

STOLL

ENDOCRINE THERAPY
IN
MALIGNANT DISEASE

Endocrine Therapy *in* *Malignant Disease*

Edited by

BASIL A. STOLL

Radiotherapy Department,
St Thomas' Hospital, London
and Royal Free Hospital, London

1972

W. B. Saunders Company Ltd

LONDON · PHILADELPHIA · TORONTO

W. B. Saunders Company Ltd: 12 Dyott Street
London WC1A 1DB
West Washington Square
Philadelphia, Pa. 19105
1835 Yonge Street
Toronto 7, Ontario

Endocrine Therapy in Malignant Disease

ISBN 0-7216-8615-X

© 1972 by W. B. Saunders Company Ltd. All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Library of Congress Catalog Card Number 78-188731

Text set in 10/11 pt. Monotype Baskerville 169, printed by letterpress, and bound in Great Britain at The Pitman Press, Bath.

Print No: 9 8 7 6 5 4 3 2 1

13 W
005

Preface

The results of the pioneering researches of Dr Charles Huggins 30 years ago led to the wide adoption of endocrine therapy in advanced prostatic cancer, and stimulated the practice of similar treatment in advanced breast cancer. In the last 10 years, endocrine therapy has established a place also in the management of cancers of the uterine body, kidney and thyroid, while steroid therapy is widely used in the treatment of the leukaemias and lymphomas. The place of endocrine therapy in the management of cancers of the cervix, ovary, testis and malignant melanoma is also being investigated.

By collating in one volume the experience of experts in the various fields, it is hoped that there will emerge a unifying concept of hormone-sensitive cancer in the human, and its rationale of treatment. To achieve this, it is essential in the first place to distinguish the clinical response to corticoid and androgenic steroids which is often observed in late cancer of *all types*. This is likely to be by a non-specific host effect, and by juxtaposing this type of response to the *specific* response of hormone-sensitive cancer to endocrine manipulation, it is hoped that our understanding of both mechanisms will be clarified.

The field of hormone therapy in malignant disease tends to involve many different

specialists—endocrinologist, urologist, gynaecologist, general surgeon, general physician and radiotherapist. Because of this diversity of specialists, and because of a very extensive world literature claiming effectiveness for multiple methods of treatment and multiple new agents, it has become increasingly difficult, even for the specialist clinician, to judge the relative merits of each form of treatment. Because of these uncertainties, it is likely that different treatment will be received for the same type of lesion according to the centre where the patient has decided to take advice.

While these uncertainties cannot yet be resolved, certain guide-lines are possible in treatment. Where two methods appear to yield similar results in the palliation of a specific type of cancer, it is obviously humane to choose the method with the lesser morbidity and lesser risk. Even if a controlled trial shows one method to yield better *overall* results than another method of treatment, this does not indicate that it should be used as a routine. Our knowledge has developed to the extent that, at least in the case of prostatic and breast cancer, we can take certain aspects of the tumour-host relationship into consideration, in determining the type of treatment necessary in

the individual patient. In the case of these tumours, reasonably reliable indices are available of three aspects of the tumour-host relationship: the pattern of the patient's hormonal environment, the activity of the tumour, and the sensitivity of the tumour to its hormonal environment.

To help in understanding the reasons for the choice of therapy, each section includes a discussion of factors which may have a bearing on the initiation and maintenance of that particular type of hormone-sensitive cancer. There will probably be noted some degree of overlap between some of the sections. This has purposely not been edited, as it permits the expression of different viewpoints in a field which has developed mainly by empiricism.

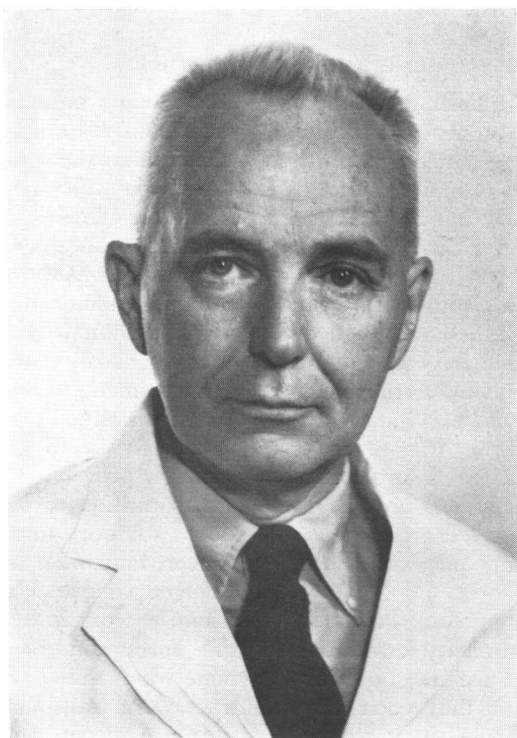
By the very nature of the volume, it makes no attempt to describe the surgical, radiotherapeutic or general management of the patient suffering from advanced malignant disease. Where it is appropriate, however,

the choice is made clear between endocrine therapy on the one hand, and radiotherapy, cytotoxic therapy or 'masterly inactivity' on the other.

Acknowledgement is gratefully made to the management of Imperial Chemical Industries Ltd, Lederle Laboratories, Roche Products Ltd, Schering Chemicals Ltd, G. D. Searle and Co. Ltd, Upjohn Ltd, and W. B. Pharmaceuticals Ltd who provided financial assistance in various clinical trials mentioned in this book. I would also like to express my gratitude to the contributors, all of whom cooperated willingly in the general plan and in providing thoughtful and original reviews of their experience. Finally, my thanks and admiration go to Mr Michael Jackson, the Editor of W. B. Saunders Co. Ltd, and to Miss Mary Bramwell, for whom nothing was too much trouble in the aim of achieving the highest standards in the production of this book.

London, 1972

Basil A. Stoll



Charles Huggins

Father of the Hormonal Treatment of Human Cancer

This commemorative volume honouring Charles Huggins on the occasion of his seventieth birthday provides a further opportunity for commenting on the career of one of the truly fascinating personalities of our time. Just 10 years ago, the scientific community expressed its indebtedness to Professor Huggins for the new insight that he had brought to the cancer problem by contributing a series of papers entitled 'On Cancer and Hormones'. The surprisingly broad range of these essays bears testimony to Huggins' scientific genius and his inspiring

leadership in many areas of experimental medicine.

Fortunately, several recent accounts of his scientific work have been presented by Charles Huggins himself and by his friends and colleagues on the occasion of the Lasker Award (1963), the Passano Award (1965), and the award of the Nobel Prize in Medicine or Physiology (1966), at which time the personal philosophy of the man and his career were also subjected to affectionate scrutiny.

In 1927, when Charles Huggins, fresh

from surgical training at Michigan, joined that remarkable group of founding members of the faculty of the University of Chicago School of Medicine, he seemed certainly destined for a career in clinical surgery, and he had in fact seriously but briefly considered the alternative of private surgical practice in Michigan. He was then—as he is now—young in spirit and enthusiastic, and as yet untouched by the seductive influences of scientific discovery which have engrossed his energies and have given his fertile mind little rest for nearly 45 years. Few would have predicted that Huggins was to have three outstanding careers: as a urological surgeon, as a creative scientist, and as a remarkable teacher who has left an indelible influence on so many young physicians and scientists.

It is deeply gratifying that Professor Huggins' enthusiasm and capacity for attacking scientific problems have in no way diminished with time and that each day continues to find him at his bench in the Ben May Laboratory of the University of Chicago, engaged in the business of discovery which he loves so much and which he regards as one of the most pleasant and satisfying vocations of man.

The present volume bears eloquent testimony to the far-reaching influence of Professor Huggins' discoveries on the endocrinology of cancer, yet it deals with merely one facet of his scientific career. The Nobel Prize was awarded to Huggins (jointly with Peyton Rous whom he deeply admired and revered) 'for his discoveries concerning the hormonal treatment of prostatic cancer', yet the significance of these discoveries was far broader, leading him to enunciate two new principles of medicine: '1. Cancer is not necessarily an autonomous and intrinsically self-perpetuating process, and 2. Cancer can be sustained and propagated by hormonal function which is not necessarily abnormal in kind or exaggerated in rate, but which is operating at normal or even subnormal levels.'

The remarkable first paper by Huggins and Hodges announcing the anti-androgenic treatment of human prostatic cancer, reveals clearly that these important discoveries were not a scientific longshot, but were the culmination of painstaking quantitative experimentation on the fundamentals of prostatic physiology. Moreover, in this same study Huggins demonstrated that androgens adversely influenced the disease process and thereby clarified the scientific rationale for his treatments. On this basis he stated that 'the method of proof of a proposition can sometimes be of greater interest than that which is proved'.

In addition to his monumental contributions to our understanding of prostatic cancer, four other broad fields of study have engaged Charles Huggins. In his first major scientific work in the early 1930s he observed the formation of well-developed ectopic bone when the epithelial cells of the urinary tract were transplanted to connective tissue sites. He recognised quite clearly that transitional epithelium could induce the transformation of fibroblasts into differentiated bone. This potentially extremely important discovery, which lay dormant for nearly 40 years, is currently attracting considerable scientific attention. In fact, Huggins himself has recently returned to a full-scale attack on this problem. He now finds that totally non-viable transplants of powdered, dehydrated, acid-demineralised matrix of bone and tooth are competent under certain conditions and with some species restrictions to induce self-perpetuating transformations of normal rodent fibroblasts into cartilage and bone. The nature of the chemical principles responsible for these transformations is currently Professor Huggins' consuming interest.

Pioneering studies on the biochemistry and physiology of the male urogenital tract, preparative for and concomitant with the work on human prostatic cancer, formed the scientific basis for the development of the hormonal treatment of this disease. A

comprehensive series of studies on mammary cancer in man and rodents were initiated in 1951 when Professor Huggins demonstrated the remarkable beneficial effects of bilateral adrenalectomy in a substantial proportion of women with advanced metastatic carcinoma of the mammary gland. In 1956 he devised a rapid and highly reproducible method for the induction of mammary tumours that were (unlike most other rodent mammary cancers) hormonally dependent. The Huggins 7,12-dimethylbenz[a]anthracene rat mammary tumour has become an invaluable laboratory model for the study of hormone-dependent breast cancers. These studies encompassed a detailed analysis of the hormonal influences favouring growth or regression of such tumours. They also contributed considerable understanding of the process of tumour induction itself, including a most penetrating analysis of the steric and electronic features contributing to the carcinogenicity of these polycyclic hydrocarbons.

Even a cursory recounting of Professor Huggins' scientific efforts should not omit mention of his studies on serum enzyme levels which he found to be such useful indicators in the monitoring of malignant disease in man. Seeking simplified methodology, he introduced the concept and coined the term 'chromogenic substrates', for colourless compounds which on hydrolytic cleavage yielded coloured products. In searching for other means for evaluating the course of cancer in man, he was led to study the characteristics of coagulation of serum proteins, and one of the most prominent by-products of these studies was the discovery of the sulphhydryl-disulphide interchange chain reaction by Huggins and Jensen in 1948. This basic concept was subsequently to play a central role in clarifying certain oddities in the formation of the three-dimensional structure of insulin and other proteins containing cystine.

It seems only fitting to close with some few words on the scientific philosophy

which has guided Charles Huggins' work and has provided insight and inspiration for so many of his students as well as his peers. We are fortunate in being able to rely not only on personal reminiscences but also on his published talk to the Markle Scholars on what Professor Huggins called 'shoptalk concerned with the craft of medical research'.

Einstein once said: 'that which is eternally incomprehensible to us in Nature is her comprehensibility', and thus he placed emphasis on the basic simplicity of the scientific principles underlying the seemingly unbelievable complex phenomena of Nature. In his own way, Charles Huggins always espoused the virtue of simplicity in the interpretation of experimental findings, and viewed complex explanations with suspicion as a possible cloak for confusion or ignorance. Although Huggins has never shunned the use of sophisticated methodology or instrumentation when necessary, much of his work has displayed the utmost simplicity in its design and economy in its execution, and has rather relied upon his extraordinary powers of observation. He has often emphasised that we are surrounded by many natural phenomena seeking to be recognised and understood. But how to experiment and to discover in the most fruitful manner requires unending practice. It is the key to success, but is an evolutionary process throughout the scientist's life. Huggins has pointed to the importance of working on noble problems which yield conceptual advances and 'influence the age by provoking activity' in others in the scientific community, always bearing in mind that medical research workers 'are the beneficiaries of the hopes and prayers of mankind for the solution of heavy problems of disease'.

At all times Charles Huggins has admonished us against the squandering of our most precious commodity—time. He has stressed the stupendous 'self-pilferage of one's time' which plagues most scientists, and has warned eloquently against the

chairbound scientist engaged in administration or in needless travel, and the futility of committee work. Charles Huggins practises what he preaches, and it is a pleasure to

find him at the approaching of his seventieth birthday exuberant, enthusiastic and addicted to the noble cause of medical discovery.

The Johns Hopkins University
Baltimore, USA

Paul Talalay

Contributors

- THOMAS H. ACKLAND, MD, MS, FRCS, FRACS, FACS, Clinical Instructor, University of Melbourne; Consultant Surgeon, Royal Melbourne Hospital, Australia.
- H. J. G. BLOOM, MD, FRCP, FFR, FACR(Hon.), Consultant Radiotherapist, Royal Marsden Hospital, London, and Institute of Cancer Research, London, and St Peter's Group of Hospitals; Honorary Consultant Radiotherapist, St George's Hospital, St Mary Abbots Hospital, and West End Hospital for Nervous Diseases.
- D. C. BODENHAM, FRCS, FRCS(Edin), Clinical Teacher in Plastic Surgery, University of Bristol; Consultant Plastic Surgeon, Frenchay and United Bristol Hospitals.
- GEORGE CRILE, Jr, MD, Senior Consultant, Department of General Surgery, Cleveland Clinic, Cleveland, Ohio, U.S.A.
- J. D. FERGUSSON, MD, FRCS, Director of Teaching and Research, Institute of Urology, University of London; Surgeon to the St Peter's Hospitals and Urologist to the Central Middlesex Hospital, London.
- K. FOTHERBY, PhD, FRIC, Reader in Biochemistry, Royal Postgraduate Medical School, University of London.
- BRENDAN HALE, DMRT, FFR, Clinical Teacher in Radiotherapy, University of Bristol; Consultant Radiotherapist, The Radiotherapy Centre, Bristol, and the Royal United Hospital, Bath.
- CHARLES HUGGINS, MD, Ben May Laboratory for Cancer Research, University of Chicago; William B. Ogden, Distinguished Service Professor.
- FRANCES JAMES, PhD, Research Fellow, Royal Postgraduate Medical School, University of London.
- ROBERT W. KISTNER, MD, FACS, FACOG, Associate Clinical Professor, Obstetrics and Gynaecology, Harvard Medical School, Boston; Senior Gynaecologist, Boston Hospital for Women; Consultant in Gynaecology, New England Baptist Hospital, Boston, U.S.A.
- J. S. MALPAS, DPhil, FRCP, Senior Lecturer in Medicine, St Bartholomew's Hospital Medical College, London; Honorary Consultant, St Bartholomew's Hospital, and Consultant Physician, St Leonard's Hospital, London.
- WALTER J. MOON, MB, BS, Department of Medicine and Department of Surgery, University of Melbourne; Chairman, Consultative Clinic, Austin Hospital, Heidelberg; Consultant

Clinical Oncologist, Preston and Northcote District Hospital; Clinical Assistant, Royal Melbourne Hospital; Clinical Medical Officer, Peter MacCallum Clinic, Melbourne, Australia.

ALBERT SEGALOFF, MD, Alton Ochsner Medical Foundation, New Orleans; Professor of Clinical Medicine, Tulane University School of Medicine; Attending Physician, Ochsner Foundation Hospital; Consultant in Internal Medicine, Tulane Unit of the Charity Hospital of Louisiana, New Orleans, U.S.A.

BASIL A. STOLL, FFR, Honorary Consultant to the Radiotherapy Department, St Thomas' Hospital, and Honorary Consultant Radiotherapist, Royal Free Hospital, London; formerly Consultant to Cancer Institute of Victoria, and Honorary Consultant to the Prince Henry's Hospital, Melbourne, Australia, and Consultant to the Radium Institute, Liverpool.

PAUL TALALAY, MD, John Jacob Abel Professor, Director of the Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University, Baltimore, U.S.A.

Contents

<i>Preface</i>	v
<i>Charles Huggins</i>	vii
<i>Contributors</i>	xv

Section I: Basic Considerations

1. <i>Biochemistry of Steroids in Normal Subjects</i>	3
K. FOTHERBY AND FRANCES JAMES	
Biosynthesis of steroids	3
Metabolism of steroids	8
Steroids in blood and urine and their estimation	13
Control of steroid secretion	19
Mechanism of action of steroid hormones	21
2. <i>Biochemistry of Steroids in Subjects with Cancer</i>	25
K. FOTHERBY AND FRANCES JAMES	
Breast cancer	26
Prostatic cancer	35
Cancer of the endometrium and cervix	39
Miscellaneous cancers	41
Role of steroids in production and remission of cancer	44
3. <i>Endocrine-Induced Regression of Cancers</i>	53
CHARLES HUGGINS	
Phosphorus metabolism in the genital tract	54
Hormonal control of prostate cancer	55
Clinical mammary cancer	57
Experimental mammary cancer	57
Hormone-deprival in control of cancer	59
Hormone-interference in cancer control	59

4. <i>Steroid Effects upon the Host and his Tumour</i>	63
WALTER J. MOON	
Corticosteroids and their synthetic analogues	64
Androgens	73
Protection against the side-effects of cytotoxic drugs	76
Oestrogens	77
Tumour-host relationships	78
5. <i>Assessment of Tumour-Host Relationship</i>	85
BASIL A. STOLL	
Clinical criteria of response	85
Laboratory criteria of tumour-host relationship	89

Section II: Breast Cancer—Endocrine Therapy

6. <i>The Basis of Endocrine Therapy</i>	111
BASIL A. STOLL	
Major hormonal influences on tumour development	114
Other influences on tumour development	117
Rationale of hormonal control in breast cancer	120
Tumour stimulation by sex steroids	124
Rationale of additive hormone therapy in breast cancer	126
7. <i>Castration and Oestrogen Therapy</i>	139
BASIL A. STOLL	
Therapeutic castration	141
Castration combined with additive hormone therapy	145
‘Prophylactic’ castration	146
Oestrogen therapy	149
8. <i>Androgen, Corticosteroid and Progestin Therapy</i>	165
BASIL A. STOLL	
Androgen therapy	165
Corticosteroid therapy	176
Progestin therapy	182
9. <i>Major Endocrine Ablation and Cytotoxic Therapy</i>	193
BASIL A. STOLL	
Major endocrine ablation therapy	193
Cytotoxic chemotherapy	202
10. <i>Synopsis of Endocrine Management in the Female and in the Male</i>	215
BASIL A. STOLL	
Sequential therapy	219
Inadequate hormonal trials	227
Breast cancer in the male	228

Section III: Prostatic Cancer—Endocrine Therapy

11. <i>The Basis of Endocrine Therapy</i>	237
J. D. FERGUSON	
The contribution of Huggins	237
Endocrine sensitivity	239
Rationale of endocrine therapy	240
Principles of endocrine management	241
Mode of action of oestrogen therapy in prostatic cancer	242
12. <i>Castration and Oestrogen Therapy</i>	247
J. D. FERGUSON	
Castration	251
Oestrogen therapy	252
13. <i>Secondary Endocrine Therapy</i>	263
J. D. FERGUSON	
Androgens in prostatic cancer	264
Progestin therapy	265
Corticosteroid therapy	266
Major ablative surgery	268
14. <i>Indices of Hormone Responsiveness</i>	273
J. D. FERGUSON	
Indices reflecting tumour activity	277
Indices reflecting the hormonal environment of the tumour	280
15. <i>Sequential Management in Advanced Disease</i>	287
J. D. FERGUSON	
Initial endocrine therapy	295
Secondary endocrine therapy	297
Place of cytotoxic therapy in management	299

Section IV: Other Tumours—Endocrine Aspects

16. <i>Endometrial Hyperplasia and Carcinoma in situ</i>	305
ROBERT W. KISTNER	
Endocrine role in initiation and progression of endometrial cancer.	305
Endometrial hyperplasia and carcinoma of the endometrium	306
Rationale for endocrine therapy	308
Endocrine therapy of endometrial hyperplasia and carcinoma in situ	309
Résumé of therapeutic regimen	316
17. <i>Endometrial and Cervical Cancer</i>	323
ROBERT W. KISTNER	
Endocrine therapy in advanced endometrial cancer	323
Hormones and cancer of the cervix	333

18. <i>Renal Cancer</i>	339
H. J. G. BLOOM	
Hormones and renal neoplasia	340
Hormonal therapy	342
Prognosis in advanced renal cancer	359
Current status and prospects for hormone therapy of renal cancer	362
19. <i>Thyroid Cancer</i>	369
GEORGE CRILE JR	
Experience in the control of papillary cancer of the thyroid by thyroid feeding	370
The danger that radiation and hypothyroidism may result in dedifferentiation of papillary into anaplastic cancer	372
Problems in the endocrine management of thyroid cancer	373
20. <i>Malignant Melanoma</i>	377
D. C. BODENHAM AND BRENDAN HALE	
Childhood and the effect of puberty	377
Pregnancy and parturition	378
Variation in survival rate according to sex	379
Spontaneous regression	379
Hormone sensitivity assessment	380
21. <i>Leukaemia and Lymphoma—Corticosteroid Therapy</i>	385
J. S. MALPAS	
The mechanism of the lympholytic effect of corticosteroids	386
Clinical effect of corticosteroids in human leukaemia and lymphoma	389
Combination chemotherapy including corticosteroids	393
Autoimmune haemolytic anaemia complicating leukaemia and lymphoma	394

Section V: Prospective Considerations

22. <i>An Evaluation of Endocrine Ablation Therapy</i>	401
THOMAS H. ACKLAND	
Dilemmas in advanced breast cancer	402
Dilemmas in both advanced breast and prostatic cancer	407
Technical aspects	413
23. <i>Planning for the Future in Hormonal Therapy</i>	421
ALBERT SEGALOFF	
Intracellular mechanisms	421
Endocrine consequences of hormonal therapy	422
Prospects for new hormonal agents	423
<i>Index</i>	427

Section I

Basic Considerations

