MEDICAL ONCOLOGY

medical aspects of malignant disease

edited by
K.D.Bagshawe

Blackwell Scientific Publications
OXFORD LONDON EDINBURGH MELBOURNE

MEDICAL ONCOLOGY

MEDICAL ASPECTS OF MALIGNANT DISEASE

EDITED BY

K. D. BAGSHAWE
MD, FRCP
Consultant Physician and Director
Department of Medical Oncology and
Leukaemia Unit
Charing Cross Hospital, London

BLACKWELL SCIENTIFIC PUBLICATIONS
OXFORD LONDON EDINBURGH MELBOURNE

LIST OF CONTRIBUTORS

BAGSHAWE K.D., MD, FRCP *Consultant Physician and Director, Department of Medical Oncology and Leukaemia Unit, Charing Cross Hospital, London*

BUCHAN R., MD, FRCS (ED) *Consultant Surgeon, Victoria Hospital, Kirkaldy, Fife*

BRUNNER K.W. MD, *Lecturer in Medical Oncology; Chief, Division of Medical Oncology, Inselspital, University Hospital, Bern, Switzerland*

CRAIG O., FRCSI, FFR, *Consultant Radiologist, St Mary's Hospital, London and Bolingbroke Hospital; Director of Clinical Studies, St Mary's Hospital Medical School; Teacher in Radiodiagnosis, University of London, Lecturer in radiological anatomy, King's College; Adviser in radiology to the Government of Malta*

CURRIE G.A., MB, MRCP *Senior Lecturer, Ludwig Institute for Cancer Research, and Chester Beatty Research Institute, Belmont, Sutton, Surrey*

DAVEY JANE B., MB, BS, DMRT *Research Assistant, Breast Unit, Royal Marsden Hospital, London*

FOADI, M.D., MD *Medical Assistant, Department of Haematology and Leukaemia Unit, Charing Cross Hospital, Medical School, London*

FORREST A.P.M., MD, CHM, FRCS (Eng., Ed. & Glas.), *Regius Professor of Clinical Surgery, University of Edinburgh*

GOLDING P.R., BSC, MB, CHB, MRCP *Consultant Physician, Derby City Hospital, Derby*

HAMILTON FAIRLEY, G., MA, DM, FRCP, MRCPATH *Professor of Medical Oncology and Director of the Imperial Cancer Research Fund Medical Oncology Research Unit, St Bartholomew's Hospital, London*

JONES C.H., BSC, PHD, F.INST.P. *Principle Physicist, Physics Department and Breast Unit; Institute of Cancer Research and Royal Marsden Hospital, London*

KAY H.E.M., MD(LOND.), FRCP, FRCPATH *Consultant Haematologist, Royal Marsden Hospital and Institute of Cancer Research, London; Secretary to the MRC Leukaemia Committee*

KOLSTAD P., MD *Professor of Gynaecology, Norweigan Radium Hospital, Montebello, Oslo-3, Norway*

LAWLER SYLVIA D., MD, MRCP, FRCPATH. *Honorary Consultant in Cytogenetics and Immunology, Department of Cytogenetics and Immunology, Royal Marsden Hospital and Senior Lecturer in the Institute of Cancer Research, London*

MCCREADY V.R., MSC, MB, BCH, DMRD, *Consultant in Nuclear Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey*

MERRICK M., MA, BM, BCH, MSC, DMRD, FFR *Consultant to the Department of Nuclear Medicine, Western General Hospital, Edinburgh*

PEGRUM G.D., MD, MRCP, MRCPATH *Reader in Haematology, Consultant Haematologist, Charing Cross Hospital, London*

ROSE F.C., MB, FRCP *Consultant Neurologist, Charing Cross Hospital, London, Consultant Neurologist, Medical Ophthalmology Unit, St Thomas's Hospital, London*

SAUNDERS CICELY, OBE, MA (Oxon), FRCP, SRN, AIMSW, DSC (Yale) *Medical Director St Christopher's Hospice, Lawrie Park Road, Sydenham, London SE26 6DZ*

SIDAWAY, M.E., MA, MRCP (Lond.), MBBCHIR (Cantab), DMRD, FFR, FRCP (Edin) *Consultant Radiologist, Charing Cross Hospital, London*

SONNTAG, R.W., MD, Deputy Chief, Division of Medical Oncology, Inselspital, University Hospital, Bern, Switzerland

SNEDDON, I.B., CBE, MBCHB, FRCP, *Consultant Dermatologist, Rupert Hallam Department of Dermatology, The Hallamshire Hospital, Sheffield and North Sheffield University Hospital; Honorary Clinical Lecturer in Dermatology, University of Sheffield*

STEEL G.G., PHD *Department of Biophysics, Institute of Cancer Research, Belmont, Sutton, Surrey*

WALDEN P.A.M., MB, BS, MRCP, D.OBST, RCOG *Senior Registrar, Department of Medical Oncology, Charing Cross Hospital, London*

PREFACE

Up to the present time, few physicians have specialized in the medical aspects of malignant disease. The physician's interest in cancer is traditionally directed towards establishing the diagnosis and from then on, his visits to the bedside tend to get fewer and shorter. Emphasis on the physiological approach to medicine in academic departments has revitalized many subjects but has largely excluded cancer from the undergraduate's field of vision. Those who have wanted to study cancer have, for the most part, had to abandon clinical medicine.

Cancer chemotherapy has been applied by radiotherapists and haematologists, whose other responsibilities have made a full commitment impossible. Anti-cancer drugs, it is true, can be prescribed without creating yet another speciality but it is relevant that the major advances in cancer chemotherapy have stemmed from units fully engaged in studying its many problems. Also a wide gulf has opened between what can be achieved with these drugs in specialized units and the generality of results accepted elsewhere.

But it would be disastrous if medical oncology were to restrict itself to cancer chemotherapy. Disciplines orientated exclusively towards therapy become intellectually isolated. The evolution of medical oncology as a branch of general medicine should bring the spirit of enquiry which has often been lacking in clinical cancer work and which should help to establish important links with other disciplines.

Study of the cancer patient and of the biological mechanisms involved in the tumour–host relationship has become essential to the development of an effective partnership between clinician and non-clinical cancer research workers. Whilst taking the initiative in this direction, it is no less important that medical oncology should strengthen its links with the discipline of general medicine which provides its recruits. The establishment of special cancer centres has certain advantages but carries the risk of exacerbating the isolation of cancer medicine. It seems essential that there should be close contact and a free flow of information along the whole of the chain formed

by basic science departments, experimental cancer research units, clinical oncology in its widest sense and general medicine.

The possibility that radiotherapy and medical oncology will ultimately fuse into a single discipline of clinical oncology should not be excluded but the breadth of training each requires is a formidable obstacle. Whatever pattern emerges in the future, it is clear that a fundamental requirement is cooperative evolution of all the disciplines involved in the clinical management of the cancer patient.

In selecting subjects for consideration in this volume, it was necessary to omit some aspects of malignant disease which are the subject of many standard texts. Histopathology, cytology, epidemiology, carcinogenesis, radiotherapy, surgical management and disease staging are not included as topics in their own right, although they are discussed as facets of the many subjects which have been brought together. Even without these, the area of cancer studies is vast and its long and active frontiers provide ample opportunity for original minds which are less attracted by the well-trodden paths of the long-established medical specialities. It is hardly surprising that advances on this frontier are found exciting even by the general public but the retreats, though less well publicized, are scarcely less exciting or frequent.

Finally, it is my pleasure to thank the contributors to this volume for their endeavours and the publishers for their patient cooperation.

I should also like to thank Leiden University Press and Microfilm International Marketing Corporation for their permission to reproduce two illustrations which appear in Chapter 4.

CONTENTS

SECTION I
GENERAL ASPECTS OF CANCER

CHAPTER 1
GENES AND CHROMOSOMES IN CANCER

SYLVIA D. LAWLER

INCIDENCE

Our genetical inheritance has a profound influence on the chance of surviving the hazards of infancy and on our achievements; but as far as cancer is concerned, except in specific instances, the influence of environmental factors is more potent than genetical ones. The main causes of death in children in order of magnitude are; accidents, cancer, respiratory diseases and congenital malformations. By the time adult life is reached, cancer and heart disease are equally common as causes of death. Sex is very important from the point of view of survival. On average, death rates are higher in males than in females in all age groups except the age range 35–45 years. In all sites, other than those peculiar to males or females, the incidence of cancer is higher in males than females.

HEREDITARY SYNDROMES

There are a few examples of genes, in the Mendelian sense, having an influence on carcinogenesis. Some hereditary syndromes that are associated with solid tumours are listed in Table 1.1 according to site. A solid tumour, in this context, is one that occurs as a primary growth in any organ other than blood, bone marrow or lymph node. All the syndromes, except xeroderma pigmentosum, show an autosomal dominant pattern of inheritance, transmission of an allele expressed in single dose being directly from either male or female parent to child. A recessive pattern of inheritance, such as is found in xeroderma pigmentosum, implies that the disease is expressed only in homozygotes; the affected offspring must inherit a deleterious allele from each parent. In these genetic conditions that influence neoplasia, the manifestation rates vary in different syndromes and between families showing the same syndrome. Detailed descriptions of the syndromes are given by Lawler (1973).

TABLE 1.1. Genetic factors and solid tumours

Syndrome	Site of tumour
Tylosis (Liverpool)	Oesphagus
Intestinal Polyposis Familial Gardner's	Colon and rectum
Xeroderma pigmentosum Multiple naevoid basal cell carcinoma Cutaneous melanoma Multiple trichoepithelioma	Skin
Intraocular melanoma Retinoblastoma	Eye
Neurofibromatosis Tuberose sclerosis Lindau's	Brain and CNS
Multiple endocrine adenomatosis Familial medullary carcinoma	Thyroid and endocrine
Multiple exotosis Werner's syndrome	Bone and connective tissue
Familial multiple-cancer	Multiple

Most of the cancers listed in Table 1.1 are extremely rare in the inherited form, but these should be considered in patient management. For example, the recognition of the pre-cancerous nature of the polyps in familial intestinal polyposis, which dates from the time that the sigmoidoscope came into general use, means that the offspring of affected individuals can be kept under observation from the age of ten upwards. Even though this genetically determined intestinal cancer is evident in only a small number of cases, the opportunity is provided for preventing cancer in a group of people known to be at risk. Rarity of the familial as opposed to the sporadic type of cancer also applies to other malignancies listed in Table 1.1, for example, melanoma of the skin or eye. Cancer of the oesophagus in association with tylosis has only been recorded in two possibly inter-related families in Liverpool (Howel-Evans 1958).

CANCER FAMILIES

The cancer family syndrome has been defined by Lynch *et al.* (1968). Such families show a high concentration of relatives with cancers in multiple sites and the lesions develop at an earlier age than is usual for the cancer of the site involved. The pattern of inheritance is autosomal dominant.

FAMILIAL INCIDENCE

It is also necessary to consider the situation in which there is an increased familial tendency for a particular type of cancer, without the involvement of a specific genetic locus. This applies particularly to the cancers which are common in or unique to females, for example, breast and uterus. Since cancer of the breast in females has such a high incidence, 69·2 per 100,000 for all ages living in England and Wales (Doll *et al.* 1968), it is difficult to demonstrate convincingly that occasional familial concentration of cases is not due to chance. The consensus of opinion is that there is an increased tendency for cancer of the breast to occur in the mothers and sisters of patients (Anderson 1972). The increased risk for the relatives is site specific, there being no increased risk for sites other than the breast, according to most workers. Similarly familial predisposition to uterine cancer has been demonstrated, but not to malignancies at any other sites (Murphy 1952).

RACIAL AND GEOGRAPHICAL FACTORS

The incidence of certain cancers varies in different races, but such differences are not necessarily due to genetic factors: they are just as likely to be caused by environmental influence and social habits. Grieve (1967) made a careful study of cancer in the different racial groups in the Cape division of South Africa. He found that the differences in incidence of cancer at most sites could be accounted for by social, economic and environmental factors. The exceptions were cancer of the lip and skin which were undoubtedly much commoner in white males than in coloured males, but they were more common in white females than in coloured males, even though at both these sites the incidence is much lower in females than males in the same racial group.

Whether the differences in incidence in the different racial groups are due to heredity or environment can to some extent be evaluated by studying morbidity statistics in immigrant populations (Haenszel & Kurihari 1968). Among the Japanese, cancer of the stomach has a higher incidence than in Caucasians, whereas carcinoma of the colon and breast is rarer than in Caucasians. When Japanese people migrated to the United States, the high rate of carcinoma of the stomach and the low rate of carcinoma of the breast were both maintained, suggesting that genetic factors were playing a role, which accords with the observation of increased familial incidence as far as cancer of the breast is concerned. On the other hand, the incidence of carcinoma of the colon rose amongst Japanese

immigrants towards the higher level typical of Whites, suggesting the importance of factors in the environment.

Racial factors have also been implicated in gestational choriocarcinoma, the malignant proliferation of trophoblastic tissue that may follow any type of pregnancy. The disease is particularly frequent among people of the Orient: Japanese, Chinese and Filipinos; at present no adequate statistics are available concerning immigrants of these populations.

BLOOD GROUPS

The incidence of polymorphisms in the blood group systems prompted people to seek for associations between blood groups and disease, the rationale being that such antigens might contribute something more than nuisance value in transfusion or hazards for the fetus in pregnancy. In this area the ABO blood group system has been the subject of the most extensive studies. The antigens of this blood group system are widely distributed throughout the body in tissues and secretions, the intestinal tract being a particularly rich source. Difficulties arise in the search for associations between a particular blood group phenotype and disease, because in order to obtain a statistically significant result when the effect is small, large numbers of patients must be compared with properly selected controls. Since there are racial differences in the distribution of the blood group systems, a racial stratification within a mixed population could lead to false conclusions about the significance of a particular antigen in relation to disease. Fortunately, very extensive control data for the distribution of the ABO blood groups in the United Kingdom have been collated at the Nuffield Blood Group Centre so there is no problem with regard to control material for studies conducted in the United Kingdom. When an association has been found in one geographical location it can be confirmed by collecting information about the same disease in a different centre. As far as the ABO blood groups are concerned, one association originally described by Aird *et al.* (1953) has been adequately confirmed in many centres. The relative incidence of carcinoma of the stomach in persons of group A is 1·20 as compared with an incidence of 1·00 in persons of group O (Roberts 1959).

Another increased risk associated with the ABO blood groups has been found in patients with choriocarcinoma. It had originally been observed that patients with the disease were more frequently of group A than matched controls. Subsequently it was found that the risk was also associated with the blood group of the husband and that the highest risk of the

disease occurred when an A woman was mated to an O husband. It is also known that group AB women have a poorer prognosis than women of other ABO blood groups. An AB woman is bound to have an ABO compatible conception so it could be said that the problem arises because these women cannot reject the conception as far as the ABO system is concerned. A group A woman mated to a husband of group O or A is also bound to have an ABO compatible fetus. On the other hand, a group O conception in a group A maternal environment would be antigenically incompatible and theoretically capable of reacting against maternal tissue. Under these circumstances the proliferation of malignant trophoblast might be encouraged. This argument is not confirmed by the facts. In the cases in which choriocarcinoma is preceded by live-term birth, the ABO group of the fetus reflects that of the tumour. In thirteen examples of this situation in which an A mother was mated to an O husband the presence of choriocarcinoma was associated with the presence of a group A child in seven cases and group O child in six. This segregation is exactly what would be expected on a random basis and therefore no evidence of selection in favour of incompatible mothers was obtained (Bagshawe *et al.* 1971). The reason for this high risk of the A patient mated to an O husband remains an enigma.

Expression of antigens belonging to the ABO system on the cell membrane is part of the hallmark of certain normal tissues. It has been observed that malignancy is associated with a loss of expression of these antigens. First described by Kay (1957), who used cell suspensions, a similar phenomenon has been found in carcinoma of the intestinal tract, cervix and bronchus, from studies using tissue sections (Davidsohn & Ni 1970).

It would appear that de-differentiation which is a characteristic of malignant cells is associated with antigenic loss. At the same time in some malignancies new antigens appear which are not expressed in normal adult tissue, but which bear a relationship to the antigens of fetal life. The carcinoembryonic antigen is an example of this; it was originally described by Gold & Freedman (1965a) as a tumour specific antigen in adenocarcinoma of the human colon, and was also shown by them (1965b) to be present in fetal tissues.

THE HL-A SYSTEM

The HL-A system plays an important role in histocompatibility reactions in man. The antigens are distributed throughout the body, but in laboratory

tests they are usually detected on lymphocytes. Genetically controlled by two closely linked loci, a maximum of four antigens can be expressed on the cells of an individual. The system is extremely polymorphic there being more than twenty-five well-defined antigens. Encouraged by the relationship between the H2 system and leukaemia in mice (Lilly *et al.* 1964), attempts have been made to find evidence of an association between particular HL-A types and human leukaemia. So far, reports suggesting such associations have not been adequately confirmed (Lawler *et al.* 1971; Walford 1972).

It seems likely from the world-wide collection of data on Hodgkin's disease that the HL-A phenotype may influence the risk of being affected, but the results were not unequivocal (Morris *et al.* 1972).

Contrary to the findings in the ABO system the HL-A system appears not to influence the risk of a woman developing gestational choriocarcinoma. Despite the fact that the tumour is foreign to the maternal host by the genetic contribution of the male parent, it has been shown that choriocarcinoma is not preferentially associated with conceptions that are more compatible with the mother on the HL-A system than would be expected by chance. The risk of a woman suffering from trophoblastic neoplasia following live-term birth, abortion or pregnancy with a hydatidiform mole is not directly related to the choice of mate as far as the HL-A system is concerned (Klouda *et al.* 1972).

CHROMOSOMES—THE NORMAL KARYOTYPE

The normal human chromosomal constitution is defined by examining cells at the metaphase stage of the division cycle. This imposes two limitations on chromosomal morphology as a measure of normality of a cell population. Firstly, the cells that are in mitosis cannot be representative of the population as a whole since only a minority of cells at a given point of time will be dividing. Secondly, the process by which the chromosomal preparations are made involves a loss of the cytological properties of the cell so that unless special techniques can be used, it is not possible to define the lineage of a cell in metaphase.

With the advent of new techniques in the 70s involving differential fluorescence patterns (Caspersson *et al.* 1970), or differential Giemsa staining (Sumner *et al.* 1971), it has become possible to define each individual chromosome in the normal set by its stained appearance at metaphase. This means that abnormal chromosomes can be defined in terms of rearrangements of normal ones and only those chromosomes whose