EVANS' HISTOLOGICAL APPEARANCES OF TUMOURS

VOLUME 1

DAVID J. B. ASHLEY

THIRD EDITION

CHURCHILL LIVINGSTONE

Evans' Histological Appearances of Tumours

David J. B. Ashley, T.D., M.D., F.R.C.Path.
Consultant Pathologist, Morriston Hospital, Swansea; Visiting Professor of Pathology, University of Chicago; Visiting Scholar, State University of New York, Downstate Medical Center; Formerly Research Fellow, Armed Forces Institute of Pathology, Washington, D.C.; Senior Registrar in Pathology, David Lewis Northern Hospital, Liverpool.

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Evans' Histological Appearances of Tumours

Preface to the Third Edition

It was a daunting prospect which faced me when I was asked take over the authorship of Dr Winston Evans' book. I was his Senior Registrar in Liverpool and have been in close touch with him over the years, and, because I share his philosophy of the nature of histopathology as a clinical as well as a scientific discipline, I have taken on the task of producing a third edition of what has become a standard work.

The whole of the text has been revised and in large part rewritten to include more recent original work in the field of tumour pathology and a number of new illustrations have been added. In particular the chapter on lymphoid tumours has been extensively revised. Some rearrangement has been necessary, tumours of the endothelium are now included with respiratory tumours rather than among tumours of vasoformative tissue, and the carcinoid and chromaffin tumours are now placed with other tumours of endocrine organs. A separate section on the teratomas has been added because of the unusual nature of these neoplasms and the unusual features of their histogenesis. A major alteration has been to add an introduction and to divide the work into sections each comprising a group of chapters on related tumours preceded by a short general essay on the group as a whole. As in the previous editions the relationship between the clinical and pathological features of the tumours is stressed. I have followed Dr Evans in aiming to produce a work which will be helpful to the practising histopathologist and to his clinical colleagues in their daily work as well as to the trainee and to the research worker.

I am indebted to my clinical colleagues who have allowed me to use data from their patients, and to many colleagues in pathology who have given me slides for illustrations. My thanks are particularly due to Dr Joan Summerell, who has discussed many aspects of the work with me.

Mrs Winston Evans has allowed me free access to the material which Dr Evans had collected in preparation for this edition.

I thank Mr Howard Fry, Mrs Linda Easton, Mr Jeffery Hole and Miss Caroline Penry, who prepared the histological specimens for me; and Mr Hole also carried out a great deal of the photographic work.

Miss Marilyn Marks, librarian to the Swansea Hospitals, helped greatly by collecting and checking many references for me.

I am particularly indebted to my research assistant Mrs Molly Rees B.A., who has typed and re-typed the manuscript, collated apparently innumerable references and has helped with the index.

During the preparation of this work I have held a research grant firstly from the Welsh Hospital Board and latterly from the Welsh Office. I am greatly indebted to them for this help.

My new publishers, Messrs Churchill Livingstone, have given me full cooperation in the preparation of the manuscript and in the editorial work necessary between the stages of typescript and print.

Swansea

DAVID J. B. ASHLEY

Extracts from the Prefaces to the First and Second Editions

'Without some knowledge of the development of the part, it is impossible to arrive at a full understanding of its disease.'

NICHOLSON.

This book is concerned not only with the histological and histogenetical aspects of tumours but also with the development of the tissues and organs from which they arise; it describes the morphology of tumours and seeks also to present certain features of their behaviour and clinical effects which, it is hoped, will be of interest to surgeon and physician as well as of assistance to the hospital pathologist. Toward this end biochemical, haematological and endocrinological features are discussed when they are considered useful in the investigation, diagnosis and prognosis of neoplastic disease. The writer has sought to provide also some information touching upon the incidence of neoplasms, their distribution and their relationship to age and sex.

The spread and mode of origin of tumours is mentioned in some detail and the possibilities of correlating the structure with the behaviour of neoplasms is outlined. In this connection it cannot be emphasized too strongly that it is sometimes impossible to express an opinion with regard to the probable behaviour of a tumour from a study of its histological characters alone, and the careful pathologist will guard against coming to a conclusion until he has not only employed every technical procedure likely to be of value but has also studied in full the clinical features of the case; for it is well known that certain growths, despite the exhibition by them of structural characters usually displayed only by malignant lesions, do not behave as such; there are other growths, apparently of well-differentiated structure, which nevertheless disseminate wildly to all parts of the body.

It is hoped that a sufficient number of illustrations of both rare and common tumours have been included so that reference to original articles for photomicrographs, which is often irksome and time consuming, is obviated; for it is always pleasing to be able to turn up an illustration when discussing a particular tumour with a clinical colleague, and to some extent the book is designed to meet this need in one volume.

The problems of classification and theories of histogenesis are presented, as so often these are relevant to the interpretation of the histological features of neoplasms, and because his views concerning the genesis of tumours are demanded frequently of the pathologist by his clinical colleagues—and also of the student by his examiners. As the understanding of histogenetical problems often can be achieved only by consideration of the normal development of tissues and organs, certain aspects of normal histogenesis, embryology and structure are presented and discussed where this seems to be of particular interest or is thought to be helpful in stressing the similarities and evaluating the differences that exist between normal and abnormal tissue reactions—especially between hyperplastic and neoplastic processes.

The number of cases and specimens available for study by any one pathologist is limited, and it is necessary therefore to correlate one's own experience with that of others; to a large extent this can be carried out only by the gathering of a sufficient number of authoritative articles and treatises from the vast literature that deals wiith neoplastic disease. In this connection the references given at the end of each chapter direct attention only to those articles and books which were consulted by the author specifically for the compilation of the text. The post-graduate student bent upon writing a 'paper' eagerly seeks lists of relevant articles, and it is hoped that among the references given in this book there will be found a sufficiency of old and new ones to meet the requirements of the would-be author.

The material used in the compilation of this book was collected almost entirely at the David Lewis Northern Hospital, Liverpool, and it is with the greatest pleasure that the author acknowledges the assistance given and interest shown by the surgeons and physicians of this hospital—Mr J. B. Oldham, V.R.D., Q.H.S., Mr P. R. Hawe, T.D., Sir Arthur Gemmell, M.C., T.D., Mr E. N. Wardle, Mr W. R. Hunter, Mr W. M. Beattie, Mr G. E. Thomas, Dr C. A. Clarke, Dr A. Thelwall Jones, Dr W. H. R. Cook, the late Professor T. P. McMurray, C.B.E., the late Mr G. E. Simpson, O.B.E., T.D., the late Dr H. S. Pemberton and the late Dr L. Cunningham—their initials appear after the serial numbers of the illustrations of material from the cases which were under their care. Particular thanks are due to Mr Philip Hawe, who read some of the manuscript and gave me much encouragement.

Slides and specimens were also supplied by friends not on the staff of the David Lewis Northern Hospital and the names of these surgeons and pathologists appear after the appropriate legends.

Dr E. K. Dawson of the University Department of Pathology, Edinburgh, read and criticized the whole of the manuscript; for her guidance and encouragement, which were of the greatest help in the preparation of this book, the author is extremely grateful. The writer is also indebted to Dr Dawson for the loan of several slides including those of a tubular adenoma of the testis and of tumours of the urachus.

The first essential for a good photomicrograph is a good section, and any excellence that may be attributed to the illustrations in this book is largely the result of the careful work carried out by Miss Catherine D. M. McDougall, A.I.M.L.T., whose remarkable skill in histology has been of inestimable value and whose photostatic memory has proved often more useful than a filing system. In addition to producing thousands of sections needed for special study and for the composition of the illustrations she has devoted many hours to the preparation of the photomicrographs and to checking the figures and their legends.

To Miss Olive Jones, secretary of the pathology department, the author expresses his unqualified appreciation for the tireless patience with which she has typed and re-typed the manuscript several times. She was invaluable also in collecting and assembling details of the patients' histories and in typing the index; in the former task she received much assistance from Miss

Marjorie Mowat. In the final stages of the manuscript Miss Sheila Manning kindly helped with the typing.

All the diagrams were drawn by Miss Gwenllian Thomas, and it is a pleasure for the author to record his thanks to her.

The task of collecting and checking many references was facilitated greatly by the generous assistance given by Mr and Mrs W. A. Lee of the Liverpool Medical Institution and by Miss Marjorie Conway of the Harold Cohen Library of Liverpool University.

I want to express my especial gratitude to my wife, Margaret, not only for her assistance with the preparation and the correction of the manuscript but also for her invaluable translations of many articles in French and German.

To my publishers, Messrs E. & S. Livingstone Ltd., I am greatly indebted for their co-operation, enthusiasm, and courtesy; no author could wish for greater consideration than was given by them.

THE preface to the first edition pertains to the second except for the addition of twelve new chapters. These have been added for the sake of completeness with respect to neoplasms arising in all organs of the body and relate to aesthesioneurocytomas and tumours of the central nervous system and of the female genital tract and placenta.

Although intrinsic tumours of the brain and spinal cord are not considered so esoteric as to be of little interest to the general pathologist, the writer still regards them as belonging more properly to the special field of the neuropathologist. Tumours of the female generative tract (ovarian neoplasms especially) are treated more extensively.

All the original chapters have been rewritten and enlarged to include newly recognized tumours and their variants. The scope of the present book has changed also inasmuch as the physiological, endocrine, clinical effects and genetic aspects of neoplasms are discussed in greater detail than in the first edition. The results of electron microscopy studies are mentioned only when they bear upon the nature and histogenesis of neoplasms.

Liverpool 1956, 1966 R. WINSTON EVANS

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Introduction

The study of the histological appearances seen in the multifarious tumours of human beings is both a useful part of clinical medicine in that the interpretation made by the pathologist is of importance to the clinician and aids in his therapeutic decisions, and is also an observational branch of science in a similar way to that in which telescope astronomy is an observational branch of physical science. For the most part the study of the histological appearances of tumours is a clinical discipline, we are clinical histopathologists and are concerned with the relationship between the appearances seen through the microscope and the clinical course of the lesion observed and with recommendations either explicit or implicit for the future treatment of the patient. It is worth while here reminding ourselves that the concept of malignancy, one of the major opinions given by a histologist, is a clinical one rather than a histological or pathological one. A malignant tumour is one which, if left untreated, will infiltrate through the tissues and may spread by metastasis to distant parts of the body and is likely to lead to the death of the patient. A certain amount of confusion has arisen in recent years over the concept of *in-situ* carcinoma, which will be discussed at somewhat more length in the section on carcinoma of the cervix, where histological appearances intermediate between those of the normal organ and those of malignant neoplastic disease for which there is adequate clinicopathological correlation, is interpreted as *in-situ* carcinoma and is regarded, on the basis of histological appearances only, as evidence of pre-malignancy. The relationships between clinical observations and histological appearances are of the utmost importance; these were stressed to a considerable extent by Dr Winston Evans in the first two editions of the book and I shall continue the tradition. In each section the relationship between clinical manifestations and the nature of the neoplasm considered will be discussed and an attempt will be made to relate the two one to the other.

Tumours are extremely frequent in human pathology. Approximately one quarter of all deaths is due to tumours, but the distribution of tumours among the various organs of the body is by no means uniform. Table I shows the numbers of deaths from tumours in 1969 in England and Wales and is extracted from the Registrar General's published statistics. In men the most frequent sites for tumours are the respiratory and digestive organs, in particular the lung, stomach and the large intestine, with a considerable number of lymphatic and haemopoetic tumours and tumours of the genito-urinary system, particularly of the prostate and bladder. In females the predominant sites are the breast, the genito-urinary organs, in

Table I Deaths in England and Wales, 1969 (from Registrar General, 1971)

Parameter	Male	Per cent of tumour deaths	Female	Per cent of tumour deaths
Total deaths	296,561		282,817	
Neoplasms	62,584	100·0	53,451	100·0
Buccal cavity and pharynx	980	1·6	650	1·2
Digestive organs	19,659	31·4	18,999	35·5
oesophagus	1,568	2·5	1,323	2·5
stomach	7,300	11·7	5,411	10·1
colon	3,980	6·4	5,915	11·1
rectum	3,122	5·0	2,761	5·2
pancreas	2,666	4.3	2,318	4·3
Respiratory system	25,573	40·9	5,356	10·0
larynx	603	1·0	123	0·2
bronchus and lung	24,651	39·4	5,056	9·5
Bone	265	0·4	221	0·4
Connective tissue	141	0·2	172	0·3
Malignant melanoma of skin	250	0·4	291	0·5
Other malignancy of skin	215	0·3	241	0·6
Breast	76	0·1	10,622	19·9
Genito-urinary organs	7,903	12·6	9,811	18·4
cervix uteri			2,417	4·5
corpus uteri			1,281	2·4
ovary			3,518	6·6
vagina and vulva			542	1·0
prostate	4,000	6·4		
testis	214	0·3		
bladder	2,656	4·2	1,108	2·1
kidney	910	1·5	569	1·1
Eye	74	0·1	80	0·1
Brain	1,017	1·6	723	1·4
Thyroid	98	0·2	308	0·6
Lymphatic and haemopoetic	3,716	5·9	3,189	6·0
Benign neoplasms	248	0·4	404	0·8

Table II Estimated total discharges and deaths in England and Wales, 1970 (from Hospital In-patient Inquiry, 1970)

Parameter		Per cent	
All causes	4,907,740	—	—
Malignant neoplasms	248,280	61·7	
Stomach	13,730		3·4
Colon and Rectum	27,680		6·9
Lung	42,740		10·6
Skin	8,550		2·1
Breast	27,290		6·8
Cervix uteri	10,740		2·7
Other uterus and ovary	6,760		1·7
Prostate	8,630		2·1
Lymphatic and haemopoetic neoplasms	24,140	6·0	
Leukaemia	9,260		2·3
Other	14,880		3·7
Benign neoplasms	130,080	32·3	
Total neoplasms	402,500	100	

particular the ovary and the cervix uteri, the stomach and intestine, the lung and the reticulo-endothelial system. Examination of the hospital in-patient inquiry (Table II) indicates that a considerable proportion of the facilities of the hospital service of Great Britain are devoted to the treating of patients with tumours, approximately one admission in 12 is because of neoplastic disease with a great preponderance of tumours of the lung, breast and gastro-intestinal tract. The relative distribution of tumour types differs from that in Table I because of the large number of admissions for the treatment of benign tumours, and because of differences in the number of admissions required for the management of patients suffering from different tumour types.

In Table III data are extracted from four of the major registries, Birmingham (Waterhouse *et al.*, 1970), Quebec (Potvin, 1970), Puerto Rico in the Caribbean (Martinez *et al.*, 1970) and Ibadan in tropical African (Edington and Hendrickse, 1970). The frequency of oesophageal and gastric cancer is particularly high in Puerto Rico (as it also is in Japan—*see* Chapter 6.2). Intestinal cancer is much less frequent in Puerto Rico and Ibadan than it is in Birmingham and Quebec, while liver cancer is particularly prevalent in Africa. The frequency of lung cancer is far higher in Britain than in the other countries and breast cancer is much more common in the 'Western' countries than in Puerto Rico and Ibadan. Cancer of the female genital tract on the other hand is least common in Birmingham although it is difficult to say to what extent this is related to differences in reporting of *in-situ* cervical carcinoma. The very high incidence of lympho-haemopoetic tumours in Africa represents the frequency of Burkitt's lymphoma. Data on tumour incidence such as that published in the compendious compilation on *Tumour Incidence in Five Continents* (Doll *et al*, 1970) shows that the particularly important sites of tumours are not exactly the same as those which are of importance as producers of death and that many patients who suffer from tumours which are by any clinical or pathological reckoning malignant are capable of being cured by modern methods of medicine and surgery (Table III). The distribution of tumours among various organs of the body is not uniform in different parts of the world.

It is, however, expedient for us to remember that tumours are ubiquitous and that tumours of almost every type can occur in almost every part of the body. In my own experience of tumour pathology, I have been forced to the conclusion that one must never use the words 'must' and 'never' in connection with discussions of the frequency or occurrence of neoplastic disease.

Tumours in children are becoming a relatively more important cause of mortality and morbidity as the control of infectious disease becomes more and more effective. The distribution of tumour types in children differs markedly from that in adults (Table IV). Tumours of the lympho-haemopoetic system form the largest group followed by tumours of the brain. The 'embryonic' tumours, neuroblastoma and nephroblastoma, fall closely behind. In contrast epithelial tumours of the respiratory and digestive tracts are very uncommon in childhood.

It is both desirable and necessary that the histopathologist should not only have a sound working knowledge of the histological appearances of the tumours which he observes but

Table III Relative frequencies of major tumour groups expressed as percentage of total tumours (from *Cancer Incidence in Five Continents*)

Anatomical location	Geographical location							
	Birmingham		Quebec		Puerto Rico		Ibadan	
	M	F	M	F	M	F	M	F
Mouth and salivary glands	3·0	1·8	9·6	2·1	12·0	4·2	5·3	3·1
Oesophagus and stomach	11·9	9·3	8·9	4·0	22·1	10·8	8·3	4·0
Intestine	12·5	13·7	12·7	12·1	4·4	5·8	2·5	2·5
Liver and gall bladder	0·9	1·2	1·3	1·5	1·9	2·2	15·4	3·6
Pancreas	2·9	2·2	2·3	1·5	2·5	1·8	2·0	0·8
Upper respiratory	1·8	0·5	2·9	0·4	3·2	0·7	3·3	1·0
Lung	29·6	4·4	13·5	2·1	6·4	2·7	1·7	1·1
Breast	0·1	24·8	0·2	24·4	0·2	11·4	0·0	12·3
Genitals	8·2	17·5	10·7	26·7	12·0	25·4	6·4	32·3
Kidney and bladder	6·1	2·5	7·9	2·9	4·3	2·3	4·0	1·5
Skin	11·3	10·3	12·5	8·9	16·4	19·0	1·8	2·9
Brain and eye	2·3	2·0	3·8	2·5	2·0	1·3	2·4	2·1
Endocrine	0·4	0·9	0·8	1·6	0·4	1·5	1·4	2·6
Bone and connective tissue	0·8	0·7	1·5	1·3	1·4	1·1	5·5	4·2
Lymphohaemopoetic	5·1	4·1	7·6	5·2	7·0	5·7	33·5	18·7

Table IV Tumour types in children (from Marsden and Steward)

Tumour type	Children (per cent)	Adults (per cent)
Lymphohaemopoetic	38	6
Glioma	17	1·5
Connective tissue	12	<1
Neuroblastoma	7	<1
Nephroblastoma	6	1·3
Teratoma	4	<1
Retinoblastoma	3	<1

also of the general pathology of neoplastic disease. The relationships between tumours and the clinical symptoms which they produce, the various chemical, biological, hormonal, genetic and immunological processes which are concerned in oncogenesis, and it is only by a detailed understanding of the mechanisms of development of tumour cells from normal cells and from the study of the embryological development of the various organs of the body that the nature of the neoplasm which one sees in practice can be understood. It is probable that in most cases tumours arise by malignant transformation of single cells with the production of a clone of cells derived from a single ancestor (Beutler *et al.*, 1967; Fialkow, 1974; Moore *et al.*, 1974). This mechanism of tumour development has been demonstrated by studies of isomorphic forms of enzymes which can be identified in tumour tissues and which can be related to the enzymes produced by the cells of the host, in particular in the case of females who are heterozygous for two allelic genes both carried on the X chromosome and, following the Lyon hypothesis, there is inactivation of one X chromosome at the time of mitotic division (Lyon, 1971). In the somatic tissues one or other X chromosome is active in any particular cell and it can be shown that in tumours of females heterozygous for the enzyme glucose-6-phosphate-dehydrogenase that the tumour cells contain enzymes only active as one of the two allelomorphic forms.

The clone of cells is wholly or partially independent of the normal control mechanisms of the host but still retains to a greater or less extent the differentiative capacity of the cells from which the tumour arises. It is this property of tumour cells which enables us to examine metastases and sometimes to be able to indicate with some degree of precision the site from which the original tumour had arisen, and the different degree and types of differentiation are of value in determining the extent of the malignant process, and the particular type of clinical outcome which may be expected. In the vast majority of cases tumours are lesions of senescence. They are seen after the individual has reached the end of reproductive life and it is probable that on an evolutionary basis neoplastic disease should be regarded as one of the mechanisms of preventing immortality which, to any species, though not perhaps to an individual, would be catastrophic.

The exceptions are the tumours of children which form a separate group (Marsden and Steward, 1968) and are often of a form which suggests an origin in foetal life. It is perhaps worthy of note that many of the experimental tumours used in research laboratories throughout the world are also tumours of young, indeed often of newborn, animals. This difference may explain some of the differences between the experimental and the observational pathology of tumours.

CLASSIFICATION

It is sometimes doubted whether the division of tumours of a given organ into innumerable sub-groups is a useful and valid exercise or whether it is merely hairsplitting. On the other hand, it is often commonly found that lesions which have considerable morphological similarity but not identity may be found to have equally considerable clinical diversity and an accurate assessment of the morphological nature of the lesion may be of considerable assistance in determining the probable clinical course and the most useful form of treatment which may be applied. Ideally, a system of classification and terminology covers the site of the tumour, the cell of origin, the mode of histogenesis, the causal effects responsible for the development of the tumour and the probable clinical outcome. In no case is it possible at the moment to establish such a detailed accurate and sufficient type of classification and we are obliged to use practical schemes of classification which act as a guide to lesions which are identifiable on histological and clinical grounds. Recently, for example, it has been possible to separate different types of seminoma which may have somewhat different prognoses and in very recent times the group of intestinal endocrine tumours has been recognized and the study of these lesions is providing useful information in the fields of clinical medicine, clinical surgery, morbid anatomy and endocrinology.

The histological diagnosis of tumours also involves sometimes identification of the secondary spread of tumours. This is of importance in the control of treatment, and demands of the pathologist a knowledge of the more usual modes by which individual tumours spread from place to place in the body (*see* especially Willis, 1973).

Progression in Tumours

It is important in the consideration of its histological appearances that a tumour can be regarded as a dynamic entity rather than as a static entity. It is probable that most tumours arise from single cells, and that in the course of development of a clinically apparent tumour which may be 10 cm in diameter that the initial tumour cells have undergone a great many successive reduplications. It is probable that the number of generations in the development of a tumour of this size is between 60 and 100, as many cells are lost in the normal process of tumour growth. The tumour is biologically different from the host in most cases, and can be regarded to some extent as an independently evolving separate population of cells which is capable, in the course of its life as a population, of evolutionary change. The concept of survival of the fittest familiar to us from Darwinian evolution, can be applied to the survival of tumour cells. In an evolutionary sense cells which are best able to multiply, to escape from hormonal and other control mechanisms of the host, and to escape from the defence mechanisms—immunity—of the host are in this sense the fittest cells and are the cells which are most likely to survive and to be present at any given time in a tumour. This concept has been worked out in great detail in the case of animal tumours, particularly by Foulds (1961), but because of the ethical difficulties of experiments and of serial biopsies which are not justified on the basis of the necessity for treatment, investigations in human subjects are rather more difficult. However, studies of the clinical features of tumours, the pathology, the cytology, the chemistry and epidemiology do support this concept in the case of the human, and changes in the biology of the tumour

cells may be reflected in changes in histological appearance which we see from examining biopsies (Figs. 0.1 and 0.2).

Clinical evidence of the phenomenon of progression is seen by certain change in the clinical course of the tumour. Many examples can be found in clinical medicine. A common terminal phase in chronic leukaemia is the development of blastic transformation so that the circulating abnormal cells instead of being relatively mature lymphocytes or myelocytes and metamyelocytes become the much more immature lymphoblasts and myeloblasts. This change is accompanied by deterioration in the clinical condition of the patient, and usually presages a fatal conclusion. Similarly, a small cutaneous melanoma may remain small in size and inconspicuous for many years, but then suddenly begin to grow rather more rapidly, and is then found to have taken on malignant characteristics and to be a malignant melanoma. The response to treatment is a clinical feature of tumours which can undergo change. In the case of carcinoma of the prostate the patient's condition may be controllable by the administration of oestrogenic hormones such as stilboestrol, and if, on the basis of improved clinical state, treatment is mistakenly stopped it may be difficult or impossible to re-establish the benefit previously obtained. In the case of tumours of the lymphatic system, it is now usual to use multiple chemotherapy, several chemotherapeutic agents are administered at the same time, or in sequence. In former days it was the practice to use one chemotherapeutic agent at a time, and it was well known that a patient was liable to respond once only to any particular method of treatment. A remission might be produced by treatment with cortico-steroids, or with radiomimetic drugs, but after the course of treatment had been finished, when relapse occurred, treatment with the same drug was likely to be ineffective. In these cases it appears that the responsiveness of the cells has diminished, in other words that a population of cells resistant to the drug has been selected by the environment in which these cells find themselves, so that a new progressed form of the tumour now exists.

Cytological examination has shown on a few occasions that the chromosome pattern of tumours changes from time to time during the course of the disease, and that a single cell line with abnormal karyotype may predominate at one time during the history of the disease (Ford and Clarke, 1963), whereas at a later stage a different cell type with a different chromosome pattern may be found. Tumour cells, as stated above, are to a great extent independent from the normal control mechanisms of the host, and a wide variation in karyotype, which would

Figs. 0.1 and 0.2 These two microphotographs are from a single slide cut from a biopsy of a cerebral tumour.
Fig. 0.1 shows a moderately cellular lesion with cells of uniform type and a few cells suggesting an origin from oligodendroglioma.
Fig. 0.2, taken less than 3 mm from the previous illustration, shows a much more cellular lesion in which there is marked pleomorphism. This part of the lesion is of grade III, the other of grade II.

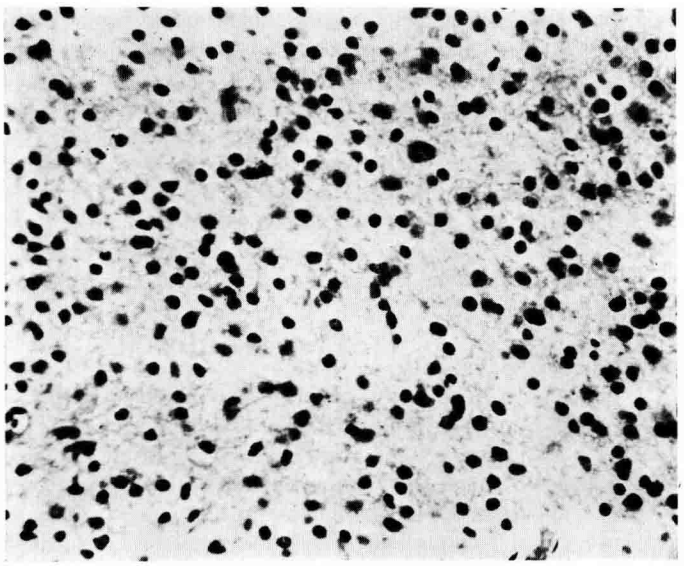

Fig. 0.1 Glioma of grade II. (H. & E.) × 400. 1180/76.

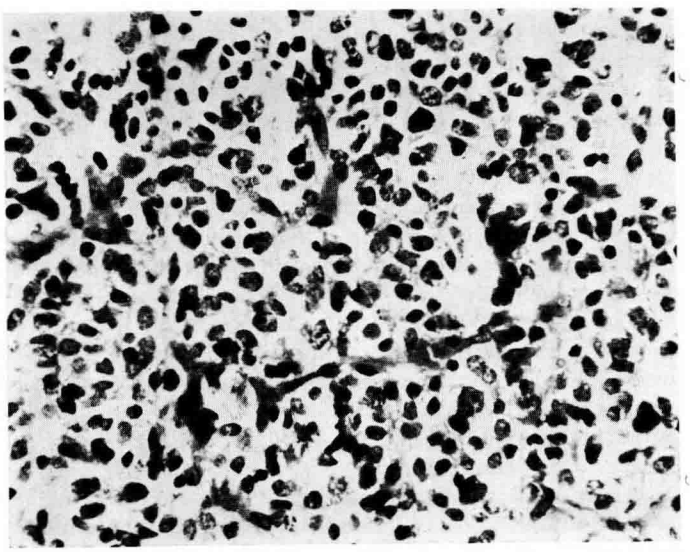

Fig. 0.2 Glioma of grade III same slide as previous figure. (H. & E.) × 400.

Figs. 0.3 and 0.4 Both of these illustrations are from a single surgical specimen. Fig. 0.3 shows a well-differentiated adenocarcinoma of the lung with gland spaces. Fig. 0.4 is from a lymph node in the lung hilum and shows a metastasis of a much less well-differentiated neoplasm in which it is difficult to be certain of a glandular origin.

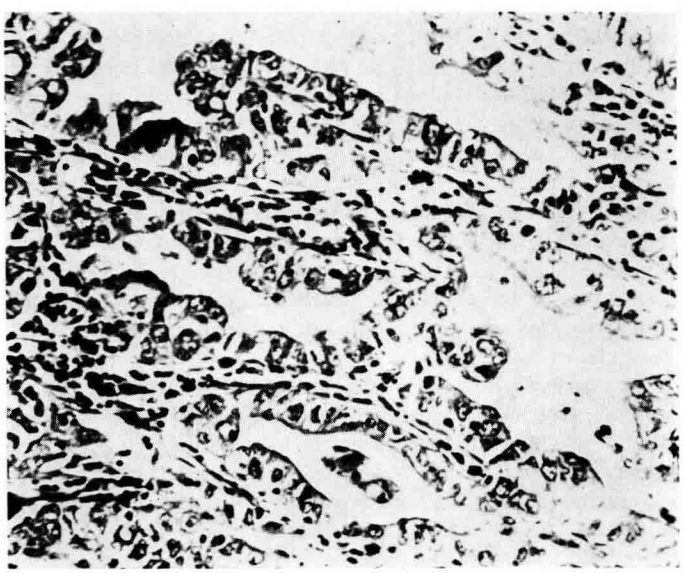

Fig. 0.3 Adenocarcinoma of lung. (H. & E.) × 250. 1834/76.

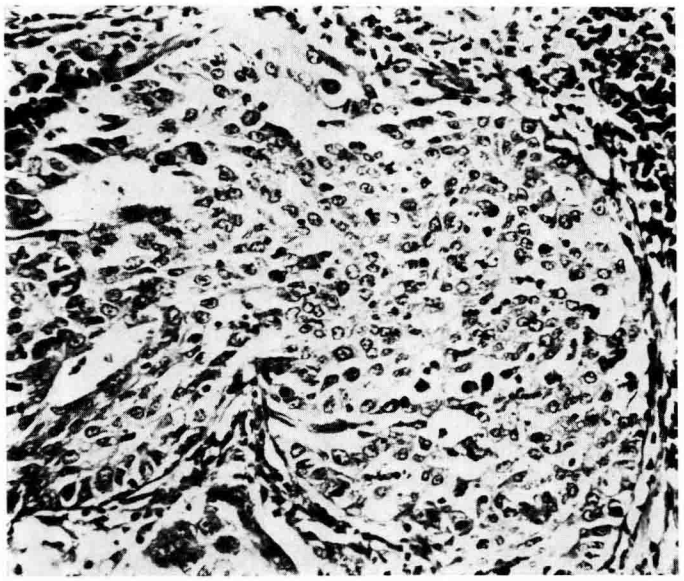

Fig. 0.4 Same case as Fig. 0.3 showing poorly differentiated tumour in a lymph node. (H. & E.) ×250.

not be tolerated in the case of normal cells, can occur and can form the useful marker to the way in which the tumour has changed its character.

In terms of classical histopathology the opportunity for examining repeated biopsies is perhaps less common than we would wish, but it is easy to demonstrate changes in histological pattern within the substance of a single tumour. In the central nervous system the oligodendroglioma is regarded as a slow growing tumour, often visible as flecks calcification on X-ray, which may produce minor symptoms for many years, these often only being recognized in retrospect, but when the patient appears for definitive treatment examination shows fragments of oligodendroglioma and also areas of the much more rapidly growing astrocytoma which is regarded as the tumour responsible for the later clinical symptoms which have made more extensive treatment and investigation necessary. Examination of secondary deposits in comparison with the original tumour frequently shows that the histological appearance of the secondary deposit corresponds to the least well differentiated part of the original tumour, and the various schemes for staging of tumours on histological grounds invariably indicate that from the clinical point of view the stage to be considered is the worst of those which are seen in the histology (Figs. 0.3 and 0.4).

Progression can be inferred from the recognition of serial stages of one tumour. For example, in the colon one can recognize an adenomatous polyp, an adenomatous polyp with intra-mucosal malignant changes frequently designated adenoma malignum, and finally a carcinoma with invasion of the submucosa and muscularis. It is quite frequent to find polyps in association with carcinoma of the colon in patients who are not suffering from the hereditary disease polyposis coli. Histological examination of a series of these polyps may show all the gradations between simple adenomatous polyp and overt carcinoma (Figs. 0.5–0.7). Similarly, in the uterus there may be sarcomatous change in a uterine fibroid, and the mixed salivary tumour may when it recurs exhibit a different histological picture, often of the type of cylindroma.

The entities of atypical endometrial hyperplasia and of latent carcinoma of the prostate (Ashley, 1965) may be early stages of a lesion which can progress to obvious carcinoma, although in the latter case, and in the case of carcinoma *in-situ* of the cervix it is posible that regression may occur rather than progression.

The production of chemical substances by tumours, hormones and the immunoglobulins of myeloma, provide additional evidence in support of this concept. A hormone producing tumour may continue to produce hormones throughout its existence, but on the other hand may, at a late stage, cease to do so. The proteins of myeloma can be identified with great accuracy, and it is now recognized that patients may develop

Figs. 0.5 to 0.7 Showing a carcinoma of the colon which had infiltrated through the muscularis and a polyp in the adjacent mucosa with intra-mucosal neoplastic change. 786/64.

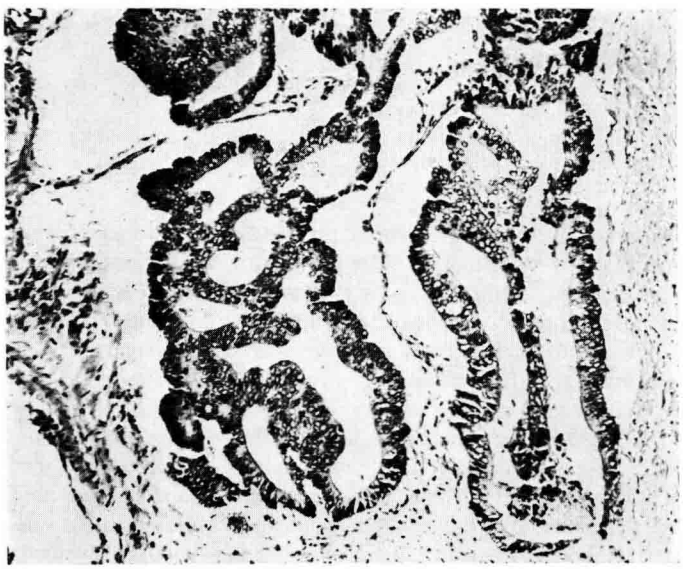

Fig. 0.5 A fairly well-differentiated adenocarcinoma of the colon invading the muscularis. (H. & E.) ×100. 786/64.

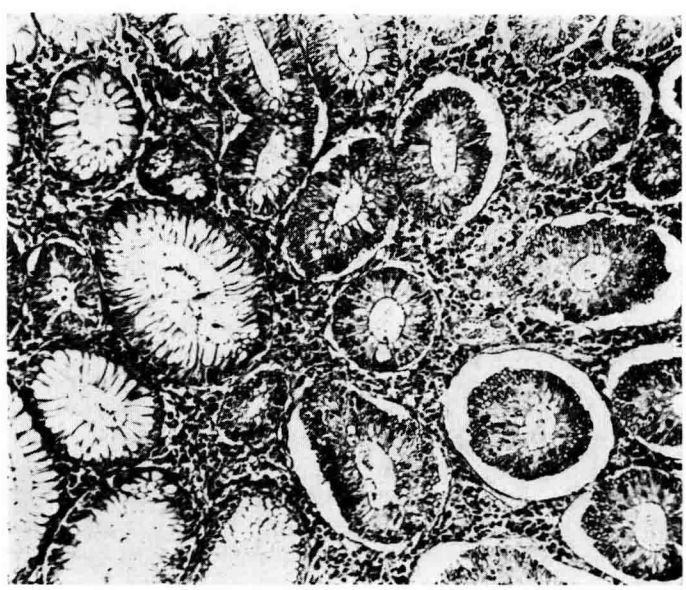

Fig. 0.6 Showing a polyp in the colonic mucosa adjacent to the tumour shown in Fig. 0.5. Part of the lesion consists of normal colonic acini, part of acini formed by cells which show little mucus and are less well differentiated. (H. & E.) ×100.

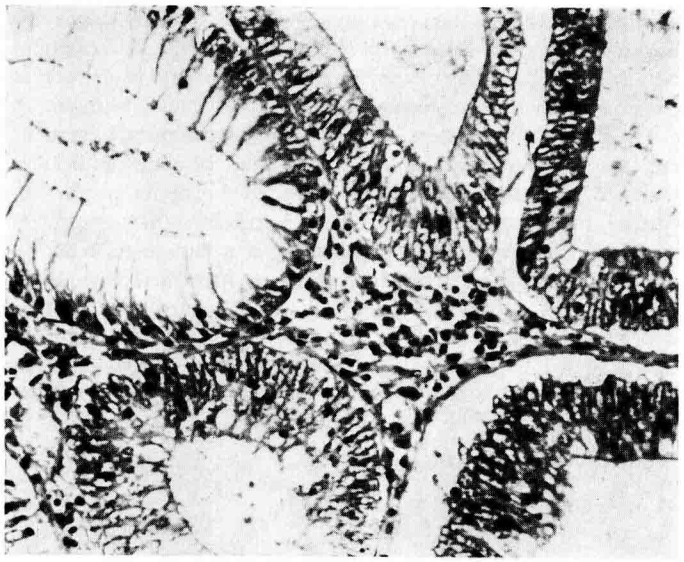

Fig. 0.7 Detail of the last specimen showing the contrast between normal and abnormal acini. (H. & E.) ×250.

a second line of cells producing a different myeloma protein, and that the two lines of cells may show a different reponse to cytotoxic drugs. It is sometimes suggested that these changes are related to the capacity of cytotoxic drugs to damage DNA in the cells. This, however, may be interpreted as an indication that the therapeutic environment may assist in the evolutionary progress of a tumour.

If it has sometimes been suggested that the apparent occurrence of progression in tumours is related to selective biopsy of tumours, and that had the entire tumour been examined on the first occasion that tissues of all the histological patterns seen in serial examination would have been found. This suggestion, to my mind, is untenable, because of the steady direction of progression in the direction of decreasing differentiation it is difficult to imagine surgical techniques by which a biopsy may be taken only from the best differentiated part of a tumour at any given moment, and the presence of less well-differentiated secondary deposits affords further evidence in support of this basic concept. An alternative suggestion that changes in histological appearances are related to reactions of the host is also unacceptable, except in terms of the varying environment in which the tumour finds itself which may contribute to evolutionary changes within the tumour cells.

It is important that this possibility should be borne in mind, because of the importance of clinico-pathological correlation in tumours, we are to a great extent concerned with advising on treatment of patients, and we need to give as good and useful information to the surgeons as we possibly can. We report a tumour in terms of its least well-differentiated part, and we should examine sufficient material from each patient to obtain a representative sample and to give a useful opinion. Serial biopsies can be helpful, and if the experimental technique of tissue culture and examination of sensitivity to chemotherapeutic agents *in vitro* becomes established we shall probably be able to gain more information about the pathological processes which are going on and at the same time as we provide immediate information from the point of view of treating the individual patient.

Regression of Tumours

Regression of tumours, although undoubtedly extremely rare, does occur, but in most cases should not be regarded as the antithesis of progression. It is probable that the spontaneous regression and disappearance of tumours may be more closely related to the immune defences of the host, to hormonal factors in the host, or to substances produced by the tumour itself. The solitary exception is perhaps the transition of neuroblastoma of the suprarenal glands, which on occasion after a period of active growth begins to slow down and on histological examination a transformation to the relatively benign ganglioneuroma is seen. Neuroblastoma of course is a tumour of the developing child and it is possible that the cells of the adrenal from which this tumour is derived are capable of response to hormonal influences, and that in the rare cases when this change does occur that some change in the output of hormones from the hypothalamus and the pituitary may have effected the change.

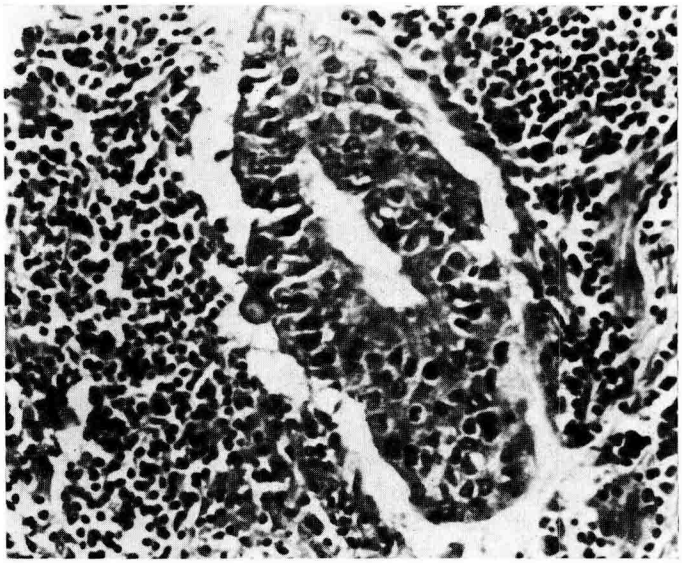

Fig. 0.8 Cancer of the lung showing a well marked lymphocytic reaction. (H. & E.) ×250. 1834/76.

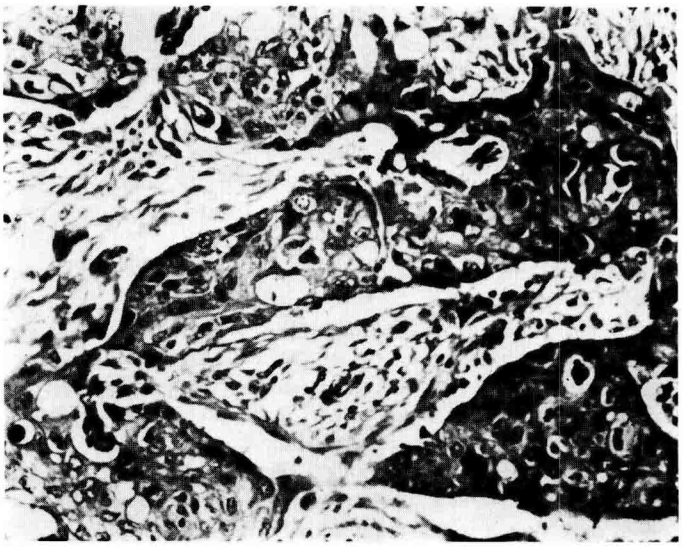

Fig. 0.9 Cancer of the lung showing loose fibrous stroma and no lymphocytic infiltration. (H. & E.) ×250. 1976/76.

Immunological Reactions to Tumours

Interest has been aroused in recent years in the different reactions provoked in the stroma of tumours, the presence of an excess of fibrous tissue or of metaplastic bone or cartilage and the presence of infiltration of lymphocytes and plasma cells which may be taken to indicate a cellular immune response to the tumour (Figs. 0.8 and 0.9). The type of reaction is sometimes correlated with the type of tumour, and it is certainly possible, in the breast for example, that the cells of a scirrhous tumour may be different to those of a medullary tumour, that the one may evoke a connective-tissue response, whereas the other does not. In many cases one sees patches of each tumour type in a single lesion upon the breast.

The Future

Future developments in the assessment of tumours by the histopathologist are difficult to predict. Electron microscopy has been of great value in the identification and categorization of similar type. Tissue culture experiments are and have been useful in the identification of cells and of the cell types from which tumours have arisen, and recent experiments have indicated that tissue culture may be a useful method of determining whether or not the cytotoxic drugs will be of value in the treatment of any particular patient. It is probable that this sort of investigation, coupled with examination of the enzymic activity of individual tumour cells, cultures of tumour cells and extracts of tumour cells, will be of help in solving some of the many problems which still face us, and in enabling us to refine the clinical pathological correlation inherent in our work. It appears to me unlikely that automation will have very much to offer in the immediate future in spite of the prospect offered by Gardner (1970). The majority of histological examination is a matter of pattern recognition and this is not readily susceptible to translation into terms of programming for computers and automatic scanning of tissue sections, although experiments on the automatic classification of assemblages of chromosomes in dividing cells and of individual cells in the blood and in smears of cervical tissue are proceeding apace, and may begin to lead the way to some sort of automatic histological examination.

Undoubtedly the study of the submicroscopic structure of both normal and neoplastic cells will lead to further advances in our knowledge of the nature of neoplasia and to the definition of tumour types which may have different clinical implications. I have indeed frequently referred throughout this work to electron microscopic studies. The use of the electron microscope is not as yet part of the diagnostic methodology of the clinical histopathologist and, while important advances in knowledge are achieved by the use of this tool, the majority of histological diagnosis is still possible with the conventional light microscope. I have not therefore included in this edition illustrations of ultramicroscopic appearances.

There is still a need for the skill, training and experience of the histopathologist, not least in the field of tumour pathology, and of the histological appearances of tumours. Changes are occurring in our understanding of the types of tumour which arise in different parts of the body and of the relationships between the appearances of the tumours and clinical manifestations, both at the time of onset and in terms of the response of treatment and ultimate prognosis. As in so many other fields of scientific endeavour the tendency is for questions to be posed and answered only for it to be found that the solution of a problem leads directly or indirectly to posing of further questions and to the defining of further problems. Many of these will depend upon the experience, observation and clinical contacts of the tumour histopathologist for their elucidation.

REFERENCES

ASHLEY, D. J. B. (1965) On the incidence of carcinoma of the prostate. *Journal of Pathology & Bacteriology*, **90**, 217.

ASHLEY, D. J. B. (1965) The biological status of carcinoma *in situ* of the uterine cervix. *Journal of Obstetrics & Gynaecology (British Commonwealth)*, **73**, 372.

BEUTLER, E., COLLINS, Z. & IRWIN, L. E. (1967) Value of genetic variants of glucose-6-phosphate dehydrogenase in tracing the origin of malignant tumours. *New England Journal of Medicine*, **276**, 389.

COCKER, J., FOX, H. & LANGLEY, F. A. (1968) Consistency in the histological diagnosis of epithelial abnormalities of the cervix uteri. *Journal of Clinical Pathology*, **21**, 67.

DEPARTMENT OF HEALTH & SOCIAL SECURITY (1972) *Report on hospital in-patient enquiry for the year 1970. Part I Tables*. London: H.M.S.O.

DOLL, R., MUIR, C. S. & WATERHOUSE, J. A. H. (1970) *Cancer Incidence in Five Continents*. Vol. II. Geneva: U.I.C.C.

EDINGTON, G. M. & HENDRICKSE, M. (1970) Cancer Incidence in Ibadan, Nigeria 1960-65. In *U.I.C.C. Cancer Incidence in Five Continents*. Vol. II. eds. Doll, R., Muir, C. S. & Waterhouse, J. A. H. Geneva: U.I.C.C.

FIALKOW, P. J. (1974) The origin and development of human tumors studied with cell markers. *New England Journal of Medicine*, **291**, 26.

FORD, C. E. & CLARKE, C. M. (1963) Cytogenetic evidence of clonal proliferation in primary reticular neoplasms. *Canadian Cancer Conference*. Vol. 5. New York: Academic Press.

FOULDS, L. (1961) Progression and carcinogenesis. *Acta Unio Internationalis Contra Cancrum*, **17**, 148.

GARDNER, D. L. (1970) Histopathology and the future. *Journal of Clinical Pathology*, **23**, 119.

LYON, M. F. (1971) Possible mechanisms of X-chromosome inactivation. *Nature (New Biology)*, **232**, 229.

MARSDEN, H. B. & STEWARD, J. K. (1968) *Tumours in Children. Recent Advances in Cancer Research*. Vol. 13. Berlin: Springer Verlag.

MARTINEZ, I., ORTIZ, M., BORRERO, E. & DIVERSÉ, E. (1970) Cancer incidence in Puerto Rico 1963–66. In *Cancer Incidence in Five Continents*. Vol. II. eds. Doll, R., Muir, C. S. & Waterhouse, J. A. H. Geneva: U.I.C.C.

MOORE, M. A. S., EKERT, H., FITZGERALD, M. G. & CARMICHAEL, A. (1974) Evidence for the clonal origin of chronic myeloid leukaemia from a sex chromosome mosaic: clinical cytological and marrow culture studies. *Blood*, **43**, 15.

POTVIN, A. R. (1970) Cancer incidence in Quebec, Canada 1963–66. In *Cancer Incidence in Five Continents*. Vol. II. Eds. Doll, R., Muir, C. S. & Waterhouse, J. A. H. Geneva: U.I.C.C.

REGISTRAR GENERAL (1971) *Statistical Review of England and Wales for the Year 1969. Part I. Tables Medical*. London: H.M.S.O.

WATERHOUSE, J. A. H., LEVI, J. M. & POWELL, J. (1970) Cancer incidence in Birmingham U.K. in 1963–66. In *Cancer Incidence in Five Continents*. Vol. II. Eds. Doll, R., Muir, C. S. & Waterhouse, J. A. H. Geneva: U.I.C.C.

WILLIS, R. A. (1973) *The Spread of Tumours in the Human Body*. 3rd Ed. London: Butterworth.

Section 1 Tumours of the Supporting Tissues of the Body