STOLL

ENDOCRINE THERAPY IN MALIGNANT DISEASE

Endocrine Therapy in Malignant Disease

Edited by

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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.

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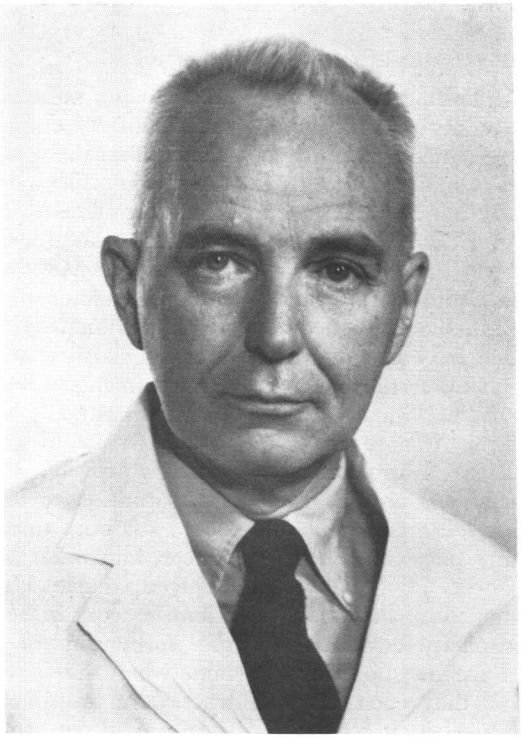
London, 1972

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 sulphydryl-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.

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