevated acid phosphatase of prostatic carcinoma to cause increased hydrolysis of the diphosphate form. This would give rise to the active drug but only in the carcinomatous areas with high concentrations of acid phosphatase (34).

It is intriguing to speculate whether immunologic characteristics of carcinomas could be used as antigenic markers to which antibodies could be synthesized for coupling to steroids. The lactalbumin of normal breast tissue has been found in small quantities in rodent mammary carcinoma and might be found in sufficient quantity to attract steroids bound to antibodies in man as well (21). Double agents containing a steroid and a mustard, a steroid and a quinone, or a carbamide have been suggested and occasionally synthesized. This approach might still bear more fruitful investigation. If the suggestion that breast cancer has been more common in patients with evidence of prolactin excess is confirmed, the possibility that an antiprolactin could be synthesized which might inactivate the endogenously produced hormone is another exploitable possibility (32).

Agents Which Are Selectively Toxic to Endocrine Organs

The effectiveness of adrenalectomy in patients who are able to undergo such surgery has made it almost the treatment of choice for patients with advanced breast cancer. Since a substantial number of patients have cardiovascular or metastatic disease problems which render the surgery or anesthesia attendant to adrenalectomy hazardous, a search for a “medical adrenalectomy” has been an important...
research area for some time. Based on the evidence presented by Cantarow, that 5-Fu can interfere with the function of the gonads, we attempted to use a combination of 5-Fu plus prednisone in treating patients with breast carcinoma at the Peter Bent Brigham Hospital who were felt to be too sick for surgical adrenalectomy. In approximately 50 patients, we have found that the response rate to the combination of 30 mg of prednisone or 75 mg of cortisone plus 5-Fu, 15 mg/kg orally or by ½ hour infusions daily for 5 to 6 days, resulted in the same 50 to 60 percent response rate as we found with adrenalectomy combined with 5-Fu (33).

In a more direct attempt to interfere with endocrine functions of the adrenal in breast cancer patients, we used aminoglutethimide (Elipten, provided through the courtesy of Ciba, Inc.), a compound known to block the biosynthesis of adrenal steroids at early stages in the synthetic cycle. In nine patients, two responses were seen although there was little evidence of complete inhibition of synthesis of corticoids, androgens, or estrogens. This may suggest that the Elipten may have a direct antitumor effect or that it is blocking the synthesis of other as yet unidentified active adrenal steroids. A suggestion that this may be so arises from the work of Liddle and his coworkers who suggested that Elipten may suppress the synthesis of an unknown steroid in some patients with hypertension. Elipten deserves further study either as a single drug or in combination with other more directly cytotoxic agents (18).

The possibility of ablating the adrenal cortex by exogenous agents has been tried with a number of compounds. Zimmerman et al. (44) attempted to use O-p' DDD (NSC 38721) to inhibit adrenal steroid function in the normal gland with only moderate success. One suggestion which is currently unexploited is the use of the carcinogenic compounds found by Huggins and Lukunishi (22) to cause adrenal apoplexy. There are also some compounds which cause anterior pituitary necrosis and which might be considered to cause a medical hypophysectomy. In the treatment of adrenal cortical carcinoma, this tumor of the steroid-producing organs might also be induced to undergo the necrosis by the Huggins type of carcinogen. Huggins and Morii (23) have also found that some structural analogs of the carcinogens induce adrenal apoplexy are capable of inducing the microsomal hydrolases which destroy the carcinogens. Therefore, when given prior to the carcinogens, they might prevent the adrenal apoplexy. Some tumors have been shown to be less capable of inducing enzymes in response to inducers than normal tissues such as liver (I). If adrenal cortical carcinoma were defective in such enzyme induction, it might be possible to pretreat the host with the noncarcinogenic enzyme inducer, thus inducing in the normal tissue a state of resistance to the carcinogen. This would be found to a lesser degree in the tumor, the adrenal cortical carcinoma thus being left relatively more susceptible to a later dose of the carcinogen.

**Effects of Nonhormonal Agents on Hormone Action**

It is known that hormones effect growth by stimulating the production of small amounts of protein which, followed by RNA and DNA, give rise to new daughter cell production (27). It is intriguing to speculate that the antitumor action of the sex steroids might be enhanced by the simultaneous administration of inhibitors of protein, RNA, or DNA synthesis. Whether compounds such as cyclic AMP could be given along with hormones in intermittent pulses so as to increase the physiologic sensitivity of target cells in the tumor might also be investigated.

**Improving the Effectiveness of Hormone Therapy by Preselecting Responding Patients**

About 75 percent of patients with breast cancer fail to respond to hormonal therapies. If one could predict these patients in advance, it might be possible to move on to nonhormonal agents or new drugs and avoid unnecessary hormonal therapy. The uptake of formate and 32P into tumor DNA can be influenced by hormones in clinically responsive patients (31, 36). Attempts have been made to measure these changes over a 1- to 2-day period after steroid therapy. The methods ought to be refined and applied more widely. Several authors have suggested that endocrine therapy is effective in patients with particular types of steroid "excretion patterns" (5, 26). Such discriminants have been based on ratios of androgens and corticoids and of estradiol and estriol. The validity of these proposed tests should be determined on a large number of patients undergoing therapy. The relative uptake by the tumor of isotope-labeled estrogen in vivo and in vitro has also been reported to enable hormone-sensitive and -resistant patients to be distinguished from each other (2, 13). Jensen has reported that the measurement of estrogen-binding protein in breast tumor cell cytoplasm may be higher in patients who will respond to adrenalectomy. Rat mammary cancer tissues which are hormone sensitive have been shown to respond to estrogen in in vitro tissue cultures by differentiation and production of specific products such as lactalbumin and galactose. A battery of such tests applied to biopsy samples of breast tumors might enable a rapid and effective recognition to be made of hormone-sensitive cancers and hence increase the effectiveness of therapy.

**References**

Endocrinology and Selective Antitumor Agents


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