NEOPLASTIC DISEASE AT VARIOUS SITES

General Editor

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VOLUME II

TUMOURS OF THE BLADDER

Edited by

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TUMOURS OF THE BLADDER

MONOGRAPHS ON NEOPLASTIC DISEASE AT VARIOUS SITES

General Editor

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GENERAL INTRODUCTION TO THE SERIES OF MONOGRAPHS ON NEOPLASTIC DISEASE AT VARIOUS SITES

THIS book is one of a series of monographs on neoplasms at individual sites. The intention is to present a detailed clinical picture of the range of neoplastic disease taking place in one particular organ or tissue at a time. The general scheme is to discuss for each site what is known of the factors leading to the development of neoplasia and the possibilities of prevention or postponement which arise from them; to consider the pathology and natural history of the disease as a means to understanding its course and modes of spread, and thus to have a more secure basis both for planning treatment and for judging its results; to examine the methods of diagnosis of the earliest manifestations or of the pre-neoplastic changes occurring, in the hope of learning to deal with these tumours more frequently and more effectively before they have ceased to be a local problem; and to assess the methods of treatment now available and their value alone or in combination so as to review what is being achieved and to see what more could reasonably be expected. A good deal of variation in presentation has been allowed for, however, because of the very different problems which arise from site to site and which themselves made this method of detailed particularization in the clinical discussion of neoplastic disease seem so desirable at the present time.

Much has been written about cancer without clear definition of what is being discussed. Many of the causative factors would seem to be organ- or tissue-specific, or at least local in their action. The natural history of this group of diseases differs markedly from one site of origin to another, even, in some special cases, when separated by no more than a few millimetres. The diagnostic problems often relate more to other diseases involving the sites in question than to cancer as an ill-defined disease entity. The really effective treatments that are available are still local ones in the great majority of cases and even those which do have some beneficial effect upon the disseminated disease are mostly specific to site of origin. A good deal more could now be done with present methods of treatment for patients with neoplastic disease if the best that is available was more generally applied, and further progress still would result at many sites from earlier treatment.

Vague generalizations about cancer are at present of little use to the individual patients suffering from the disease; a specific particularization about neoplasms at a given site is often of immediate practical value and may point the way to a deeper understanding. The detailed clinical approach to this great problem may be in danger of occupying rather less of our attention than it deserves because of a wishful expectation that some simple solution covering all sites of origin will one day be provided for us.

One of the chief difficulties in the study of neoplastic disease at individual sites is in obtaining sufficient clinical experience. Although these diseases are common, so many parts are involved and the patients are so widely distributed throughout the medical service, that few doctors see many patients with tumours of one particular tissue or organ during their whole lifetime. In 1944 a group of postgraduate teaching hospitals in London started a scheme for joint consultation and co-operation in the treatment of patients with certain tumours. In this way they hoped to pool their experience and to acquire sufficient clinical material for detailed study. This series of monographs is based on the work of this group of hospitals and has been made possible by the large number of patients with tumours at individual sites seen by members of the staffs concerned. It is not intended that the material for these books should be strictly confined to this hospital group, however, but that they should include wide clinical experience wherever it may be found and enlist expert help whenever it is available.

Both the co-operating hospital scheme and the preparation of this series of monographs have for long been of great personal interest to me and I am extremely grateful to my colleagues in my own and in the other hospitals concerned for their unselfish and generous assistance. I took my plan to Mr Charles Macmillan of Messrs E. & S. Livingstone Limited in 1955 and was met with enthusiasm and an immediate promise of help which has been provided in abundance since that day. His response has now led to the establishment of this series, made possible only by a great deal of hard work on the part of many people over a period of years.

Each resulting monograph, in its final form, appears through the efforts of an individual editor working within the general framework laid down. I owe a personal debt of gratitude to each one of them for their forbearance, enthusiasm and unstinted labour. I am also deeply indebted, as they are, to the many contributors who have worked with us in our attempt to realize our aim.

D. W. SMITHERS.

PREFACE

BLADDER tumours present a problem which is of interest to many sections of the medical profession. No longer the exclusive province of the urological surgeon, these tumours provide a fruitful field for study and speculation to statisticians, industrial or experimental organic chemists, pathologists, radiotherapists, physicians and surgeons alike.

The industrial risk has been appreciated for nearly three-quarters of a century. Formerly described as aniline dye cancer of the bladder, it is now appreciated that these tumours may be produced by a large number of chemical compounds. It is to be expected that some tumours, which for lack of information we refer to as spontaneous in origin, may prove to be due to an environmental exposure to particular chemicals, of the dangers of which we are not yet aware.

It is of interest that the tumours produced by known chemicals appear to be similar in every respect to those that appear ' spontaneously '. This observation has naturally led to a comparison between these two groups of tumours in an attempt to find a common factor. Experimental evidence has shown that 2-naphthylamine or 4-aminodiphenyl (the two most effective carcinogenic agents) when added to a normal diet, produce tumours by the action of their metabolic end products excreted in the urine coming into contact with the urinary tract epithelium. There are few tumour sites where such an interesting and progressive body of organic chemical research is going on or where tumours can be produced experimentally which appear so similar to those occurring naturally.

In a growing and ageing population cancer is responsible for the death of more and more people. When the chance of dying of cancer at any age is compared for groups of people born in different years it is seen that this chance is in fact decreasing except for certain sites, notably the lung and the bladder. These are two organs in which cancer is an increasing rather than a decreasing risk, at each age, for each succeeding generation.

In spite of all modern advances in prevention and treatment the mortality from bladder tumours, as shown by cohort analysis, is rising, especially in younger men and in more industrial centres where a possible industrial factor might be suspected but which has not yet been identified. It may well be that clues to further industrial factors may be found through careful cross questioning of a patient with bladder tumour in relation to the details of his employment in various industries.

Few clinicians appreciate the rights of compensation. Except, perhaps, to ask the patient if he is an aniline dye worker, the majority go no further into his occupation. As Occupational Tumours of the Bladder is a prescribed disease and as the terms of the prescription may be extended with better

understanding of the chemical factors responsible, doctors should have a working knowledge of the terms of the N.H.S. 1946 Act.

Exfoliative cytology is a method of detection which is of value in screening industrial workmen. Few workmen could be expected to submit to routine cystoscopy but all can have urine examinations at frequent intervals. Exfoliative cytology need not only be used in the industrial practice—the recognition of tumour cells in the urine of any patient in whom the diagnosis has not been suspected may alone be sufficient justification for a cystoscopy. The diagnosis should not be made on exfoliated cells alone but their presence is an indication for immediate further investigation.

The sound, modern pathological approach to bladder tumours owes a great deal to the enthusiasm and interest of Dr. Cuthbert Dukes. The method of classification by histological grade and the clinical stage, a method which can be used for every tumour whatever the subsequent treatment may be, has the two outstanding advantages of accuracy and simplicity. Attempts to classify tumours by histology alone or by the extent of spread alone are inadequate. It is interesting to observe that in the United States a very similar classification by grade and stage has also found favour. The use of words rather than numbers to describe the stage and the use of words to define the main characteristics of the tumour grade has prevented misconceptions. The majority of clinicians appreciate what a ' papillary anaplastic transitional cell tumour of a muscular stage ' represents—how many appreciate a ' grade 3 - 2 B ii '?

To a few, tumours are either benign or malignant, and the idea of a continuous gradient of malignancy may be a new one. In the bladder, where tumours of many different types may arise, the concept of a gradient of malignancy conforms much better to their behaviour than an attempt at a sharp and arbitrary division into benign and malignant. In the material which we have at our disposal from 1950 we have attempted to show by clinical, clinopathological and pathological investigations that this method of classification is sufficiently accurate to allow satisfactory comparison of results and to be a fair guide to prognosis.

The clinical study of tumours, especially in the bladder, is a fascinating one. Bladder tumours lend themselves to exact assessment more readily perhaps than those at most other sites. The presenting symptom of haematuria, in 78 per cent. the sole presenting symptom and in another 9 per cent. associated with frequency or dysuria, is dramatic and usually takes the patient promptly to his doctor. Very little will be gained by educating the public further about haematuria—they already know it is serious. Far too often the delay occurs through failure by doctors and consultants to make a proper assessment or a correct diagnosis.

Bladder tumours can be investigated with a high degree of accuracy provided care is taken over the clinical assessment. The modern cystoscope with good irrigation, bright light and clear optical system is a thing of beauty

compared with many of its predecessors ; tumours can be inspected and pieces removed for biopsy (if necessary on several occasions). Bladder tumours can often be palpated and the effect of infiltration may also be studied by intravenous pyelography. The urinary environment in which these tumours are growing can be investigated, various chemicals may be added or others removed from the urine. The tumours can be treated by simple endoscopic methods, by the most radical surgery, by many combinations of surgical or radiotherapeutic method, or by radiotherapy alone. They may be then treated prophylactically, with the idea of preventing recurrences, by compounds such as 1 : 4 saccharolactone ; attempts are even being made to see if the late cases may be influenced by chemotherapeutic agents.

Which of these methods is the best for each type of tumour can only be decided by the pooling of a large volume of material, graded and staged in comparable fashion and followed up meticulously. Personal bias, to endoscopy, surgery or radiotherapy, will only be reduced by the collection of adequate material from many sources and a genuine attempt to see what all methods available can do for these patients. This has been one of the objects of the Bladder Tumour Registry run jointly by the Institute of Urology and the Royal Marsden Hospital. Cases from eight of the larger centres in Great Britain are now being collected under comparable conditions but this material is not yet available for use in this volume.

With regard to the treatment of these tumours our material confirms the observation of Jewett that once the muscle has been penetrated the chances of cure by local forms of therapy diminish rapidly. When, however, the tumour is in the early stages or is of relatively slow growing type there are protagonists for many forms of therapy, all of which may be successful at times. Each one has some complications to set against its success—whether mortality or morbidity. To evaluate forms of therapy is difficult, even more so when many of the patients are old and frail, and the choice may have to lie with the least effective but safest method. In some cases this choice may rightly be one of masterly inactivity. In our material we have not tried to use any one form of therapy to the exclusion of others. All patients treated at the Royal Marsden Hospital have some form of radiotherapy as the first stage in preference to surgery, unless the lesions are such that surgery is clearly indicated.

Surgery and radiotherapy have been used together for certain types of lesion, especially single lesions confined to the mucosal or muscular layers. Surgery has been employed after radiotherapy whenever it was seen that the tumour had failed to regress or when reactivation of the tumour was noticed. Radiotherapy following surgery has been used routinely on all cases of partial cystectomy where infiltration into the muscular wall was present or where there was evidence of lymphatic permeation. Surgery has also been employed to deal with the complications of radiotherapy. Saccharolactone is being used in an attempt to prevent further tumour formation once the primary tumour has been controlled.

One of the most fascinating aspects of bladder tumours is that we may at last be approaching an understanding of some of the reasons why they develop. The possibility of an inborn metabolic error, or an error induced by environmental factors resulting in the excretion of abnormal metabolites which are responsible for giving rise to bladder tumours, has passed beyond mere speculation. Ortho-amino-phenols have been identified in excess in the urine of patients with spontaneous bladder tumours. These chemicals may be inhibited by the use of 1 : 4 saccharolactone. Much interesting speculation about degree of damage which is reversible and the regression of tumours following ureteric transplants flows from these observations.

We have attempted to analyse all the material which has been registered through the Joint Urological Clinic serving the Royal Marsden, St. Peter's, St. Paul's and St. Philip's Hospitals. No patient seen, whether treated or untreated, has been excluded from this analysis. We have attempted to analyse only the larger series of published treatment results chiefly to demonstrate the need for some acceptable method of comparison between the work of different centres. In particular we have drawn attention to the three cardinal points:

(a) That every patient seen, whether treated, untreated, or sent for treatment elsewhere must be recorded, including all those treated previously as well as new cases,

(b) that every case should be classified by histology and clinical stage, but if this is not possible then the statement must be made that no histology was available or no clinical stage could be given,

(c) that every patient must be followed up and the condition on each anniversary of the first planned treatment must be recorded or the patient described as lost to follow up at that anniversary and counted as dead.

If sufficient clinicians can be persuaded to collect their information on a common and comparable basis it will be possible for us to learn what treatment in each type of case is most likely to have the most beneficial effect on the patient and perhaps to move towards prevention of the development of the disease in some and of its recurrence in others.

The title of this volume has been chosen as Tumours of the Bladder rather than Cancer of the Bladder for two reasons:—

Firstly, we do not believe that the lesions described form a single disease, there are many factors in aetiology, industrial, infective, irritative or metabolic, and probably even more that are still unknown. The tumours behave in differing fashions clinically, in their response to treatment and in the post mortem findings.

Secondly, we do not believe that an arbitrary division can be made between papilloma and carcinoma, because the whole process of neoplasia ranges from the most benign to the most malignant types of tumour. To attempt to divide tumours either clinically or histologically into one or the other of these groups is misleading. The more important factors may well be the degree of differentiation—papillary or solid, whether the basement

membrane is broken through or whether infiltration has extended beyond the mid point of the muscular layer. All of these factors are of much greater importance than attempting an artificially strict division into benign papilloma or malignant carcinoma.

D. M. WALLACE.

LONDON, 1959

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The material on which this symposium is based is derived from the practice of many Surgeons both Urological and General. To them I am indebted for permission to register their cases in the Registry and also for their help in trying to evolve a system of classification which can be used by many people. Their co-operation in meticulous examination of the patient has been invaluable. In particular I would like to thank Mr. A. R. C. Higham and Mr. D. Innes Williams for the use of the pictures of their cases of the pheochromocytoma and the carcinosarcoma.

The first co-operating radiotherapist in our clinic was Dr. Dick Walton, now Director of the Manitoba Cancer Institute. He was largely responsible for the initiation of the joint clinic so that it started not merely as a scientific investigation but as an example of friendly co-operation.

In the Radiotherapy section we are indebted to Dr. Warren Sinclair, Dr. Trott and Mrs. Dyche of the Department of Physics, Royal Marsden Hospital, for the calculations and physical data on isotopes.

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The photographs are the work of Mr. Bartholomew and the charts and drawings were produced by Miss Freda Wadsworth, both from the Institute of Urology, London. To both of these artists I am greatly indebted for the trouble they took before the final illustrations were agreed.

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I personally would like to acknowledge financial assistance from the Institute of Urology, London, which has enabled the Bladder Tumour Registry to evolve through several vicissitudes. I want also to acknowledge the co-operation this Registry has received from Urological units throughout the country, Glasgow, Edinburgh, Liverpool and Dublin, which is now permitting the accumulation of a vast store of information concerning bladder tumours and the effects of various methods of treatment.

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