Scientific Foundations of

ONCOLOGY

T Symington

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PREFACE

For many years it has been a truism to comment on the rapid growth of specialized knowledge in medicine—in the course of which it has become only too clear that growth of knowledge has increasingly outstripped growth of understanding. The problem is seen in one of its most acute forms in oncology, a subject which has quickly come to draw on virtually all the techniques and conceptual resources of the biomedical sciences. Additional intensive specialization within the subject is inescapable; and it is this very diversity and complexity of techniques and approaches that tend to make any attempt at an integrative approach to oncology less, rather than more, feasible. Such a tendency may, of course, be a self-evident consequence of the nature of oncology itself—literally, the study of tumours but, more realistically, the study of all the phenomena which comprise the neoplastic process. It may also be argued that any attempt to appraise current knowledge in oncology (even in broad terms) is naive and, at this stage, wholly inappropriate—the time when such an exercise might have been profitable being long since past. Furthermore, the rapid rate of expansion of the subject must mean that many current views are likely to be wrong and that others will have to be refurbished in the future. Except for the fortunate possessor of that faculty which Professor Wilfred Trotter called "the intuition of reality", any attempt to sift the permanent from the evanescent must seem to be presumptuous.

Oncology thus presents a most formidable problem to its practitioners, irrespective of their training and expertise; but it may well be felt that many of these problems are the consequence of faulty communication and defective exchange of ideas and experience. As in any other aspect of scientific medicine, the first essential is to shrink the invidious distinction between clinical and experimental activities to an irreducible minimum; we believe that this distinction is particularly pernicious in oncology and that it has served as much as any other single factor in impeding understanding and fruitful collaboration. It must at once be conceded that communication between different kinds of oncologists may be difficult, but it is essential that lines of communication are established and strengthened. Clinical oncologists must acquire a knowledge of at least the general biological principles of the neoplastic process and gain some acquaintance with the research methods which impinge on their own interests; non-clinical oncologists must have opportunities to become more aware of the problems and exigencies of human cancer in a clinical setting. It is only through bilateral approaches of this kind that the work of clinical and experimental oncologists can be viewed as complementary rather than separate activities.

It was with considerations such as these in mind that the present book was planned. The choice of topics is, we believe, reasonably catholic and comprehensive within the limitations imposed by the single pair of covers of a single volume. The individual chapters are intended as self-contained summaries of current knowledge rather than as review articles, but we have refrained from imposing too rigid a format on the various contributions. Different aspects of oncology merit different approaches: in several fields the state of knowledge is sufficiently advanced for discussion and speculation to be carried on at a reasonably high level of scientific sophistication, but in others the simplest questions remain unanswered. No attempt has been made to iron out some of the controversies and "irritant facts" (cf. Professor C. H. Waddington) that are presented here: it would be fatuous to do so and, in any case, we hope that the reader will be stimulated by them. They serve to remind us of the deficiencies, as well as the remarkable advances, in our knowledge of the neoplastic process.

PREFACE

The book is primarily intended for clinical and non-clinical postgraduates to give them what we believe are authoritative summaries of modern trends in scientific oncology. At the same time it should serve as a reference source for undergraduates, particularly in medicine and biology.

We are deeply indebted to our distinguished contributors for their diligence and forbearance; they have taught us a great deal. Many others have also helped to produce this book. At the Institute of Cancer Research, they include Miss Marjorie Butt (an unflagging editorial assistant) and Mrs. Audrey Inglefield; Mr. Dennis Brunning and the library staff; and Mr. Kenneth Moreman and members of the photographic and art departments. The resources of the library of the Royal Society of Medicine were (as always) invaluable. And at William Heinemann Medical Books Ltd., it is a pleasure to acknowledge the enthusiasm, tolerance and expert guidance provided by Mr. Richard Emery.

Just before publication of this book we have to record the tragic death of one of our most distinguished contributors, Professor Gordon Hamilton Fairley.

T.S.
R.L.C.

If we begin with certainties we shall end in doubts; but if we begin with doubts, and are patient in them, we shall end in certainties

Francis Bacon
Advancement of Learning (1605)

Those who have read of everything are thought to understand everything too; but it is not always so—reading furnishes the mind only with materials of knowledge; it is thinking that makes what is read ours. We are of the ruminating kind, and it is not enough to cram ourselves with a great load of collections; unless we chew them over again, they will not give us strength and nourishment.

John Locke
Essay concerning Human Understanding (1690)

False facts are highly injurious to the progress of science, for they often long endure; but false views, if supported by some evidence, do little harm, as every one takes a salutary pleasure in proving their falseness.

Charles Darwin
The Descent of Man (1871)

Seek simplicity, and distrust it.

Alfred North Whitehead
Concept of Nature (1920)

It is a mistake to suppose, as it is so easy to do, that science enjoins upon us the view that any given idea is true or false and there is an end of it; an idea may be neither demonstrably true or false, and yet be useful and interesting

Wilfred Trotter
Observation and Experiment and their use in Medical Sciences (1930)
The Collected Papers of Wilfred Trotter FRS (1946)

The real distinction between medicine and science is not a matter of method, nor is it the recognition that man is something more than a machine. It is a matter of aims. The object of the true scientist is discovery; the object of the doctor is to plan the method of action judged to be of best value to the individual. That the aims are different is undeniable; fortunately they do not have to be invariably in conflict.

Lord Platt
Medical Science: Master or Servant (1967)

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SECTION II

BIOCHEMISTRY OF NEOPLASIA

SECTION I

GENERAL PATHOLOGY OF TUMOURS AND TUMOUR CELLS

1. PRE-NEOPLASIA: IS IT AN ENTITY?

W. H. BUTLER AND GLENYS JONES

In any discussion of pre-neoplasia, it is obviously necessary to characterize the salient characteristics of neoplasia itself. Irrespective of whether a particular lesion is benign or malignant, neoplasia may be conveniently regarded as autonomous proliferative growth of tissue outside the normal physiological control of the host. Willis (1967) adds the further qualification that the proliferative growth must continue after cessation of the evoking stimulus though in certain instances, notably virus-induced neoplasms, it is difficult to decide whether such a condition is met. A malignant neoplasm has the additional capacity to invade adjacent tissues and, in many instances, to metastasize. In a clinical context, it is usually feasible to characterize neoplasms as benign or malignant and to distinguish between them, though in some instances—notably in certain tumours of the endocrine glands—this may prove extremely difficult; it is, however, less easy to recognize pre-neoplastic conditions. In the light of the foregoing discussion, pre-neoplasia may be "pre-benign" or "pre-malignant"; but virtually nothing is known of pre-benign neoplastic states and the following account will deal solely with pre-malignant neoplasia.

The problems involved in defining pre-neoplasia in biological terms are most apparent when one considers the time course of a developing neoplastic lesion and the characteristics by which it is recognized. In order to establish a neoplasm as malignant, it is generally necessary to demonstrate the biological properties of invasion and/or metastasis. It follows that *before* the emergence of these characteristics, many malignant tumours will go unrecognized.* Sequential studies of developing tumours in animals have not resolved this problem and, in any case, such an approach is not feasible in man.

In clinical practice, a lesion is commonly designated as pre-neoplastic when it is associated with an increased incidence of malignant tumours at some future time. This does not necessarily imply that the early lesion will itself invariably progress to malignant neoplasia; some may do so but others may only be associated with an increased risk of future neoplastic development, either at the same or at another site. The number of recognized pre-malignant lesions is now considerable and they are too extensive to be reviewed comprehensively here. Instead a more general classification is put forward.

PRE-NEOPLASIA IN MAN

Conditions recognized clinically as pre-malignant may be subdivided into three groups. The *first* group comprises diseases which are not themselves neoplastic or, indeed, primarily proliferative but which carry an increased risk of neoplasia. Examples include genetic abnormalities such as Down's syndrome (Trisomy 21) and xeroderma pigmentosum. The first of these is associated with an increased incidence of acute leukaemia (Rosner and Lee, 1972) while xeroderma pigmentosum, an autosomal recessive disease of the skin, is characterized by multiple basal or squamous cell carcinomas together with melanomas and angiomas (Swanbeck, 1971). The condition is discussed in detail in Chapter 52. Also included in this first category is a group of acquired inflammatory and degenerative conditions exemplified by ulcerative colitis, tropical ulcers of the skin and leukoplakia of the vulva and tongue. Ulcerative colitis is associated with an increased incidence of multiple adenocarcinomas of the colon and rectum (Edwards and Truelove, 1964; Morson and Pang, 1967; Devroede *et al.*, 1972); the other three conditions listed are associated with squamous carcinomas of the appropriate sites (Davies *et al.*, 1968; Woodcock, 1973). Another example is provided by the atrophic gastric mucosa associated with achlorhydria in pernicious anaemia, which may give rise to gastric carcinoma. All these lesions are characterized by chronic inflammation but what role, if any, is played by the inflammatory process itself in the development of neoplasia is uncertain. The question is a vexed one which has attracted argument intermittently since the time of Virchow; but some information has accrued from experimental studies showing that subcutaneous implants of various inert substances may induce sarcomas at the site of implantation and that such tumours are preceded by local inflammation and an intense fibroblastic response (*see* Chapter 53). Further support for the importance of chronic inflammation in the development of some neoplasms has come from investigations into chemically-induced sarcomas in the subcutaneous tissues (Grasso, 1970). It was found that the injected chemical evoked a localized chronic inflammatory response which preceded the development of a local tumour, and Grasso has suggested that persistent inflammation is a necessary stage in the process of tumour induction in this particular experimental system. But in spite of such work in animals, the mechanisms whereby certain inflammatory lesions in man such as ulcerative colitis or tropical ulcers predispose to an increased incidence of local tumours remain obscure.

The *second* major group of clinical syndromes associated with an increased incidence of neoplasia is exemplified by lesions which are proliferative in nature though the

* An important distinction should be noted here between pre-malignant neoplasia and *tumour progression*—from benign to malignant—which we regard as a separate phenomenon.