Man, Cancer and Immunity

ALISTAIR J. COCHRAN

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ALISTAIR J. COCHRAN, M.D.

Reader in Pathology
University Department of Pathology
Western Infirmary, Glasgow

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Foreword

by Georg Klein

This book is a balanced report of the widely different views of tumour immunology which while not partisan is nevertheless committed. It does not cover everything published in the field of human tumour immunology in recent years, although it covers most of the relevant studies. It emphasizes that while a variety of host responses have been shown to act against human tumours not all of them are necessarily immunological. The author gives a good appraisal of experimental tumour immunology, yet stresses the impossibility of directly translating animal studies to man. Since the book is primarily written for clinicians, it rightly emphasizes that the lack of a total understanding of the mechanisms of biological phenomena does not exclude the possibility that some of the phenomena may find applications in the diagnosis and/or the follow up of cancer patients prior to the development of an appreciation of their biological significance.

Appropriately, the book starts from the clinical observations which have shown sporadically, anecdotally, but imperiously and persistently that host responses exist against human tumours. It is made clear that modern developments in this area started by the unequivocal demonstration that some animal tumours are immunogenic in the hosts in which they arise. This is particularly true for chemically and virally induced tumours, and much less so, or not so for spontaneous tumours. The increasing complexity of the "immunological orchestra" is emphasized and it is made clear that results obtained in a given system cannot be translated to any other. By implication, *human tumour immunology must be based on direct enquiries into the human system itself.*

The history of tumour immunology is characterized by many ups and downs. Early enthusiasm about the possibility of protection by immunization, based on results obtained in studies of long transplanted tumours was replaced by complete pessimism when it became clear that the reactions

detected were directed against transplantation antigens rather than antigens unique to the tumours. In the early 1960s tumour associated or tumour specific transplantation antigens were discovered on chemically and virally induced tumours. Since these antigens were capable of inducing rejection reactions in critically syngeneic or even in autologous hosts, a second wave of enthusiasm was generated for studies of immunology. The concept that some tumours contained unique antigenic molecules gained surprisingly rapid acceptance in view of the considerable volume of earlier negative studies. It is even more surprising that there followed sweeping generalizations postulating that *all* animal and human tumours were probably antigenic. Although voices of warning against the uncritical acceptance of such generalization have not been lacking, they have been largely ignored sometimes even by those who did the relevant experiments but who have been subsequently carried away by the optimistic spirit of the times. Yet, there is increasing evidence that not all tumours are necessarily recognized by the immune responses of the host. And why should they be? Virus-induced tumours bear the same surface-associated antigen, as long as they are produced by the same virus. In this special situation surveillance has a clear target to focus on and, in the cases where the species had previous extensive contact with the virus, is aided by an immense prehistory of natural selection.

Spontaneous tumours seem likely to represent a very different situation. These are tumours which arise without experimental interference and emerge at the end of a prolonged progression which is now understood to be the gradual evolution of cellular independence from a variety of local and general restrictive influences including hormonal and, no doubt, immunological factors. If tumour associated antigens do arise in slow-developing spontaneous tumours it would be expected that they would meet a strong selective pressure resulting in low immunogenic or non-immunogenic tumours, in contrast to the rapidly developing tumours induced by strong chemical carcinogens or powerful oncogenic viruses.

The question whether all potential tumour cells are recognized by the immune response and tumour outgrowth is a matter of subsequent breakdown of such responses or, alternatively, whether there has been an absence of recognition *ab initio*, not because tumour cells do not differ in membrane and other properties, but because their own micro-evolution (progression) has moulded them into a chameleon-like non-recognisability by the Ir (immune responsiveness) gene equipment of the host, is not merely of academic interest. Obviously, both experimental and practical measures will have to be quite different in the two situations outlined. In the former case, the problem is how to correct a malfunctioning response, in the latter, how to induce the host to recognize neoplasia associated membrane changes which are not spontaneously antigenic.

It is easy to be disappointed by the lack of progress in tumour immunology and the lack of major technological advances applicable in the clinic. This reaction, however, is in large measure a result of the quite unreasonable levels of expectation engendered by the intense pressures developed by the anxiety of clinicians, laymen, research administrators and politicians to apply laboratory results to patient management with minimal delay. These pressures, in addition to overheating our levels of expectation are counter productive by endangering the traditional and well founded "gradualism" by which the advance of scientific knowledge occurs. Specifically accelerated speculation leads to erroneous concepts and the uncritical and unnecessarily prolonged investigation of such concepts, which in turn perpetuates central fallacies and myths.

Tumour immunology certainly has its share of middle-aged and elderly myths but there are some indications that these are now being recognised for what they are and that the subject is presently proceeding on a more strengthened scientific basis. The main priority remains the generation in a variety of laboratories of that scientific atmosphere without which progress is impossible and which permits the generation and *recognition* of the significant unexpected spin off result. Obviously we are at the *very beginning* of this whole game and have *barely scratched its surface.* I would compare the present situation in tumour immunology to the first developments of the H-2 field or the earliest recognition of transplantation antigens by the use of inbred strains. Manipulating the immune response in favour of the cancer patient may or may not be feasible, but we are unlikely to know this answer in the short term.

This book is a timely review of the many strands of evidence which point to a host-response to cancer, and of the initial experimental attempts to investigate this interesting phenomenon. It provides a readable account of the somewhat shaky foundations on which a more rigidly scientific discipline of tumour immunology could be erected.

Stockholm
April 1978

For Janie, Angus and Sara

Preface

My early research activities, begun at the suggestion of the late Professor D. F. Cappell, were concerned with clinicopathological factors which related to the death or survival of patients with malignant melanoma. The results of these studies made it clear that the outcome in this situation depended on numerous characteristics of the tumour cells and the patient and the manner in which patient and tumour interacted. The realisation that there were host reactions to tumour cells came at a time of expanding interest in the role of immunity in many different diseases including cancer. I have therefore spent much of the last ten years thinking about and investigating immunity and tumours in animals and man and remain convinced that host responses, including immune reactions, play an important part in the control of tumour development and spread. This notion is widely shared although, with the passage of time, it has become increasingly clear that the involvement of immune factors in malignant disease is complex and subtle.

Discussion with colleagues who are not immediately involved in research into tumour immunology has made it clear that the subject is one about which many would wish to be better informed. However, the voluminous literature on tumour-related immunology and relatively complex technical jargon of the immunologist make it difficult for the general reader to obtain a balanced viewpoint. This seems especially a problem for individuals who graduated before the new wave of immunology had broken on medical and general science courses. This monograph attempts to provide a general account of the major principles of tumour immunity and an attempt has been made to limit the content of jargon and where this has proved impossible to explain in a relatively simple manner the terms used. This was the initial intention and if I have failed in this aim I must ask my readers to, as far as possible, take the thought for the deed. I have concentrated on the situation in man and discuss animal findings only when this is necessary to support a concept, or where human studies are lacking. The subject and its literature proliferate at a frightening pace and the subject matter, while as up to date as I could make it in the Autumn of 1977, will certainly be out of date in

parts by the time of publication. It should, however, provide a relatively stable platform from which the reader may venture into specific areas of the subsequent literature.

My views have been very much influenced by contact and discussion with many physicians and scientists in the United Kingdom and many other parts of the world. These contacts have been invaluable and it is my sincere hope that this source of intellectual stimulation will continue to remain available to me. I have received immense support and stimulus from Professor J. R. Anderson of this Department and Professors Eva and Georg Klein of the Department of Tumor Biology, Karolinska Institute, Stockholm. I have had the good fortune to collaborate with and receive the friendship of many stimulating colleagues including Drs. Peter Gunvén, Jan Stjernswärd, Francis Wiener, Rolf Kiessling, Bal Gothoskar and Ulrich Jehn in Sweden and Professors Donald Morton, Wallace Clark, Sidney Golub, Leon Rosenberg, Herbert Wohl and Max Essex in the United States. My work in Glasgow has been made possible by invaluable associations with Professor Rona Mackie, Drs. Walter Spilg, Catherine Ross, Robert Grant and Alan Jackson, Ms. Deirdre Hoyle, Lindsay Morrison and Gaye Todd. As most of the original studies described have involved patients these would have been impossible without the kindness of many clinical colleagues who permitted me to study their patients in the Karolinska Sjukhuset, Stockholm, The Western Infirmary, Gartnavel General Hospital, The Royal Infirmary, The West of Scotland Regional Plastic Surgery Centre at Canniesburn Hospital, The West of Scotland Regional Radiotherapy and Oncology Service, Stobhill General Hospital, The Victoria Infirmary, The Royal Hospital for Sick Children, The Southern General Hospital and Hairmyres Hospital.

The production of the book has involved many people and it is a pleasure to be able to thank them publicly. Mrs. Maureen Ralston skilfully and patiently typed the book in draft and final form. Photographs were kindly provided by Professor Tom Gibson (Fig. 2.2), Professor Rona Mackie (Fig. 2.3), Dr. Gavin Sandilands (Fig. 6.1), and Dr. Robert Grant (Fig. 8.6). Mr. Peter Kerrigan advised on photography and helped in many practical ways. Mr. Robin Callender arranged for the production of the line drawings. The book was read at various stages by Professor J. R. Anderson, Dr. Andrew Sandison, Dr. Geoffrey Clements, Dr. Alan Jackson and Professor Rona Mackie from all of whom much sage counsel was received. I am indebted to Professor Georg Klein for his foreword which provides such an excellent beginning to the book.

My wife and children patiently supported me during the gestation period of the book and valiantly bore with any slight increment in my grumpiness and my greater than usual obsession with the laboratory.

Glasgow *July 1978*

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Introduction

Cancer commands more interest than ever before in virtually all sections of the community. This disease, which is a major cause of death in adults in the developed countries, has generated interest, emotion and fear which used to be the province of infectious disease in general and tuberculosis in particular. Interest is not confined solely to the medical and allied professions, but is high in governmental and international agencies concerned with health care. The public at large is increasingly aware of and informed about the nature and problems of malignant disease. This increasing general awareness of cancer is partly the result and partly the cause of the increased coverage of malignant disease in publications available to the general public. The upsurge in interest has brought benefits in the form of increased governmental support of cancer research, the emergence of oncology as a new clinical speciality and the development of multi-disciplinary centres of excellence where accumulated experience from referred patients permits optimum treatment of relatively rare cancers. Not least among these benefits is the gradual acceptance by the public that cancer is, like other human ailments, to some degree explicable on the basis of orthodox theories of pathology and clinical medicine and is, in its early stages, at least relatively responsive to well-established forms of therapy.

The translation of cancer from an abstruse medical concept to a subject widely discussed and well understood by a proportion of the lay public presents new problems to physicians dealing with the informed cancer patient or the relatives of such patients. Sources of cancer information are now very different from the blandly non-committal entries of "Home Doctor" books and "Domestic Medical Encyclopaedias" and range from the deliberately diffuse replies of correspondents who answer medical questions in local and national newspapers to the very precisely detailed and generally

accurate accounts of specific cancers and of aspects of cancer treatment and research which appear from time to time in high circulation periodicals, on radio and in television documentaries.

The practitioner may expect to encounter patients who are informed, not only about the nature, significance and prognosis of a particular cancer, but also about growth areas in developmental cancer therapy and experimental cancer research. Regardless of the extent of their own expertise patients reasonably expect that their physicians will be able to give a valid opinion on the many facets of their disease and its treatment. This can present real problems, especially in areas such as radiation biology, the pharmacology of chemotherapy, multiple agent chemotherapy, the relationship of viruses to cancer, the molecular biology of cancer and immunological aspects of cancer where there have been recent and rapid developments. This book is intended to give a general account of the last topic and it is hoped that it will help the reader to appreciate the extent, nature and significance of immune reactions which develop in response to cancer cells. I have also attempted to indicate those areas where immunology may be exploited to assist in cancer diagnosis and in the management of patients with malignant disease.

That cancers which appear identical on cytological, histological, histochemical and functional grounds behave quite differently in terms of local growth and speed and extent of distant spread in different patients is the everyday experience of those involved in the clinical care of cancer patients. This is really not a surprising observation and depends upon variables relating to the patient, characteristics of the tumour cells and on an equally wide range of variation in the reaction of the tumour bearing host to the tumour. The nature, extent and biological significance of this reaction not only differs from patient to patient, but also changes within the same patient as the tumour progresses or regresses. The reaction may also alter as a result of anti-tumour therapy, intercurrent disease and treatment directed to coexisting conditions unrelated to the cancer.

Many different characteristics of a cell dictate whether it will survive or not within the relatively demanding environment of the human body. It is likely that all cells are subjected to a detailed and continuing scrutiny and that only cells possessed of certain clearly defined and quite remarkable characteristics survive. The mechanisms involved in this scrutiny are certainly complex and involve many known body systems such as the macrophages, cells of the lymphocyte series, mast cells, neutrophils, basophils, eosinophils and the complex humoral molecules of the inflammatory mechanisms. These are known factors but it is equally possible that other as yet unidentified types of cell-cell interaction and mutual identification are involved and it is possible that the systems so far identified are relatively unimportant in the identification and control of deleterious mutants, including potential and actual

cancer cells. Be this as it may, much interest has focused on the role of immunology in cancer. This is partly because this system is slightly better understood than most others and the classical and fruitful studies of the immunology of infectious disease, blood transfusion, auto-immune disease and organ transplantation have made available a multiplicity of techniques for immunological studies, *in vitro* and *in vivo*. The very multiplicity of techniques which has been developed reflects the lack of simply executed, reliable immunological assays of cell-mediated and humoral immunity which can readily be correlated with significant clinical events. It is salutary that immunological tests do not always distinguish sharply between patients with limited primary cancer and those with more advanced disease; a distinction which is all too readily made in the majority of cancer patients by the simplest clinical investigations.

Immunological study of cancer patients nonetheless offers a variety of highly desirable prospects. At a clinical level the identification of tumour products, including tumour associated antigens, offers the prospect of relatively simple screening tests for the identification of early cancers. A simple and reliable approach of this kind which does not involve expensive equipment or surgical intervention would permit the repeated examination of high risk groups, with the prospect of early diagnosis. Serial monitoring of patients after excision of a primary tumour is already practicable, employing the repeated assessment of blood levels of tumour markers and products such as human chorionic gonadotrophins, carcino-embryonic antigen and alpha-fetoprotein. Increasing levels of these materials predict the development of recurrences and metastases before they become clinically detectable, which permits the early introduction of aggressive adjuvant therapy. Such products are available for only a limited number of tumours and may never become available for all tumours. Where tumour markers are not available a possible alternative approach is the detection and serial quantification of the strength of tumour-directed immune responses, as manifested by anti-tumour antibodies and lymphocytes sensitised to tumour associated antigens.

Immunologically based tumour diagnosis and patient monitoring seem real and reasonably immediate prospects. The "holy grail" of the cancer immunologist, however, is the development of immunological techniques for the prevention or treatment of cancer. Such techniques would ideally develop from a deeper understanding of the biology and immunology of cancer. Regrettably, this desirable level of understanding seems distinctly remote and this associated with the massive scale of the social, economic and clinical problems which result from the high incidence of cancer has prompted many pragmatic and possibly premature attempts at immunotherapy of cancer in man. In defence of this pragmatism it should, however, be realised that

medicine abounds in examples of highly successful therapeutic approaches which preceded an understanding of their biological basis by many years.

It is of course possible that the high hopes for cancer diagnosis, patient monitoring and cancer treatment by immunological means may come to naught. Alternative and more efficient techniques employing quite separate approaches may be developed contemporaneously with or in succession to the immunological approaches. Whether this occurs or not it seems very probable that the present extensive efforts to study immunological aspects of cancer will achieve some advance in our basic understanding of cancer. And this, of itself, will be a worthwhile result and may provide a more advanced platform from which future and perhaps definitive studies may be mounted.

2

Clinical Observations Suggestive of a Host Response

The active investigation of tumour immunity employing immunisation and subsequent challenge by transplantation of tumour cells, a basic and highly productive approach used extensively in animal studies, has been severely limited in man by ethical considerations. As a result of this there has developed a very extensive literature on the application of *in vitro* tests to the study of tumour related and general immune reactions in cancer patients. This records numerous interesting phenomena, some of which mirror the results obtained in animals, but all presenting the major problem, that their relevance to events *in vivo* is difficult to assess. Such an assessment usually necessitates complex and time-consuming serial studies of moderately large numbers of patients to permit analysis of the role of factors such as advancing or regressing tumour, the various forms of treatment employed and intercurrent non-malignant disease. A substantial part of this book is concerned with an account of such *in vitro* phenomena. However, before undertaking an analysis of the clinical relevance of such contrived observations, it seems appropriate to search for clinical evidence of host defensive factors active against malignant disease. Nature's experiments have yielded much interesting information to the discerning eye in other clinical situations and have often indicated those areas in which laboratory investigations are most likely to be productive.

Immunological Surveillance

The most obvious function of the immunological system is to recognise and respond to foreign materials introduced into the body and to contain them by the production of specifically reactive antibody molecules and specifically

sensitised lymphocytes, or to accept them by specific tolerance. The most obvious sources of such foreign antigens are micro-organisms and ingested or inhaled materials. It has however been argued that in addition to these gross responses there is a more subtle continuous "policing" of the body by roving macrophages and lymphocytes (immunological surveillance) which identify and react with any foreign "non-self" antigens encountered (Thomas, 1959; Burnet, 1967, 1970). In this way, in addition to microbial antigens and antigens on inanimate materials introduced by nose or mouth, endogenous host cells which develop an altered antigenic profile, either "spontaneously" or as a result of the action of micro-organisms or chemicals after the period of self-recognition and its associated tolerance (which ends at or around birth) will be identified as foreign and evoke an immune response. Burnet's suggestion is that cells recognisable as immunologically foreign, are identified and destroyed by the immune system. On the basis of what is known about the antigenicity of tumour cells (Chapter 4) it seems likely that mutant clones, including those with actual or potential malignant characteristics, would be susceptible to this type of immunological control. This concept has been a tremendous stimulus to thought and experiment in tumour immunology, but in the light of accumulating experimental and clinical observation certainly requires some modification (Prehn and Lappé, 1971).

If the immune surveillance theory, as originally conceived, is correct, it is predictable that individuals who have an inherited or acquired deficiency of their immunological apparatus will be more likely to develop cancer than are immunologically intact individuals. This is, to a limited extent, true. However, the increased frequency of tumours in the immunologically abnormal does not reflect the incidence of tumour types seen in the general population, there being a preponderance of tumours of the lymphoid system. This single observation makes it difficult to accept the original concept of general immunological surveillance as a means of controlling the development of tumours of all the various organ-systems. There are certainly dissatisfied critics of the unqualified acceptance of immune surveillance as a major or universally active process limiting tumour development. These critics base their concern on the low immunogenicity of most spontaneous tumours in animals and of tumours induced *in vitro* (Prehn, 1970), the fact that small numbers of highly antigenic tumour cells can thrive *in vivo* ("sneaking through") (Humphreys *et al.*, 1962; Potter *et al.*, 1969) where larger numbers are eliminated and the relatively small and generally unrepresentative increase in tumours in immunologically crippled animals and immunologically abnormal humans. The proponents of immune surveillance, however, claim that the clinically detectable tumour is the exception which proves the rule, that strongly antigenic tumours are