2 Cancer and the Immune Response

Second Edition

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Cancer and the Immune Response

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Second Edition

Edward Arnold

General Preface to Series

The impact of immunological thought on medical practice has been increasing at a steady rate now for nearly twenty years. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumour therapy, particularly in the balanced use of surgery and radiotherapy. Moreover, immunological knowledge in other fields has allowed us to understand more readily the mechanisms whereby a single aetiological agent can produce a wide range of different clinical manifestations. Different disease patterns occur depending on the nature of the immunological reaction causing tissue damage. A completely different symptom complex from reactions involving soluble immune complexes reacting with the complement cascade will be found in those involving the reaction of specifically sensitized lymphocytes with antigen as part of a cell-mediated or delayed hypersensitivity reaction.

As a massive amount of new scientific material accumulates in this field, the clinician is frequently left behind and perplexed. Each year a new scientific journal is published specializing in fields as diverse as immunogenetics, immunochemistry or immunological techniques. We have journals emanating from continents as well as countries. The wealth of material is often bewildering. Simple textbooks of immunology are often too simple, whereas review articles may be too complicated for the specialist physician or surgeon who wants a treatise on those aspects of the subject particularly relevant to his own field of interest. It is hoped that this series will fulfil some of these needs by giving comparatively short reviews that will lay emphasis on immunological subjects which should appeal to both clinicians and those working in clinical laboratories. The aim is to provide the busy clinician in a particular field of medicine with a short volume relevant to his practice written by a specialist. It should introduce the reader to the immunological approach to his subject and indicate how modern immunological thought might influence his day to day work in the wards or clinical laboratory.

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Preface to Second Edition

An overview will of necessity result in oversights. This edition continues with a clinical emphasis and is not concerned with the minutiae of elaborate experiments designed to study intricate mechanisms. It is painted with broad brush strokes and is intended to provide a landscape rather than a miniature, the background is biology, the foreground clinical cancer medicine. Immunotherapy for the treatment of cancer has become a growth industry but an industry which has so far failed to deliver the goods. I have tried, where possible, to examine this failure and to highlight areas of promise and to re-emphasize the need for a more rational scientifically-based approach to the problem. The failure of immunotherapy so far is not, I maintain, a reason for pessimism. It is a reason for caution, for a rigorous scientific approach, for properly controlled studies.

1979 G.A.C.

Preface to First Edition

The purpose of this monograph is to provide an introduction to some presentday ideas about the immunology of malignant disease and an appropriate background for the clinical application of such ideas. Much of it is concerned with what might be as well as what is and what has been. It is primarily for clinicians and for those concerned with the care and investigation of cancer patients.

The immunological aspects of cancer are many and varied and are the subject of intense investigation at present. There is almost universal optimism about the potential value of these studies in detecting, curing and even preventing cancer. It is imperative that such optimism be tempered with a careful appraisal of what we really know and how that knowledge can be applied. We must not discard the usual care and scrupulous investigation which normally precedes the introduction of any new clinical approach to a disease in favour of a 'nothing to lose' attitude which has frequently and regrettably been the main characteristic of many previous attempts to employ immunological phenomena for the treatment of cancer patients. This monograph is nothing if not a plea for a rational objective approach to the clinical investigation of such immunological problems and their potential use in the clinic. Tumour immunology, especially when applied to therapy, is an intellectual minefield; it is so easy to put a foot in the wrong place. It may of course be possible to obtain results in a blind rush, but the odds are against it. Only by cautious progress, by close examination of the ground before each step is taken can reasonable forward progress be achieved.

Cancer research frequently involves a series of intuitive leaps from the crumbling debris of one hypothesis to the scaffolding of the next. This is clearly illustrated by recent progress in the immunology of tumours. With the extensive research into this topic undertaken in recent years hypotheses have become as numerous and as ephemeral as the mayfly. Any discussion of the current status of such immunological research in the cancer field must of necessity entail a description of many complex postulates most of which may eventually be shown to be false. All knowledge is provisional; it awaits refutation. Adoption of this essentially hypothetico-deductive attitude has revolutionized research in the biological sciences in recent years. It has however made the writing of a monograph such as this somewhat complex. In attempting to present a résumé of the current research situation and of future prospects one cannot merely present experimental data bereft of the appropriate suprastructure of ideas. However, it would also be unprofitable to indulge in too many flights of fancy which do not of necessity contribute to the underlying theme, although they may make temporary sense of the most recently described experimental results. Some hypotheses have been retained which have withstood attempts at experimental refutation, which seem relevant to clinical situations and which to some extent are capable of suspending disbelief.

There are two ways of interpreting an experimental observation. The first is to regard it as valid in its own right and to consider it against a background of potential

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in *vivo* significance; the other view is to assess each new finding in the light of the latest hypothesis; how well does it fit? If an observation does not fit into such a preconceived pattern of ideas, both the observation itself and the theory come under suspicion. If the observation can be validated experimentally, then the hypothesis must be discarded or amended. However the retention of elegant hypothetical systems often becomes paramount. An hypothesis must be viewed in the light of experimental results and not vice versa. This is especially so in tumour immunology. The history of this subject illustrates the frequent inadequacy of the orthodox opinion. Ideas about immunological surveillance or T-B cell interaction, for instance, are all very entertaining but do they in fact help to understand what happens to cancer patients? Clinicians can surely be forgiven for regarding academic immunology with scepticism. Orthodoxy is often based on the most tenuous foundations and must always be viewed with suspicion. It is a convenient but often temporary framework which frequently has to yield to the heterodox.

Many people have contributed to the construction of this monograph, both practically and intellectually. Firstly for kindly providing illustrations I would like to thank Dr H. J. G. Bloom and Mr P. R. Riddle. The editors of the *British Journal of Cancer* and the *British Medical Journal* kindly gave permission for the reproduction of diagrams. Detailed acknowledgements are given in the legends to the illustrations. Mr K. Moreman and his staff from the Photography Department. Chester Beatty Research Institute, gave invaluable assistance in the preparation of most of the diagrams. The manuscript was expertly typed by Mrs E. Maloney and I thank her for her skill and forbearance.

I owe a special debt of gratitude to Professor Peter Alexander and to the late Professor Gordon Hamilton Fairley. For their encouragement, advice, enthusiasm, critical supervision and tolerance I thank them.

Sutton, 1974

G.A.C.

CURRENT TOPICS IN IMMUNOLOGY

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Introduction

Cancer can be described but as yet defies scientific definition. The most important features of malignant tumours, from a clinical viewpoint, are the growth of cells in a disorganized fashion, the tendency of tumour cells to invade and to disseminate and the apparent failure of normal growth control mechanisms. The dominant theme in the conceptual framework underlying our knowledge of the biology of cancer is that it represents an intrinsic cellular defect which results in the escape of the tumour from the restraints which the host imposes on the growth of normal cells. Thus cancer is frequently regarded as the inexorable growth of a totally autonomous and delinquent tissue mass. This autonomy of tumour cells has been the keystone of theoretical understanding and clinical practice for many years. However, the overall applicability of such a conceptual approach was weakened by the work of Huggins (1941), who by his demonstration of the hormone dependence of some tumours emphasized that mutual interactions between host and tumour could influence the clinical progress of malignant neoplasms.

This crucial finding re-emphasized the possibility that other host-mediated mechanisms may exert some influence on the progressive growth and spread of tumours. Since the later decades of the last century the possible role of immunological responses in resistance to the development and growth of malignant tumours has been the subject of extensive speculation and some experimentation. The concept of tumour resistance was crystallized by Ehrlich (1906) although he attributed it to nutritional factors. The presence of specific antigens on experimental tumours was even hinted at by several transplantation experiments such as those by Clowes and Baeslack (1905). Although this early work, elegantly summarized and dismissed by Woglom (1929), supported the notion that tumours possessed antigens capable of eliciting specific immunological responses in the host, it was all based on inadequate experimental data and consequently fell into disrepute.

The renaissance of tumour immunology had to await the development of suitably in-bred strains of experimental animal and an increased understanding of immunogenetics and the biology of tissue transplantation. In experimental systems, at least, there is now abundant evidence for an important role of specific immunological reactions in the natural history of tumours. In man such evidence has been difficult to obtain, and although inconclusive so far, suggests that similar immune reactions may make an important contribution to host resistance to tumour growth.

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Although the existence of tumour-specific antigens on animal and human tumours and of host reactions to them has dispelled the concept of the total autonomy of tumours, it has provided us with further conceptual difficulties. The biological significance of tumour cell 'neoantigens' is obscure. The abnormal behaviour of tumour cells *in vivo* and *in vitro* suggests that major structural alterations in the cell surface are involved in the malignant transformation of cells. It is possible that such surface aberrations are detected by the exquisitely fine sensitivity of the immune response to distinguish between 'self' and 'not self' and thus these anomalous structures at the cell periphery, which may well be an integral feature of malignancy are recognized as specific antigens. Whether or not such structural determinants are the result of 'somatic' mutation provides a topic for fruitful speculation. They may be the product of mutational changes in the structural genes coding for the cell surface or alternatively they may result from derepression of genes normally expressed only in early embryonic life. Recent experimental evidence supports this latter view, as do histological studies of tumours which often reveal a reversion of structure to a more primitive embryonic form. There are many features of malignant tumours which are shared by the mammalian embryo: their capacity for rapid growth and invasion and the immunological relationship between host and tumour are similar in many ways.

Perhaps the most convincing reason for an academic interest in tumour immunology is the fine discrimination shown by the immune response. Immunology could provide techniques for the detection of significant, consistent and exploitable differences between normal and malignant cells. Once detected, such a hypothetical tumour-specific feature would become the target for biochemical study. The long term hope of tumour immunologists must surely lie in biochemical explanations for the phenomena detected and the possible development of truly tumour-selective cytotoxic drugs.

What is the clinical value of an examination of immunological reactions to tumours? What has it to offer clinical oncologists? In the present state of the art potential application rather than practical reality must be the main topic of any such discussion. However, there are indications from present research that the practical benefits of tumour immunology may be reaped in the fields of diagnosis and prophylaxis as well as therapy. Before such speculations can be realized several important questions have to be answered. Does the cancer patient mount a specific immune response to antigens on his own tumour? Do such reactions influence the natural history of tumour growth? Are there any clinically detectable correlations between immunological status and behaviour of the tumour? Can immunological 'engineering' influence the patient's immune responses to his own tumour? Is the use of such immunological manipulations associated with clinically detectable changes in the patient's tumour? Such questions, although crucial, avoid a central paradox implicit in any statement about immune reactions to tumours. If tumours are antigenic and the host capable of reacting to these antigens, how can a tumour develop and grow in the face of a potentially cytocidal immune response? Only when the mechanisms underlying this apparent paradox have been elucidated will a rational approach to clinical tumour immunology become possible. This may well be happening at the moment. What follows is an attempt to present some of the more compelling evidence which has led to the present enthusiasm for studying the immunology of tumours.

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Tumour-specific Antigens in Experimental Animals

Historical introduction

That host resistance to tumour growth may be in part a manifestation of immunological responses to antigens on the surface of tumour cells was first suggested nearly a century ago. The intense interest in the experimental pathology of tumours shown by late Victorian biologists was accompanied by the development of tumour transplantation techniques in a variety of experimental animals. Of course at that time there was no such thing as an in-bred strain of such animals and all those used were genetically far from homogeneous. Some authors even used recently captured wild rodents. Nothing was known about allograft rejection and thus it is not surprising that many people observed and described the rejection of transplanted tumours. Subsequent rechallenge of animals that had rejected tumours revealed resistance to tumour growth which appeared to be immunologically specific.

From their experience of the immunology of bacteria many workers went on to examine the possibility of developing anti-tumour antisera. This approach was applied to some early attempts at the passive immunotherapy or serotherapy of human cancer despite the lack of convincing effects in animal experiments. In 1895, Hericourt and Richet treated 50 patients with anti-tumour antisera raised in dogs and in donkeys. Although poorly documented, they claimed substantial beneficial effects from this treatment, but needless to say no evidence of objective tumour regression was presented.

Perhaps the best early description of immunological resistance to tumour growth was that provided by Clowes and Baeslack (1905). These authors encountered animals in which spontaneous regression of transplanted tumours was a common phenomenon. They neatly demonstrated that, when challenged with tissues from the same line of tumour, those animals whose tumours had regressed were resistant to challenge. Such a model system was examined by many workers and the general conclusions reached were that such tumour resistance was not hereditary and could not be transferred with serum. It was a generally held view that immunity to transplantable tumours was a different phenomenon from bacterial immunity which was at that time believed to be entirely serum-mediated. Ehrlich had earlier postulated that tumour resistance was due to specific nutritional deficiencies, a phenomenon which he called athreptic immunity, but this notion was eventually discarded by other authors in favour of specific immunological mechanisms.

Animal and human experimentation, mainly directed towards the development of specific immunological methods of treating cancer, continued unabated until the first world war.

In 1929 Woglom published an elegant and vitriolic review entitled *Immunity to Transplantable Tumours.* This article marked a turning point in the history of tumour immunology in that it demolished the foundations laid by all the earlier animal experimentation. By pointing out the lack of genetic homogeneity in the experimental animals, Woglom revealed that there was little or no evidence for the existence of tumour-specific immunological responses. This review article, a classic of its type, is replete with memorable aphorisms which are as applicable today as they were then. He states, for instance, that 'cancer research is a discipline requiring some apprenticeship, and that not everyone with an inoculating needle and a dozen white mice can plunge in and emerge with a discovery.'

Perhaps the most significant experimental findings to come out of these earlier dark ages of tumour immunology, and which survived the acid of Woglom's pen, were those of Murphy (1926) who elegantly incriminated the lymphocyte in the immunological reactions of the host to an implanted tumour. Thus, in the absence of any detectable serum-mediated mechanisms, the possibility that cell-associated reactions might be involved in tumour immunity was first promoted. The confirmation of such a radical idea had to await the description of allogeneic tissue rejection and the mechanisms underlying histocompatibility, which in turn were only elucidated following the development of genetically uniform strains of in-bred mice.

In the early 1940's in the Jackson Laboratories at Bar Harbour such a strain of mouse became available. This strain, the C3H and its various sublines, is still in use today. In 1943, Gross, realizing the inadequacy of the earlier tumour resistance experiments by workers such as Clowes and Baeslack (1905), essentially repeated the same basic experimental protocol, but in these new in-bred mice. He induced tumours with methylcholanthrene and the subsequent sarcomas were then transplanted in the syngeneic mice by intradermal inoculation. About 20 per cent of the intradermal tumours grew for a while and then regressed. Gross was then able to show that these 'regressor' mice were resistant to subsequent challenge with the same tumour line. C3H mice show a high incidence of spontaneous mammary tumours. In some of the mice resistant to the sarcoma, spontaneous mammary tumours developed at the expected rate. He was then able to conclude that the resistance to tumour growth was immunologically specific and by inference provide evidence for the existence of antigens specific for the tumour. Confirmation of this work had to wait until 1953 when Foley drew similar conclusions after challenging mice whose tumours had been excised. However, the value of these observations depended to a great extent on the genetic homogeneity of the in-bred mice and they were criticized because of the possible influence of residual heterozygosity. However, Prehn and Main (1957) were able to eliminate this possibility from their experiments and at last the existence of tumour antigens was beyond dispute.

Further evidence for the antigenicity of experimental tumours was then provided by very many workers, and for a general review of this pioneering research the reader is referred to the excellent review article by Old and Boyse (1966). Tumour-specific resistance to challenge can be evoked by amputation of a tumour-bearing limb, radical excision of the tumour, by ligation of the tumour or by pre-treatment of the animals with irradiated tumour cells. Any antigens detected by

this transplanation type of assay are known as tumour-specific transplantation antigens (TSTA), or tumour-rejection antigens (TRA). By the use of careful transplantation techniques, such as challenging with graded doses of tumour cells, such TSTA have been detected on most experimental tumours thus examined. It began to look as if the development of these apparent neo-antigens was an essential ingredient of the malignant transformation of cells. It is still not clear as to whether truly non-immunogenic tumours exist. It is conceivable, however, that tumours may be antigenic, but non-immunogenic. In other words, they possess membrane determinants capable of a specific interaction with one element or another of the immune response, but the cells are incapable of inducing tumour resistance.

Remembering that the definition of TSTA depends on the use of transplantation resistance experiments for their detection, several distinct patterns of antigenicity have been recognized in experimental model systems.

Chemically-induced tumours

Even when tumours of identical histological appearance, induced by exposure to the same chemical carcinogen in syngeneic animals, are examined for antigenicity their TSTA appear to be individually specific. Two tumours induced in the same animal by the same carcinogen will also demonstrate unique and distinct antigenic properties. There are suggestions in the literature that there may be a background of weaker cross-reacting antigens as well as these individually specific stronger antigens (Reiner and Southam, 1967). There are also suggestions that some of the antigens detectable on chemically-induced tumours may cross-react with embryonic antigens (p. 11).

Virus-induced tumours

The TSTA on virally-induced tumours are common to all tumours induced by the same virus. However, this simple statement requires considerable elaboration. Firstly, there is evidence that as well as cross-reacting antigens there may also be unique 'individual' antigens. This has been demonstrated in some virally-induced C3H mammary tumours by Heppner and Pierce (1969). Furthermore, in some virus-induced tumours there are group-specific viral antigens as well as the other antigenic products of the viral genome. In some viral tumours as many as twelve distinctive antigens have been discovered in the same cells. As a general rule the TSTA on tumours induced by DNA viruses such as Polyoma, SV40 and the adenoviruses show group cross-reactivity only. The oncorna-viruses such as Moloney, Rauscher, Graffi and Friend viruses induce tumours which show both group cross-reacting antigens and virus-specific antigens. Primary infection of the host as an adult with most of these viruses results in solid immunity to the virus and resistance to its oncogenic effects. When the viruses are administered to the newborn, tumours subsequently develop after the animal matures. Such animals have been rendered 'tolerant' to the viral antigens.

In strains of mice possessing mammary tumour viruses (MTV) the transmission of virus particles is vertical, being mediated by suckling. The neonatal administration

of virus in this manner induces specific immunological unreactivity, and thus the virus and the subsequent mammary tumours are propagated within the strain of mouse. A detailed analysis of the complexities of their virology is beyond the scope of this book.

Plastic film-induced tumours

The insertion of inert films into experimental animals induces a variety of sarcomas. Such tumours have been examined by Klein *et al.* (1963) and the pattern of TSTA on such tumours is similar to the chemically-induced tumours, although in general film-induced sarcomas are less immunogenic (i.e. the TSTA are 'weaker').

Ultraviolet light-induced tumours

There is considerable evidence, albeit circumstantial, that solar radiation in the ultraviolet spectrum (UV) plays a substantial role in the induction of skin cancer in man. Squamous cell and basal cell carcinomas as well as malignant melanoma can be attributed to UV light exposure. In experimental animals UV light can be shown to be both an initiator and a promoter of skin carcinogenesis. In such animals UV induced tumours are powerfully immunogenic, transplantation to syngeneic recipients leading to rejection rather than tumour growth. Transplantation of such tumours is usually only accomplished by immunosuppression of the recipients. A report by Daynes and colleagues (1977) has indicated that exposure to UV light *per se* can modify the host's immune response to a syngeneic UV induced tumour. The nature of this UV light induced immunological suppression is quite unknown although suppressor cells have been incriminated, but it may be a significant feature of the biology of UV light induced tumours since they have shown that the rate of tumour growth depends on the dose of UV light administered before challenge. The complexity of these observations is emphasized by the finding that UV light has no effect on deliberate attempts to induce tumour immunity by excision of a growing primary tumour.

This is a fascinating series of observations which have considerable significance for students of human skin cancer. For instance, the apparent sunlight related increase in the incidence of malignant melanoma in unexposed sites of the body, often used as an argument for an abscopal (or distant) humoral effect of the radiation, may well be explained by the use of this model system.

Spontaneous tumours

Spontaneous tumours are those which arise in an animal population without the deliberate use of any carcinogenic stimulus. Furthermore, the term is sometimes reserved for tumours arising in strains of low tumour incidence. This definition, of course, says nothing about the cause of these tumours except that it is unknown. Some so-called spontaneous tumours have been shown to be due to environmental carcinogens such as mycotoxins in food or in materials used in care of the animals,

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