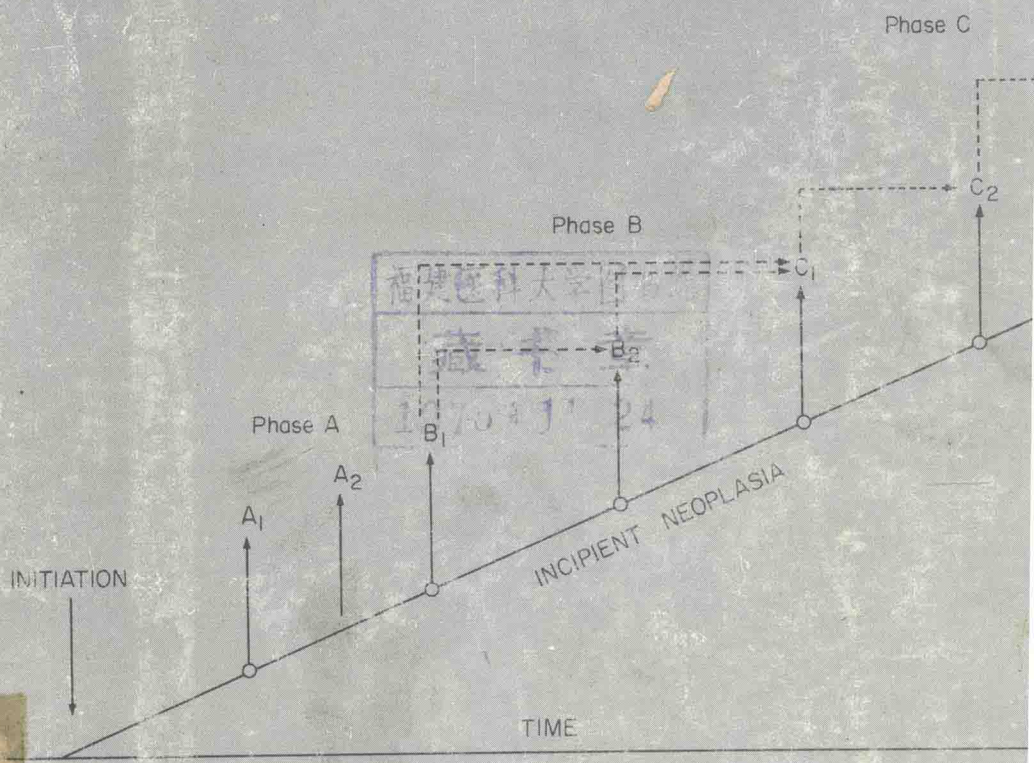
NEOPLASTIC DEVELOPMENT 2

LESLIE FOULDS



ACADEMIC PRESS
LONDON NEW YORK SAN FRANCISCO
A Subsidiary of Harcourt Brace Jovanovich, Publishers

NEOPLASTIC DEVELOPMENT

LESLIE FOULDS
London

VOLUME 2

1975
ACADEMIC PRESS
London New York San Francisco
A Subsidiary of Harcourt Brace Jovanovich

ACADEMIC PRESS INC. (LONDON) LTD.
24/28 Oval Road,
London NW1

United States Edition published by
ACADEMIC PRESS INC.
111 Fifth Avenue
New York, New York 10003

Library of Congress Catalog Card Number: 70–82389
ISBN: 0–12–262802–0

PRINTED IN GREAT BRITAIN BY
W & J Mackay Limited
Chatham, Kent

Preface

When the task of writing this book was undertaken there were three main objectives in view. The first was to present the underlying principle that neoplasia is a dynamic, continuing process where the various characteristics of a tumour, or of different parts of an area of neoplasia, will proceed independently. This principle can explain many of the difficulties presented by the vast range of patterns of behaviour and of the clinical and histological appearances of tumours, even in a single organ.

Secondly, to relate this principle to our knowledge of normal cellular, tissue and organ development and differentiation as well as to neoplastic development. This is a two-way process; developmental biologists can learn much from studies in cancer research as well as the reverse. Volume 1 of this book was particularly concerned with this aspect, but it is brought up to date and amplified in this volume, particularly in the chapter on "Virus Neoplasia".

The third objective, and the prime one in this second volume, was to select a variety of organs and special situations and to analyse and compare the study of neoplastic development in animals and in man in those organs so that it can be seen how the epigenetic principle applies in each case. The author was not so rash as to say that "neoplastic development at *this* site proceeds in *this* way and therefore *this* is the correct management". It is hoped however that a better understanding of the developmental processes will lead to a more rational approach to the prevention and treatment of human cancer.

"Cancer research" started as an attempt to help clinicians to understand the causes and development of the "disease" in *man* with a view to its prevention and to suggest possible "cures" or, at least, hopeful methods of treatment. Since that time these objectives have been too often forgotten; laboratory research and clinical practice have tended to go their separate ways. This is not always bad as, for example, the increase in our knowledge of normal development and differentiation already mentioned. One cause for the separation is the impossible volume of the relevant literature, some of it in areas of science where the applications to an understanding of neoplasia would not be apparent to clinicians even if they did read it. This also is a two-way situation, the mass of medical literature contains clinical observations whose importance may be missed by the laboratory worker.

No book can possibly review the whole of the laboratory and clinical

research into neoplasia of even a single organ, let alone do so critically. This book does *not* attempt the impossible. It does, however, try to look at the *development* of neoplasia, from origins much earlier than any clinical manifestations, in a selection of organs in animals and in man and to follow this development critically to see to what extent the underlying principle fits the facts.

The book is therefore written for both laboratory cancer research workers and for all those clinicians who want to see the broader implications of neoplastic development as they might apply to their management of patients as well as for general biologists interested in development.

The author himself wrote: "In this volume I have tried to relate the horizontal description of the development of cancer to a vertical examination of cancer of specific organs and systems in the body. I have also tried to indicate useful comparisons with neoplasia in animals (not all comparisons, still less extrapolations, are as useful as has been claimed), to discuss the efficacy of various treatments, not all of which live up to the claims of their protagonists, and to look closely at trials and diagnostic techniques. . . ."

* * *

It was a tragedy that the author should himself die of cancer before the book could be published. The first page-proofs arrived about one week before his death. It has fallen to me to try to superintend the final details. Any errors in the text or the references and any shortcomings of the indexing should not be blamed on him.

Several chapters carry "Additional References"; these are references which are cited in the text but not included in the main reference sections.

Chapter 12, the General Discussion, is certainly incomplete. It is always difficult to write a general summary of a work of this size and he was still working on it when his declining health forced him to stop. In the chapter on virus neoplasia (Chapter 11) he refers to an intention to discuss the relationship between the modern concept of a virus as a piece of genetic material, which might even originate inside the cell, and the underlying principle of neoplasia as an epigenetic process which dominates the whole of this volume. Unfortunately he never wrote this discussion. It is not difficult to see how it would have developed, particularly in relation to Temin's protovirus hypothesis (see Chapter 11), and its absence detracts nothing from the overall impact of the book, however sorry we may be not to have it included. It would have been speculation and not, like the rest of the book, an analysis of facts.

This whole work has really been the work of a lifetime and it is now nearly five years since Volume 1 was published. The list of people who have helped in the preparation of this volume is enormous. There are those for example

who have read the drafts of individual chapters and whose comments have often proved of great value. May I thank them all and apologise that they are not named here. I know my father would have wished me to thank particularly the staff of the production department at Academic Press in London. Not only have they been unfailingly helpful and patient but have also been very real friends. I would like to add my own tribute and thanks to them.

Above all however, I would like to thank my mother on his behalf, and not just for typing much of the manuscript, or for nursing him in his final illness. It is not easy to be married to a man whose whole life is so much devoted to a single object, his work. It requires self-sacrifice, patience and devotion of a very high order. I hope that she will find some reward in seeing this book finally published.

JOHN FOULDS

Foreword
by
Professor Sir David Smithers
M.D., F.R.C.P., F.R.C.S., F.F.R.

Leslie Foulds devoted his life to cancer research. His retiring manner and his deafness held him back in public discussion and perhaps delayed recognition of his outstanding ability. However, his name became well known to everyone engaged in cancer research chiefly through his work on the irregular progression of tumours in several of their growth characteristics. His many valuable contributions to his subject and his scholarly workmanship were widely recognised. No narrow worker in a restricted field of doubtful relevance, Leslie Foulds attempted the elucidation of broad important aspects of synthesis and understanding as Volume 1 of this book so ably demonstrated.

This second volume has been awaited with some impatience by his friends and colleagues. It has taken five years to arrive but has been well worth waiting for. It is a remarkable achievement essaying, as it does, the most difficult task of providing a comprehensive study of the evolutional pathology of cancerous reactions. These reactions are seen as a changing, progressive, long-term developmental process not as a sudden or even specific intra-cellular malignant transformation while, nevertheless, acknowledging the vital role of changes in the effective genome performance of disorganised cells. Leslie Foulds held that, despite their highly stable genetic material, the developmental capacity of cells varied considerably with time and place because the limited choice of opportunities for expression of the total genome they enjoyed was under the influence of their environment. He placed the cancer process in line with normal development and tissue control. His account of the cancerous reactions, unlike that given by some others, is compatible, as all such hypotheses must be, with clinical observation where such things as progression, regression, maturation, conditional persistence and metaplasia are there for all to see. His work has been in the great tradition of such noteable pathologists as Sir Robert Muir and G. W. de P. Nicholson.

The general principles of developmental biology are pursued in the main body of this book through the most detailed accounts of some of the epithelial and endocrine tumours, from maintenance of tissue homeostasis to the unrestrained growth of metastasising cancers, presenting evidence for the basic components of his general concept both from work with laboratory animals

and man. This book has the great and none too common advantage of being rooted in clinical medicine, where these problems arise, while surveying the scene from a wide experience in laboratory research.

Leslie Foulds and I had favourite desks in the same part of the Wellcome Library at the Royal Society of Medicine and as I passed him at work I was wont to make insinuating remarks about my desire to read this book while I was still able to do so. He wrote to me on December 30th, 1973, when he knew that he was dying, to say "I finished the last chapter of Volume 2 in a fashion just before Christmas but if I have time I should like to alter the last 2 or 3 pages". I rang him up just before he died to assure him of the impact which this book must certainly make. It will I am sure stand as a worthy tribute to the life work of a man who sought understanding rather than fame and who boldly chose one of the most difficult fields of medical research in which to exercise his mind. We have many brilliant people who concentrate their efforts on solving parts of problems, we have too few who lead us forward by helping us to see the implications of varied research efforts in relation to those observations made in clinical medicine which sooner or later have to be explained. Leslie Foulds in his last work has guided us towards this objective, a noble aim and a considerable achievement.

Contents

CHAPTER 1

Introduction

This book was conceived many years ago as a comprehensive study of the developmental pathology of neoplasia based in the first place on inferences from studies of tumour progression, and later on a much extended and generalized concept of neoplasia as a process of sequential neoplastic development extending over a long period of time, which, in man, might amount to several decades and be manifested by a wide variety of lesions that might emerge contemporaneously or consecutively at various times and places. The generalized concept is presented in 1, 3* and summarized schematically in a generalized diagram showing various possible developmental pathways. The diagram is reproduced with minor emendations as Fig. 1 of this chapter.

The general concept is advanced as a working hypothesis and as such its validity and generality need to be tested by application to a wider range of phenomena covering the whole course of neoplastic development from beginning to end, and in relation to the diverse circumstances prevailing in a substantial range of organs and tissues. Moreover, it should be consistent with well-substantiated general principles of normal developmental biology on the one hand, and on the other hand with clinical experience of human neoplastic diseases in a similar range of organs and tissues. More than once, I have been shocked to hear the opinion, from well-intentioned laboratory workers, that it was essential to demonstrate compatibility with general biological principles but that it was not essential, and probably would not be profitable, to spend much time on the human disease, apparently on the ground that man is the least reliable experimental animal. I reject this opinion. In any branch of science it is important to confront inferences from laboratory experiment with the stark realities of natural phenomena, which in the present context are the neoplastic diseases of mankind. It is especially important at this time when the growing estrangement between clinical practice and laboratory research is leading to grave doubts, not wholly restricted to clinicians, about the ability of laboratory research, as now conducted, to make any substantial contribution to the alleviation of human suffering attributable to neoplastic

*Here and hereafter references to Volume 1 (Foulds, 1960) are given as **1** followed by a numeral to indicate the chapter or, when more appropriate, by a page or figure reference.

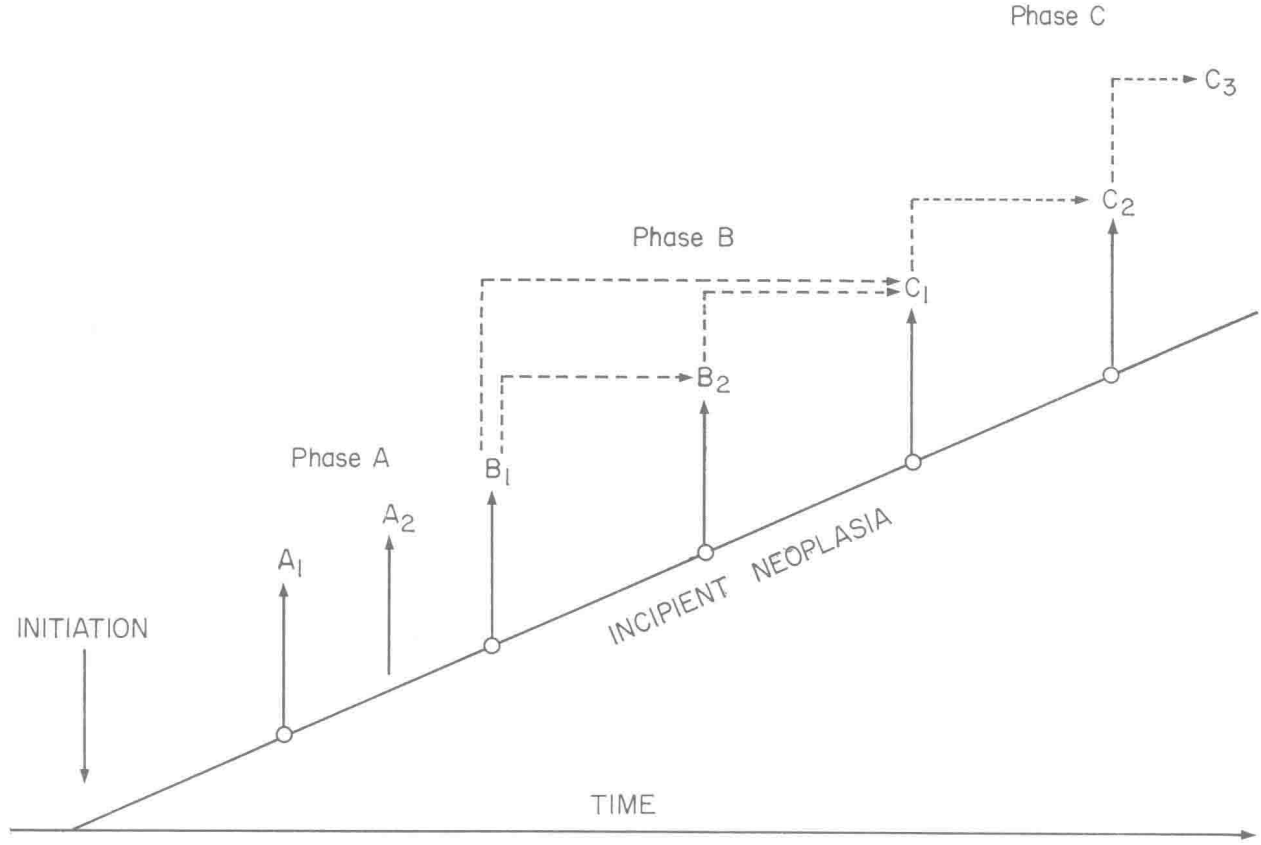

Phase C
C3
C2
Phase B
C1
B2
Phase A
B1
A2
A1
INITIATION
INCIPIENT NEOPLASIA
TIME

Figure 1

disease. Writing from the standpoint of a medically-qualified experimental pathologist with a long-standing interest in both developmental biology and medical practice but with no direct participation in either of them, I hope to illustrate in this volume the complementary and essential but diverse contributions of biological theory, laboratory analysis and clinical experience of the human disease to a comprehensive view of the nature and general principles of neoplastic development in animals and in man. Although ostensibly based to a large extent on laboratory experience, the generalized concept has been influenced to a substantial extent by the principles of normal developmental biology and by clinico-pathological studies of the human disease. It may be useful as a preamble to the discussion of the stages of neoplastic development, to recall some of the concepts of normal developmental biology discussed in Volume 1 that are closely relevant to neoplasia.

I. Some General Principles of Developmental Biology

So far as I can judge from reactions to the first volume, the discussion there given of general principles of biological organization and developmental biology is broadly acceptable to professional biologists and the concepts and terminology there developed are used freely throughout this volume and are essential to the general argument. As could be predicted, some of that discussion has been outdated but chiefly in details that do not seriously affect the general argument. A possible exception is the general acceptance of the phenomenon of *reverse transcription* which refers to the transmission of genetic information from RNA to DNA. Although not specifically mentioned in Crick's *Central Dogma* (1, 8), no clear example having then been observed, it is not inconsistent with it. It has been applied chiefly to the study of RNA tumour viruses and will be mentioned again in that context in Chapter 11. An especially important concept is that of *embryonic competence* advanced by Waddington forty years ago. The term applied primarily to the ability of embryonic tissues to react to specified inductive stimuli. As later described by Waddington, competence is a state of physiological reactivity in which a tissue is poised between two or more paths of development and may follow one or other according to the prevailing environmental conditions. Competence implies an essential element of choice between multiple options. Well-substantiated experiments showed that competence changed autonomously with time and by providing new choices of developmental pathways supplied a basis for sequential development and diversification. Grobstein later introduced a concept of *developmental capacity* basically similar to that of competence except that it was freed from the requirement of a specified extrinsic stimulus and, on this account was applicable to a wider range of developmental phenomena. In Grobstein's terminology, developmental

capacity referred to "the range and character of the demonstrable and immediate developmental alternatives". In this form, the concept of developmental capacity has proved usefully applicable to the study of neoplastic development. Neoplastic capacity provides, similarly, a choice of developmental pathways leading to diverse manifestations of the neoplastic disease; it does not rigidly specify which of the options will be chosen or, otherwise expressed, which of the prospective developmental fates, if any, will in fact be realized.

It is noteworthy that the concept of embryonic competence was invented and used profitably to account for empirical observations without waiting for knowledge of its material basis. It was proposed in Volume 1 that competence and, likewise, developmental capacity were based on a state of the cell genetic material, referred to as the *facultative genome*, that provides a limited choice of opportunities for the partial and differential utilization of the total genome. The material basis of the facultative genome is not yet known but some of its properties have been studied and described (1, 11). It is here presumed that neoplastic *developmental capacity* is similarly based.

It may be useful to mention now the new concepts of genetic materials and genetic actions that have emerged during the past 20 years, if only because of the frequent references, especially in the literature of experimental cancer research, to the importance of unspecified "genetic factors" in this or that neoplastic phenomenon. The study of genetics is no longer directed wholly, or even mainly, to the phenomenon of Mendelian inheritance through the germ line; it is concerned no less with the participation of the genome in the everyday life of somatic cells. For the purposes of this discussion, two general principles need especial emphasis. The first is that genetic DNA is a stable replicable material that possesses no intrinsic "activity"; it exerts its effects only when linked with conformably-patterned dynamic systems referred to as biotonic systems (1, 9) or more usually, following Nanney's terminology, as epigenetic systems (1, 11) whose great complexity is unlikely to be resolved by currently-available biochemical procedures. The "expression" of genetic patterns in phenotypic characters depends on a sequence of processes of which only the first two, transcription and translation of DNA, have as yet been studied in detail. The highly important corollary is that, whereas the genetic *material* is intrinsically highly stable, genetic *action* or *expression* is subject to regulation by extrinsic, or in a broad sense "environmental" factors operating through the labile, dynamic, epigenetic systems. The second important principle is that the whole of the genetic material transmitted through the germ cells and designated the *total genome*, although supposedly present in all somatic cells, is never in effective use in them at any one time; only a fraction of the genetic patterns theoretically present in the total genome is "expressed" as an *effective genome* by linkage with appropriate epigenetic

systems. Furthermore, the range of genetic patterns *available* for use as effective genomes changes from time to time and at different sites in the developing organism. The term *facultative genome* was invented to refer to the multiple sets of genetic patterns available for use as effective genomes that direct the various alternative paths of development presumed in Grobstein's concept of developmental capacity. The mechanisms that establish the availability of the multiple options provided by the facultative genome are still mysterious. Those that regulate the orderly changes in the facultative genome and, consequently, in the developmental capacity that must be presumed to direct the course of normal sequential development are no less mysterious and it has been considered necessary to invent the concept of a *programme of development* to refer to the phenomenon without specifying its material basis. In essence, this is a re-incarnation of the old but little-heeded concept of the intrinsic *directiveness* of developmental processes (1, 12); with its cybernetic gloss, the concept seems quickly to have become sufficiently respectable to be absorbed without protest into the vocabulary of developmental biology (Markert, 1968).

It is now widely agreed that the *selective* or *differential* utilization of the genome based on a multiplicity of developmental options, as described in the preceding paragraph, is the basis of the process of *differentiation* that leads to the diversification and specialization of cells and tissues in normal development (1, 11, 12). Experimental embryologists distinguished an initial step of *determination* that decided which of the various developmental pathways specified by the developmental *capacity* would, in fact, be brought into effective action at a later time. The term *determination* lost favour as being too restrictive when it was shown that the choice of developmental pathway was not irrevocable but could be abrogated by extrinsic circumstances. Unfortunately, it has been revived by Ephrussi (1970). Grobstein described the initial step as the establishment of "developmental bias without overt signs", Paul Weiss called it "strain differentiation" and I have referred to it as "preselection of an effective genome" (1, 11). None of these terms has come into general use; each implies a *provisional decision in advance of performance* and the *anticipation* of future events as noted in the early discussions of the *directiveness* of normal development. The subsequent steps of differentiation have been well described by Weiss in a number of reviews cited in 1, 12. They entail "activation" of the preselected effective genome by linkage with epigenetic systems and its consequent transcription and translation followed by a series of biochemical and morphological changes leading to the overt manifestation of the structural and chemical phenotypic differences that characterize the diverse specialized cells and tissues. The term *differentiation* is imprecise to the extent that the clear distinction between *strain differentiation* and its manifest consequences is often not made clear. In the medical