

PROGRESS in
CLINICAL and
BIOLOGICAL RESEARCH
VOLUME 142

HORMONES AND CANCER

EDITORS: **Erlio Gorpide**
Ricardo Calandra
Carlos Levy
Roberto J. Soto

ALAN R. LISS, INC., NEW YORK

HORMONES AND CANCER

Proceedings of the International Symposium on Hormones
and Cancer held in Buenos Aires, Argentina May 9–13, 1983

Editors

ERLIO GURPIDE

Mt. Sinai School of Medicine
Mt. Sinai Hospital
New York, New York

RICARDO CALANDRA

Laboratorio de Esteroides
Instituto de Biología y Medicina Experimental
Buenos Aires, Argentina

CARLOS LEVY

División de Endocrinología
Hospital Ramos Mejía
Buenos Aires, Argentina

ROBERTO J. SOTO

Fundación Argentina de Endocrinología
Buenos Aires, Argentina

ALAN R. LISS, INC. • NEW YORK

Address all Inquiries to the Publisher
Alan R. Liss, Inc., 150 Fifth Avenue, New York, NY 10011

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Library of Congress Cataloging in Publication Data

International Symposium on Hormones and Cancer (1983:
Buenos Aires, Argentina)
Hormones and Cancer

Bibliography: p.

Includes index.

1. Cancer—Endocrine aspects—Congresses.

I. Gurside, Erlio, 1927- . II. Title. [DNLM:

1. Hormones—Pharmacodynamics—Congresses. 2. Neoplasms,
Hormone-dependent—Congresses. W1 PR668E v.142 / QZ 200
I6123h 1983]

RC268.2.I58 1984 616.99'4071 83-24830

ISBN 0-8451-0142-0

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Contributors

Alberto Baldi, Laboratorio de Esteroides, Instituto de Biología y Medicina Experimental, Buenos Aires, Argentina [97]

Etienne-Emile Baulieu, CNRS ER 125 and INSERM Unit 33, Lab Hormones, 94270 Bicêtre, France [133, 167]

Stephen B. Baylin, Department of Medicine and The Oncology Center, The Johns Hopkins Hospital, Baltimore, MD 21205 [291]

Nadine Binart, CNRS ER 125 and INSERM Unit 33, Lab Hormones, 94270 Bicêtre, France [167]

Clara D. Bloomfield, Department of Medicine, Section of Medical Oncology, University of Minnesota, Minneapolis, MN 55455 [195, 223]

Rosalyn Blumenthal, Department of Obstetrics, Gynecology, and Reproductive Science, Mount Sinai School of Medicine, New York, NY 10029 [145]

Jack E. Bodwell, Department of Physiology, Dartmouth Medical School, Hanover, NH 03755 [181]

Nicholas Bruchovsky, Department of Cancer Endocrinology, Cancer Control Agency of British Columbia, Vancouver, British Columbia, Canada [247]

Ricardo S. Calandra, Laboratorio de Esteroides, Instituto de Biología y Medicina Experimental, Buenos Aires, Argentina [xiii, 97]

Françoise Capony, Unit 148, Institut National de la Santé et de la Recherche Médicale (INSERM), 60, Rue de Navacelles, Montpellier 34100, France [37]

Jan Carlstedt-Duke, Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden [207]

Maria-Grazia Catelli, CNRS ER 125 and INSERM Unit 33, Lab Hormones, 94270 Bicêtre, France [167]

Dany Chalbos, Unit 148, Institut National de la Santé et de la Recherche Médicale (INSERM), 60, Rue de Navacelles, Montpellier 34100, France [37]

Eduardo H. Charreau, Laboratorio de Esteroides, Instituto de Biología y Medicina Experimental, Buenos Aires, Argentina [97]

C.J. Conti, Institute for Cancer Research, University of Texas at Austin, Austin, TX 78712 [119]

Erik Dahlberg, Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital F69, Huddinge, Sweden [261]

Marie-Anne de Larminat, Laboratorio de Esteroides, Instituto de Biología y Medicina Experimental, Buenos Aires, Argentina [247]

J.R. Depaoli, Instituto de Cardiología, Academia Nacional de Medicina, Buenos Aires, Argentina [119]

Giulio De Rossi, Hematology Department, State University, Rome, Italy [235]

The number in brackets following each affiliation indicates the opening page of that author's article.

Eugene R. DeSombre, Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, IL 60637 [1]

Ejnar Eriksson, Department of Surgery, Section of Trauma, Karolinska Hospital, Stockholm, Sweden [261]

Guidalberto Fabris, Istituto di Anatomia e Istologia Patologica, Università di Ferrara, Ferrara 44100, Italy [109]

Honorée Fleming, Department of Obstetrics, Gynecology, and Reproductive Science, Mount Sinai School of Medicine, New York, NY 10029 [145]

Marcel Garcia, Unit 148, Institut National de la Santé et de la Recherche Médicale (INSERM), 60, Rue de Navacelles, Montpellier 34100, France [37]

Martine George, Institut Gustave Roussy, 94800 Villejuif, France [167]

L.E. Gerschenson, Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262 [119]

Patricia Glikman, División de Endocrinología, Hospital Ramos Mejía, Buenos Aires, Argentina [133]

Achille Gravanis, CNRS ER 125 and INSERM Unit 33, Lab Hormones, 94270 Bicêtre, France [167]

Geoffrey L. Greene, Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, IL 60637 [1]

Erlio Gulpide, Department of Obstetrics, Gynecology, and Reproductive Science, Mount Sinai School of Medicine, New York, NY 10029 [xiii, 145]

Jan-Åke Gustafsson, Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital F69, Huddinge, Sweden [207,261]

Paul M. Guyre, Department of Physiology, Dartmouth Medical School, Hanover, NH 03755 [181]

Tom Häggmark, Department of Surgery, Section of Trauma, Karolinska Hospital, Stockholm, Sweden [261]

Nikki J. Holbrook, Department of Physiology, Dartmouth Medical School, Hanover, NH 03755 [195]

Stefano Iacobelli, Laboratorio di Endocrinologia Molecolare, Catholic University S. Cuore, Rome, Italy [53, 235]

Elwood V. Jensen, Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, IL 60637 [1]

William J. King, Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, IL 60637 [1]

Jerzy Kulski, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20205 [63]

Claude Laval, Centre René Huguenin, 92211 Saint Cloud, France [167]

Carlos Levy, División de Endocrinología, Hospital Ramos Mejía, Buenos Aires, Argentina [xiii, 133]

R. Lieberman, Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262 [119]

M. Lynch, Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262 [119]

Franco Mandelli, Hematology Department, State University, Rome, Italy [235]

Elisabetta Marchetti, Istituto di Anatomia e Istologia Patologica, Università di Ferrara, Ferrara 44100, Italy [109]

Paolo Marchetti, Department of Obstetrics and Gynecology, Catholic University S. Cuore, Rome, Italy [235]

Geoffrey Mendelsohn, Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD 21205 [291]

Jan Mester, Unité 33, INSERM, Lab Hormones, 94270 Bicêtre, France [133]

Allan U. Munck, Department of Physiology, Dartmouth Medical School, Hanover, NH 03755 [181, 195, 223]

Vittoria Natoli, Laboratorio di Endocrinologia Molecolare, Università Cattolica S. Cuore, 00168 Rome, Italy [53]

Italo Nenci, Istituto di Anatomia e Istologia Patologica, Università di Ferrara, Ferrara 44100, Italy [23, 109]

Kevin R. Nicholas, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20205 [63]

Sam Okret, Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden [207]

D. Orlicky, Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262 [119]

Patrizia Querzoli, Istituto di Anatomia e Istologia Patologica, Università di Ferrara, Ferrara 44100, Italy [109]

Paul S. Rennie, Department of Cancer Endocrinology, Cancer Control Agency of British Columbia, Vancouver, British Columbia, Canada [247]

Anna Paola Rimondi, Istituto di Anatomia e Istologia Patologica, Università di Ferrara, Ferrara 44100, Italy [109]

A. Rivas-Berrios, Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262 [119]

Paul Robel, CNRS ER 125 and INSERM Unit 33, Lab Hormones, 94270 Bicêtre, France [167]

Henri Rochefort, Unité d'Endocrinologie Cellulaire et Moléculaire, Unit 148, Institut National de la Santé et de la Recherche Médicale (INSERM), 60, Rue de Navacelles, Montpellier 34100, France [37, 79]

Lydie Roger-Jallais, Centre René Huguenin, 92211 Saint Cloud, France [167]

Monique Royer de Giaroli, Laboratorio de Esteroides, Instituto de Biología y Medicina Experimental, Buenos Aires, Argentina [97]

Tõnu Saartok, Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital F69, Huddinge, and Department of Surgery, Section of Trauma, Karolinska Hospital, Stockholm, Sweden [261]

Lakshmanan Sankaran, National In-

stitute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20205 [63]

Giovanni Scambia, Laboratorio di Endocrinologia Molecolare, Università Cattolica S. Cuore, 00168 Rome, Italy [53]

Carlos Scorticati, Servicio de Urología, Instituto Oncología Angel Roffo, U.B.A., Buenos Aires, Argentina [247]

Kendall A. Smith, The Immunology Program, Norris Cotton Cancer Center, Dartmouth Medical School, Hanover, NH 03755 [223]

Marek Snochowski, Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital F69, Huddinge, Sweden, and Institute of Animal Physiology and Nutrition, Polish Academy of Sciences, Jablonna-near-Warsaw, Poland [261]

Roberto J. Soto, Fundación Argentina de Endocrinología, Buenos Aires, Argentina [xiii, 133]

Yale J. Topper, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20205 [63]

Irene Vegh, División de Endocrinología, Hospital Ramos Mejía, Buenos Aires, Argentina [133]

Frédéric Veith, Unit 148, Institut National de la Santé et de la Recherche Médicale (INSERM), 60, Rue de Navacelles, Montpellier 34100, France [37]

Françoise Vignon, Unit 148, Institut National de la Santé et de la Recherche Médicale (INSERM), 60, Rue de Navacelles, Montpellier 34100, France [37]

Bruce Westley, Unit 148, Institut National de la Santé et de la Recherche Médicale (INSERM), 60, Rue de Navacelles, Montpellier 34100, France [37]

Örjan Wrangé, Department of Medical Nutrition, Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden [207]

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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.

**Erlio Gorpide
Ricardo Calandra
Carlos Levy
Roberto J. Soto**

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ESTROGEN RECEPTORS, ANTIBODIES AND HORMONE DEPENDENT CANCER

Eugene R. DeSombre, Geoffrey L. Greene,
William J. King and Elwood V. Jensen

The Ben May Laboratory for Cancer Research
The University of Chicago
Chicago, Ill. 60637

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,

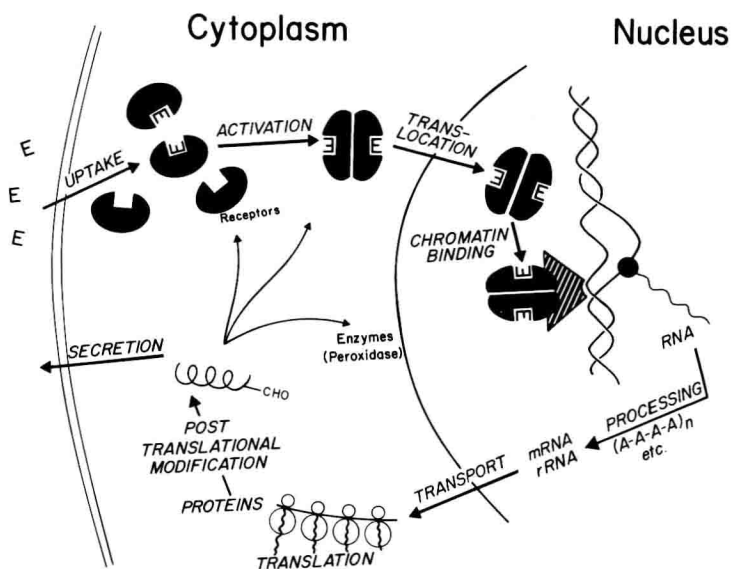


Fig. 1. Schematic diagram of the estrogen interaction pathway and biochemical response in target cells.

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