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HORMONES AND CANCER

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Preface

One of the main objectives of Fundación Argentina de Endocrinología (FAE) is to encourage the progress of basic and clinical endocrinology in Argentina. To this end FAE has already sponsored seven International Symposia to foster interactions between our local scientists and endocrinologists with foremost authority in selected areas of endocrinology.

This volume contains the Proceedings of the Seventh International Symposium organized and sponsored by FAE in Buenos Aires, and devoted to the topic HORMONES AND CANCER.

It deals with the influence that hormones have on the development, maintenance, growth, and evolution of hormone-sensitive tumors—one of the most interesting fields of cancer research.

The activity of hormones as inducers, co-inducers or modifiers of neoplastic processes has to be examined in light of molecular mechanisms of hormone action. It is at this level that the understanding of the intimate relation of a hormone with its receptor, and the resulting modification of genetic expression of the cell, become the key for a better diagnosis and treatment of hormone-dependent tumors.

Recent advances in the knowledge of mechanisms of action of steroid and peptide hormones have changed the classical approach to clinical oncology; studies on the control of endocrine responsive neoplasms now involve multidisciplinary efforts.

This book contains the contributions of several widely known experts working in biochemistry, molecular biology, endocrinology, pathology, and medical oncology. The topics presented include descriptions of methods used to determine hormone receptor levels, mechanisms of action of hormones and antihormones, tests for the prediction of tumor responsiveness to hormones, clinical use of biological tumor markers, and treatment of hormone-dependent cancer.

We wish to thank all who participated in this Symposium and particularly the speakers for their contribution to this important volume. We also wish to express our recognition to Alan R. Liss, Inc., New York, for their assistance in this publication.

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ESTROGEN RECEPTORS, ANTIBODIES AND HORMONE DEPENDENT CANCER

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INTRODUCTION

Experiments conducted in many laboratories throughout the world have led to a recognition that steroid hormones in general effect their biologic responses in target tissues through the mediation of high affinity, specific binding proteins, called receptors, which are present in unique amounts in such responsive tissues. The large body of knowledge about steroid hormone mechanism of action has been derived almost entirely from studies in which a radiolabeled steroid hormone has been used as the marker to elucidate the details of the interaction of hormone with responsive cells. Initial studies in vivo (Glascock and Hoekstra, 1959, Jensen and Jacobson, 1960) demonstrated that target tissues for the hormone could take up and retain physiologic amounts of radiolabeled estrogens against a concentration gradient with the blood and that, at least in the immature animal, this uptake occurred without requiring metabolism of the active estrogen. Subsequent studies indicated that while most of the estrogen taken up by target tissues in vivo, or at physiological temperatures in vitro, was associated with the nucleus, smaller but still significant amounts of estrogen were in low salt extracts, and were believed to be extranuclear (Jensen et al, 1968). However after the introduction by Toft and Gorski (1966) of sedimentation analytical methods for the study of receptors, it was found that upon homogenization of the uterus of untreated immature rats with hypotonic Tris-EDTA pH 7.4 buffer almost all of the tissue content of the estrogen receptor protein was obtained in the high speed supernatant or cytosolic

fraction. When such cytosolic estrogen receptor was incubated with estrogen it underwent an estrogen and temperature-dependent change (Gorski et al, 1968; Jensen et al, 1968), which could be recognized by a change in its sedimentation character from 4S to 5S in 0.4 M KCl. The transformed estrogen receptor complex was indistinguishable from the receptor complex extracted by KCl from nuclei of uteri of estrogen-treated immature rats. Hence a general pathway for the interaction of estrogen with a target cell, Fig. 1, evolved in which the steroid entering the cell,

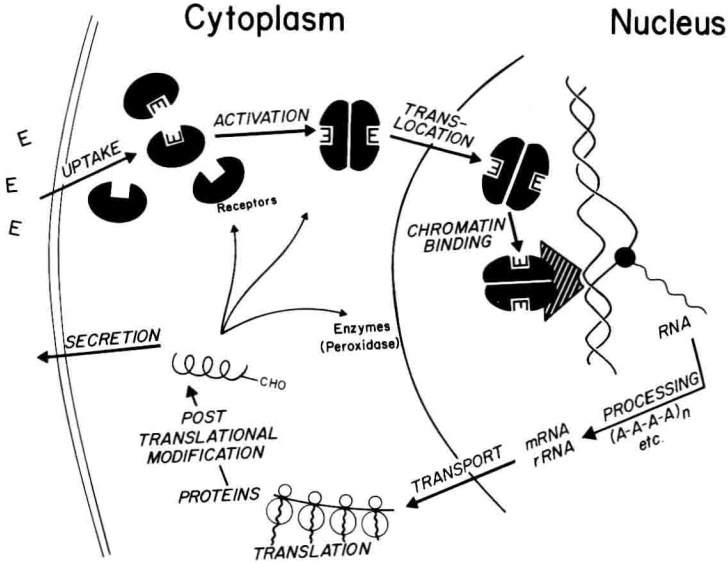

Fig. 1. Schematic diagram of the estrogen interaction pathway and biochemical response in target cells.

probably by passive diffusion, rapidly binds to its receptor protein, believed to be present in excess amounts as free receptor in the extranuclear region of the cell. The association of estrogen with its receptor leads to a complex which undergoes activation, possibly involving a dimerization (Notides et al, 1975), to a form which is

translocated to the nucleus and associates with some yet-to-be definitively characterized acceptors. It appears that this estrogen receptor interaction gives rise to the subsequent initiation of new nucleic acid synthesis leading to the protein, growth and cellular responses that are characteristic of the overall hormone response.

HORMONE DEPENDENCY OF BREAST CANCER

It has been known for some time that some cancers are hormone-dependent. Already in 1896 Beatson reported that several premenopausal breast cancer patients obtained dramatic remission of metastatic disease following removal of their ovaries. However the general acceptance of endocrine ablative surgery for hormone-dependent cancers followed the introduction of orchiectomy for the treatment of prostatic cancer (Huggins and Hodges, 1941), and the use of adrenalectomy (Huggins and Bergenstal, 1952) and hypophysectomy (Luft and Olivecrona, 1953; Pearson et al, 1956) for the treatment of metastatic breast cancer in postmenopausal women.

Thus by the early 1960s when studies in animals were beginning to clarify the nature of differences between the interactions of steroids with target and non-target tissues, it became especially important to apply this emerging basic knowledge to help clinicians properly diagnose and treat breast cancer patients. While the use of endocrine ablation for advanced breast cancer had by this time become a preferred treatment, only 25-35% of all patients obtained benefit. Early studies using tritiated estrogen in vivo in women about to undergo adrenalectomy (Folca et al, 1961) suggested that, as had been found in target tissues of experimental animals, the hormone-dependent lesions, that is cancers of patients who subsequently benefitted from ablative surgery, appeared to show preferential uptake of radioactive estrogen.

While such an in vivo study helped demonstrate an important difference between responsive and non-responsive breast cancers, it did not provide a practical approach to routine diagnosis of the endocrine responsiveness of a lesion. We applied an in vitro assay, developed for animal tissues, in which slices of the breast cancer were incubated with physiologic concentrations of tritiated estradiol