PATHOLOGY
OF
TUMOURS

THIRD EDITION

BY

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To my wife Margaret

PREFACE TO THE THIRD EDITION

SINCE THE publication of the second edition of this book 7 years ago, there have been many additions to our knowledge of experimental carcinogenesis, and clarification on many points regarding microscopic structure and histogenesis of several classes of tumours. For this edition all chapters have been revised and the text has been added to or rewritten on the following subjects: the experimental production of tumours, tumours of animals, carcino-sarcoma, epithelial tumours of the tibia and other long bones, the congenital epulides, bronchial carcinoma (especially causation, structure and smear diagnosis), syndromes with pancreatic islet tumours, arrhenoblastoma, dysgerminoma, the smear diagnosis of uterine cancer, infantile testicular carcinoma, haemangiopericytoma, chemodectomas, embryonic hepatic tumours, and lesions of the vascular system associated with malignant tumours. From the huge literature of the last 7 years, only a small selection could be incorporated, and I have adhered to my rule of including only references to works which I have myself consulted. But I hope that the 800 additional references which have been included are fairly representative of the best recent work. In addition, I wish to acknowledge my indebtedness to the following recently published general works on tumours, and to commend them to readers as sources of further references and as presenting fresh viewpoints, sometimes differing from my own:

(a) *Cancer*. Edited by R. W. Raven. Vols. 1–6 (1957–1959). London: Butterworth and Co.
(b) *Atlas of Tumour Pathology*. Armed Forces Institute of Pathology. (1949–1959). Washington, D.C. (Of the proposed 39 fascicles of this unique and invaluable work, 26 have appeared.)
(c) *Histological Appearances of Tumours*. By R. Winston Evans. (1956). Edinburgh and London: E. and S. Livingstone Ltd. (A valuable text accompanies 980 excellent illustrations.)
(d) *Cancer Cells*. By E. V. Cowdry. (1955). Philadelphia and London: W. B. Saunders Co.

I owe a very great aggregate debt to many fellow pathologists, both British and overseas, for sending me interesting specimens, for the stimulus of discussions, and for drawing attention to errors in the previous edition. The task of revision has been greatly lightened by the clerical help of my wife, Margaret, and by the courtesy and consideration of my Publishers.

RUPERT A. WILLIS.

" Riverside,"
Nancledra,
Penzance.
June, 1960

PREFACE TO THE SECOND EDITION

THERE HAS been no epoch-making discovery in tumour pathology since the first edition of this book appeared 5 years ago, but our knowledge has been amplified and clarified in many directions. For this edition the text has been considerably altered or rewritten on the following subjects: the experimental production of tumours, the aetiology of bronchial carcinoma, Brenner tumours, masculinizing tumours of the ovary, the new names applied to some of the rarer tumours or tumour-like lesions of bone, " myoblastoma ", the metabolic aspects of myelomatosis, tumours of chemoreceptors, and the histogenesis of pigmented moles and melanomas. From the huge number of relevant papers and books of the last 5 years, only a small fraction could be selected for incorporation, and I have adhered to my rule of including only references to works which I have personally consulted. It is inevitable, then, that many other papers of value have been omitted; but the 400 additional references which have been included are, I believe, fairly representative of the best of recent work in the various parts of the subject. A second edition of " The Spread of Tumours in the Human Body ", published last year, now provides an up-to-date supplement to Chapters 9 and 10 of the present work.

I am conscious of a very great aggregate debt to many fellow pathologists for gifts of instructive specimens, for the stimulus of discussions, and for drawing attention to errors in the previous edition. Dr. Teoh Tiaw Bee of Hong Kong gave me Figs. 230 and 231, and also prepared new and better prints of a number of the other figures; and Miss Zaidée Milner greatly lightened the task of ensuring the accuracy of references and rewritten passages.

RUPERT A. WILLIS.

LEEDS, *March*, 1953.

PREFACE TO THE FIRST EDITION

THIS BOOK is the outcome of my special interest in tumours during 20 years as a hospital pathologist. Most of the material on which it is based was studied in the pathology laboratories of the Alfred Hospital, Melbourne, between the years 1930 and 1945, and some of the work was written in this period, during part of which I held also a research appointment in the Pathology Department of the University of Melbourne. In a great measure, then, the book is a Melbourne product. Yet, I am fortunate in my present post at the Royal College of Surgeons in that this is in part a research appointment; so that, during the past two years, in addition to carrying out routine duties in the restoration of the museum and in teaching, I have also been able to complete the present work. A few comments regarding the contents are necessary.

General scope of the work.—While aiming to give a useful general outline of each topic, I also wished the book to be a personal record of my own observations and conclusions. Throughout, therefore, I have used my own material as fully as possible, and have introduced many brief reports of personally studied cases illustrative of the subjects under discussion. For the same reason, I have made frequent reference to my own published papers and to my earlier book, "The Spread of Tumours in the Human Body", the contents of which in many ways supplements that of the present larger work. On controversial matters, too, while indicating that they are controversial, I have preferred to avoid non-committal vagueness and to state plainly my own present opinions, even though these may have to be modified in the light of future experience.

The book is addressed primarily to pathologists, research workers and senior students; but I am not without hope that clinicians also may find it useful, and that even elementary students may find it intelligible. My conviction that much has yet to be learnt from the comparative pathology of tumours is shown by a chapter on this subject in Part I and by sections devoted to it in the chapters of Part II.

Illustrations.—The figures are all from personally studied material, and most of them have not previously been published. With few exceptions they are microphotographs; illustrations of gross type-specimens are unnecessary for those to whom the book is addressed, and indeed are often not very instructive even for elementary students, who will learn much more from actual specimens at operations and necropsies and in the museum. In selecting the figures, I have often omitted those illustrating the well known appearances of common tumours, such as are to be found in nearly every text-book; I have preferred rather to show less familiar and special features, and particularly the range of structure possible in tumours of the less common kinds. I have tried also to avoid needless reduplication of figures showing similar structural types of growth; e.g. since the range of structure of squamous-cell carcinoma is adequately illustrated for tumours of the skin and oral cavity, I have given few or no illustrations of this type of growth in the oesophagus, uterus, vulva and penis. Most of the figures

are from cases reported in the text, and the legends often supplement the text descriptions. Except where the legends state that special stains were used, the figures were prepared from paraffin sections stained by one or another of the ordinary haematoxylin methods. The magnification of all figures is given.

References.—The reference lists given at the ends of the chapters are far from complete; I know that I have omitted many important references which might have been preferable to some of those included. To the writers of important papers which are omitted, I tender my apologies. My excuse is that no man can possibly read more than a small fraction of the literature on even a small section of the subject, and I have preferred to base my discussion on what I have read or at least consulted. For a writer to give long lists of references to papers he has not seen is always futile and often dishonest. On controversial matters, I have tried to select my reading impartially, but I am well aware that I may not always have succeeded in this. Whatever omissions I may be guilty of in my reference lists, I can at least claim that they comprise works which, with very few exceptions, I have personally consulted in the original. Works listed in bold type are those which I have found particularly useful, as marking important discoveries, or as good reviews with useful lists of further references, or for other reasons which I have in many instances stated in parentheses.

Acknowledgements.—My happy association during 15 years with the members of the medical and surgical staff of the Alfred Hospital—too many to mention all by name—placed me deeply in their debt for stimulating discussions in ward and laboratory and for free access to the records of their cases. Individual acknowledgement is made in the text to those who have permitted me to record the histories of privately treated patients. With pleasure I express also my indebtedness to Professor P. MacCallum, of the University of Melbourne, with whose Department I was happily associated as a research worker for nearly 18 years.

Many others of my fellow-pathologists, both in Australia and Great Britain, have helped me by the exchange of specimens and ideas; I can thank them only collectively, for they are too numerous to name. But I must record my special indebtedness to two of them. Most of my manuscript was read by Professor G. W. Nicholson, formerly of Guy's Hospital, who made many valuable suggestions and criticisms. Those who value his writings as highly as I do will understand how privileged I feel to have had such a mentor. My second special debt is to Dr. Leila M. Hawksley, formerly pathologist to the Cancer Hospital, London, who has given me many valuable specimens of unusual tumours, especially of the gonads, bones and muscles, and who has helped me to clarify my ideas on many debatable points.

The dedication of this book to my wife, Margaret Willis, is more than usually appropriate, for not only has she given unstinted wifely encouragement to studies which meant surrender of many of our accustomed pleasures, but she also made many of the microscopical preparations, aided in many dissections and took some of the photographs. I record with pleasure my special thanks to Mr. Reg Prosser, of the Alfred Hospital Pathology Department, for his expert preparation of many thousands of microscopical sections; to Mr. Frank Watson, of the Buckston Browne Research Farm, for his preparation of the majority of the microphotographs; to my secretary, Miss Patricia Leicester, whose efficiency and enthusiasm

greatly lightened the task of preparing the manuscript ; and to Mr. W. R. Le Fanu, Librarian to the College, and his staff for much bibliographic help under difficult conditions.

For permission to reproduce from my published papers Figs. 2–7, 12, 13, 286, 301 and 302, I am indebted to the Editor of the *American Journal of Cancer* and of *Cancer Research*. The Editor of the *Journal of Pathology and Bacteriology* kindly permitted me to reproduce Figs. 39–41, 167, 189, 382, 454, 464–468, 470, 471, 473, 475, 477–490, 492 and 493. Figures 185–188, 309, 312 and 386 are reproduced by permission of the Editor of the *Medical Journal of Australia*.

An author could not wish for greater consideration and courtesy than my Publishers have given me.

RUPERT A. WILLIS.

LONDON, *May*, 1947.

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CHAPTER 1

DEFINITION OF TUMOUR

DEFINITION

IT IS scarcely necessary to state that in this work the word *tumour* is used in the restricted or specific sense of a true neoplasm, and not in its ancient and general sense of any localized swelling, which included also inflammatory and reparative masses, hyperplasias, simple cystic swellings and malformations. Indeed, a main task of this chapter will be to determine in what ways true tumours or neoplasms differ from all of these.

In his admirable Erasmus Wilson Lectures in 1925, Nicholson maintained "that it is impossible to define a tumour. Wherever we look we see that tumours exhibit no differences in kind but only differences in degree—and these often the slightest—from the other tissues of the body. I have tried for years to formulate a definition, but have failed. Others have been bolder. I will not weary you with their definitions, every one of which breaks down at one or more points". In spite of this deterring statement by one whose knowledge and judgement demand the greatest respect, I nevertheless shall essay a definition. I believe that it is possible to frame a satisfactory definition, avoiding the grosser defects of some previous attempts, and clarifying by explanatory notes those obscurities which the very brevity of defining creates.

A tumour is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change.

ANALYSIS OF THE DEFINITION

(1) "An abnormal mass of tissue"

The essential tissue of a tumour is the actively growing cells of a specific kind or kinds which comprise the tumour proper, as distinct from incidental cells of other kinds which form the stroma of the growth or which are due to secondary inflammatory or phagocytic reactions in it. Thus the essential tissue of a myoma is its muscle fibres; its connective tissue strands and blood-vessels are merely the supporting and vascular framework of the tumour tissue proper. So also in a malignant tumour, for example a scirrhous carcinoma of the breast, although wide areas of the growth may consist of much dense fibrous tissue with only scattered groups of epithelial cells, there is no doubt that these cells only have suffered neoplastic change, and that the excessive fibrous tissue results merely from reactive changes in the stroma. In tumours, then, as in normal organs, we must distinguish parenchyma or tumour tissue proper from stroma or merely supporting and vascular tissues.

In most tumours the neoplastic tissue consists of cells of a single kind derived from a single kind of tissue. Tumour classification and nomenclature are largely based on this fact. Thus a myoma is a tumour whose parenchyma consists of muscle fibres only; a chondroma is composed solely of cartilaginous tissue;

a carcinoma consists only of malignant epithelial cells ; and so on. The development of a tumour in a particular region thus usually implicates only one of the various tissues of the region ; a carcinoma is a growth of the epithelial elements of the part, the connective, muscular, and adipose tissues and blood-vessels of which do not share in the neoplastic change ; a glioma arises from and consists of neuroglial cells alone, and the nerve cells, connective tissues and vessels of the affected area do not participate in the growth save only incidentally as a stroma to it.

Some tumours, however, are truly mixed or composite, in that they consist of two or more kinds of neoplastic tissue. The most familiar example is the ordinary fibro-adenoma of the breast, the epithelial and connective tissue components of which are both neoplastic. So, also, in the rare mixed tumours of the adult uterus or thyroid, both epithelial and non-epithelial tissues are si multaneously involved. The mixed tumours of childhood and the teratomas are special classes of neoplasms, the origins of which are related to disturbances of growth at early periods of development.

(2) " Growth in excess of and uncoordinated with that of the normal tissues "

Uncoordinated cellular proliferation, in excess of that of the normal tissues, is a main characteristic of neoplasia, distinguishing it from all other kinds of pathological proliferations, whether inflammatory, reparative or hyperplastic. Nicholson, in spite of his disinclination, already cited, to define neoplasia, nevertheless in a later work (1933) recognized this failure of co-ordinated growth as its essential character. He said, " The bulk and activities of a somatic tissue, whether strictly normal or hyperplastic to any extent, are co-ordinated with those of the organism. Not so with tumours. Failure of co-ordination is the distinctive character of every tumour".

There are some normal tissues the cells of which, in the adult body at least, rarely or never multiply, e.g. muscle fibres or nerve cells. A progressively growing tumour composed of such cells, i.e. a myoma or a ganglioneuroma, clearly possesses proliferative power in excess of the normal rate, which is zero. Other tissues of the body, however, such as surface epithelia and the haemopoietic tissues, normally exhibit mitotic proliferation of their cells to replace those which are constantly lost. A tumour of such tissues exhibits mitotic activity in excess of this normal replacement rate ; the tumour outgrows its parent tissue, slowly or rapidly, forming an ever-increasing superfluous mass. Very rapidly growing tumours exhibit relatively enormous numbers of mitotic figures ; I have sections of carcinomas in which nearly 10 per cent of the tumour cells are in mitosis, a proportion greatly exceeding that for the corresponding normal epithelia.

(3) " Excessive growth persisting after cessation of the stimuli which evoked the change "

Usually, once a tumour is engendered, its cells continue indefinitely to outgrow those of the normal tissue. It is true that, of certain classes of tumours, individual examples of arrested growth or even retrogression are seen, but this does not invalidate the general proposition. Of benign tumours, uterine myomas afford good examples of these characteristics. While cessation of growth is not

uncommon in individual tumours of this kind, the majority of myomas grow progressively and often to a huge size. The individual myoma which exhausts its power of growth during the lifetime of the body in which it lives is not thereby to be placed in a different class from all the other progressively growing myomas. In rare cases, even malignant tumours have been known to become quiescent or even to disappear. This, however, does not invalidate the all too general rule that unteated malignant tumours grow progressively to a fatal termination, and the occasional exceptional tumour is none the less a tumour of the same class as its fellows.

The most distinctive characteristic of a neoplasm is that it retains its property of persistent excessive growth independently of the stimuli which evoked it. There is ample evidence of this, in spite of the defects in our knowledge of the causation of many kinds of tumours. The experimental evidence alone is conclusive. Experimentally produced tumours of every kind may develop long after applications of the chemical or physical carcinogens have been discontinued, and the growth of established tumours proceeds indefinitely without further applications of the carcinogens. This irreversible neoplastic habit of growth, not dependent on the continued presence of the evoking agent, is most strikingly apparent with transplantable tumours; for these can be transferred by successive passages to many other animals and yet retain their neoplastic properties unimpaired. Cultures of tumour cells *in vitro* also maintain their peculiar properties, and grow into tumours when engrafted into fresh hosts.

So also with human tumours; of those the extrinsic causative agents of which are known, many develop long after these agents have ceased to act. Mule-spinner's cancer, lung cancer in the Schneeberg miner, actinic cancers of the fair-skinned farmer or sailor—these may all appear many years after the victims have retired from their hazardous occupations. Of course, there are many patients who are still engaged in these occupations at the time when their tumours first appear; but such continuous exposure to carcinogenic stimuli is clearly not essential for the initiation of tumours, much less for their continued growth once they have developed.

It may be objected that there is no proof that, during the genesis and subsequent growth of a tumour, the responsible carcinogen has ceased to act; but that, for example, a carcinogenic hydrocarbon *may* be retained in infinitesimal but effective amounts in the cells of the established tumour evoked by it. A little reflection, however, will show the untenability of this view. We know from experiments (*see* Chapter 4) that extremely minute quantities of chemical carcinogens, e.g. 0·0004 milligram of dibenzanthracene, can evoke transplantable tumours. To suppose that such minute quantities are retained in the tissues, to be distributed indefinitely amongst all the cells of the growing tumour, its metastases and its transplants, is to suppose the impossible; there would not be enough molecules of the substance to permit of such unlimited distribution. Again, the genesis and growth of tumours evoked by ultra-violet light, X-rays or other radiations, are clearly not dependent on continued applications of rays: the actinic or X-ray cancer may appear and progress long after exposure has ceased. It might be argued that the radiations act only indirectly by producing a chemical carcinogen

in the tissues and that it is this which persists in and maintains the growth of the resulting tumour; but this, of course, is the same impossible supposition as we have just rejected.

It is clear that tumour growth cannot be conceived as being maintained by the continued stimulation of the tumour tissue by the same agents as evoked it. These agents must act by initially inducing in the cells irreversible changes of metabolism and proliferation, which are then transmitted indefinitely to the descendants of the initially changed cells—in the primary tumour, in its metastases, in transplants and in explants *in vitro*. The nature of these changes, the very essence of the neoplastic reaction is still unknown; it is discussed further in Chapter 11.

DEFECTS OF SOME PREVIOUS DEFINITIONS

Some previous definitions of tumour have failed in that they have omitted the all-important characteristic of continued disproportionate growth independent of evoking stimuli. Thus Powell White's definition, adopted by both Adami and Kettle, defined a tumour as a "mass of cells, tissues or organs, resembling those normally present in the body, but arranged atypically, which grow at the expense of the organism without, at the same time, subserving any useful purpose therein". Because this definition said nothing of a tumour's progressive disproportionate growth, it failed to distinguish tumours from malformations, to all of which it was perfectly applicable. Failure to make this distinction has led to the unwarranted inclusion of a number of simple malformations amongst tumours, an error which is discussed further below.

The unlimited disproportionate growth of tumours has led many writers to infer, erroneously, that tumours possess complete autonomy and are exempt from the laws of normal growth. Thus MacCallum's definition included the statement that tumours "grow without any regard for the laws which govern and restrain the growth of normal tissues"; and it has often been asserted that tumours grow "without control", "in an anarchic manner", "lawlessly" or "as parasites". Ewing defined a tumour as "an autonomous new-growth of tissue". But, as Nicholson (1921) so emphatically insisted, and as Foulds (1940) has more recently repeated, the orderly architecture and functional activity of many tumours refute such views. Again Nicholson (1933) pertinently said, "It is all very well to prate of the laws of normal growth which are 'transgressed' by autonomous tumours. But it would be better still to enumerate these laws, to show how they are 'enforced' in normality and in morbid states in which there is no autonomy of the peccant part, and above all to decide on the guilty party when they are 'broken'". Tumours are neither "lawless" nor "autonomous" in the sense that they obey peculiar laws of their own. The idea that tumours are "lawless", "anarchic" or "parasitic" clearly arises from too exclusive a view of the malignant tumours of rapid growth, poor cellular differentiation and destructive effects. These malignant qualities obtain in only a proportion of tumours, and then in very variable degrees. The terms "autonomy" or "lawlessness" as applied to tumours are indeed but figurative ways of expressing their main characteristic, namely, their continued excessive cellular