Advances in Gastroenterology

Gastrointestinal and Hepatobiliary Cancer

Edited by H.J.F. Hodgson
and S.R. Bloom

GASTROINTESTINAL AND HEPATOBILIARY CANCER

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LONDON
CHAPMAN AND HALL

First published 1983
by Chapman and Hall Ltd,
11 New Fetter Lane, London EC4P 4EE

Printed in Great Britain at the
University Press, Cambridge

ISBN 0 412 23690 7

British Library Cataloguing in Publication Data

Gastrointestinal and hepatobiliary cancer.—
(Advances in gastroenterology series)
1. Gastrointestinal system—Cancer
2. Biliary tract—Cancer
I. Hodgson, H.J.F. II. Bloom, S.R.
III. Series
616.99'433 RC280.S8

ISBN 0–412–23690–7

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Preface

This book does not set out to be a comprehensive textbook of gastrointestinal and hepatobiliary cancer. Rather, it surveys a number of areas in which recent developments have occurred, both in the clinical field and the scientific.

One particular motive governing the choice of subjects was a wish to bridge the divide that arises too easily between clinicians and laboratory scientists. Nonetheless we have acknowledged the reality of this divide by arranging the book in two parts. In the first, shorter part of the book (Chapters 1–5), various aspects of the cancer process have been surveyed – the nature of the malignant cell, illustrations of the process of carcinogenesis, the immune response to cancer, and aspects of epidemiology. Although the study of these has not yet transformed the approach to the individual with cancer, it is from these subjects that fundamental changes in clinical management will at some time – not we trust too far in the future – arise.

In the second part of the book, clinical aspects of cancer management are reviewed, ranging from techniques for screening and early diagnosis of tumours, to current treatment by surgery, chemotherapy and radiotherapy. We have also selected a number of topics to highlight the contribution that laboratory-based research has made both to the understanding of clinical disease manifestations – for example in the endocrine manifestations of pancreatic tumours, and the non-metastatic distant complications of cancers – and to diagnosis, illustrated by the detection of tumour-associated antigens and the abnormal immunoglobulins of α-chain disease.

Whilst the prognosis of gastrointestinal tumours remains grim, the last decade has seen major advances in our knowledge of them. Continued improvement in the management of gut and liver cancer will require the fullest co-operation between doctors and scientists, and we offer this volume as a contribution to that understanding.

Financial support was gratefully received from Eaton Laboratories, Woking, for the reproduction of colour Plates 1 and 2 facing page 158.

H.J.F. Hodgson
S.R. Bloom

List of Abbreviations

ACD	adult coeliac disease
ACTH	adrenocorticotrophic hormone
ADCC	antibody-dependent cell-mediated cytotoxicity
ADH	antidiuretic hormone
AIDS	acquired immune deficiency
ALL	acute lymphoblastic leukaemia
AMMN	acetoxymethyl-methylnitrosamine
AOM	azoxymethane
APUD	amine, precursor uptake and decarboxylation
BCNU	1,3 bis (2 chloroethyl)-1-nitrosourea
BGP	biliary glycoprotein
CAGA	cancer-associated galactosyltransferase acceptor
CAT	computerized axial tomography
α-CD	α-chain disease
CEA	carcinoembryonic antigen
CLIP	corticotrophin-like intermediate lobe peptide
CPALP	carcinoplacental alkaline phosphatase
DIC	disseminated intravascular coagulation
DMH	1,2-dimethylhydrazine
ECOG	Eastern Cooperative Onocology Group
EGF	epidermal growth factor
ERCP	endoscopic retrograde cholangiopancreatography
FAM	5-FU, adriamycin, mitomycin C
FBA	fecal bile acid
FGF	fibroblast growth factor
FLM	fraction-labelled mitoses
α-FP	α-fetoprotein
FSA	fetal sulphoglycoprotein
FSH	follicle stimulating hormone
5-FU	5-fluorouracil
5FUDR	floxuridine
G	generation time
G-6-PD	glucose-6-phosphate dehydrogenase
GT	galactosyltransferase
hCG	chorionic gonadotrophin
hCS	chorionic somatomammotrophin

5HT	5-hydroxytryptamine
Ig	immunoglobulin
IGF	insulin-like growth factor
IPSID	immunoproliferative small intestinal disease
LAI	leucocyte adherence inhibition
LDH	lactate dehydrogenase
LETS	large external transformation sensitive
LH	luteinizing hormone
M	mitotic phase
MAHA	microangiopathic haemolytic anaemia
MAM	methylazoxymethanol
MEA	multiendocrine adenomatosis
MER	methanol extracted residue
MGBG	methylglyoxalbis (guanylhydrazone)
MNNG	*N*-methyl-*N'*nitro-nitrosoguanidine
MNU	methylnitrosourea
α-MO	α-methylornithine
MW	molecular weight
NBTE	non-bacterial thrombolic endocarditis
NDC	nuclear dehydrogenating *Clostridia*
NK	natural killer cell
NPDase	nucleotide phosphodiesterase
NSILA	non-suppressible insulin-like activity
ODC	ornithine decarboxylase
PCAA	pancreatic cancer-associated antigen
PCT	porphyria cutanea tarda
PDTL	primary digestive tract lymphoma
PHDRT	precision high dose radiotherapy
POA	pancreatic oncofetal antigen
PP	pancreatic polypeptide
PSIL	primary small intestine lymphoma
PSS	progressive systemic sclerosis
PTC	percutaneous transhepatic cholangiography
PTH	parathormone
PUSIL	primary upper intestinal lymphoma
PVA	polyvinyl alcohol
R	restriction point
S	synthesis phase
SAS	Supraregional Assay Service
SGF	Sarcoma growth factor
SMF	streptozotocin, mitomycin C, 5-FU
TGF	transforming growth factor
TPA	12-*O*-tetra-decanoylphorbol-13-acetate

TSH	thyroid stimulating hormone
VIP	vasoactive intestinal polypeptide
WDHA	watery diarrhoea, hypokalaemia, achlorhydria
ZES	Zollinger–Ellison Syndrome
ZGM	zinc glycinate marker

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PART ONE

Fundamental Aspects

CHAPTER ONE

The Biology of the Cancer Cell

MILTON M. WEISER and WAYNE D. KLOHS

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1.1 Introduction

Clinically, the definition of cancer rarely poses a problem; we define cancer by its action against the host. Cancer is viewed as an attacking force, a growing parasitic, consuming, exuberantly-living antilife army of cells. Paradoxically, cancers appear to arise from normal tissue, grow in a manner that is 'so singularly changed as no longer to obey the fundamental law whereby the cellular constituents of an organism exist in harmony and act together to maintain it' [1]. Cancers 'disobey the law of organism' [1], and become outlaws destroying the host and, in so doing, destroying themselves. Cancers grow, replace normal tissue, spread and set up new foci of growth, outgrow their blood supply killing some of their own cells, and use up the energy sources of the host. They elude host armies of lymphocytes and antibodies, dissolve collagen and erode bone. Cancers, ironically with help from man, can be maintained in tissue culture as immortal. Henrietta Lacks died but her cervical cancer lives on in laboratories around the world as the HeLa cell and, even then, this cell line has a propensity for 'contaminating' other tissue culture lines and spreading, to ruin experiments and cast doubts on years of work and theories [2]. Even in the laboratory, in its sterile confines of covered petri dishes, controlled environment and laminar-flow hoods, the cancerous HeLa cell remains true to form, a destructive outlaw.

This book, concerned with the outlaw cancer cells of the gastrointestinal system, will delineate possible causes, define premalignant cellular characteristics, evaluate the status of tumour markers in gastrointestinal malignancies, try to understand why host defences have failed, and ultimately ask: what is to be done? There are two approaches

to answering this question: one is a trial and error approach to the development of new diagnostic and therapeutic modalities. Alternatively, one can investigate the metabolism and molecular biology of cancer cells in order to learn how cancer originates and what are its critical properties, data that should yield new ways of preventing and treating the disease without destroying the host.

In this chapter we will discuss the second approach to the question. We will outline what is presently known about the cancer cell and the recent controversies over the molecular mechanism of carcinogenesis. An attempt will be made to characterize metabolically and morphologically the transformed phenotype. In particular, we will concentrate on recent progress in understanding growth control and cell surface changes. Lastly, we will define the cellular alterations detected in gastrointestinal cancers.

1.1.1 *Cellular basis of tumourigenicity*

Controversies arise in trying to fit the facts to theories of the cellular basis of cancer induction, as recently discussed by Cairns [3] and in an editorial in *Nature* [4]. Any tumourigenic theory or combination of theories must be able to explain the experimental induction of tumours by chemicals and viruses and by such varied manoeuvres as plastic implantation or an animal's access to unlimited food [5, 6]. One also has to explain the lag in cancer induction after viral inoculation [3], the lack of evidence for a viral aetiology in most human tumours, the genetic predisposition of some human tumours (e.g. familial polyposis coli), and the increased incidence of intestinal cancers in inflammatory bowel disease [7, 8, 9], coeliac disease [10, 11] and immune deficiency syndromes [12], diseases of obvious varied aetiologies and pathogenic mechanisms. We will describe four current theories on the cellular requirements for tumour development: the clonal origin theory [13, 14], the multicellular origin theory [14], the theory of genetic rearrangement [3, 15], and the faulty differentiation theory [16, 17].

Most acceptable theories on the origin of cancer assume that the primary event(s) occurs in the nucleus with an alteration in gene structure or control of gene expression. This is based on the dogma of the primacy of DNA in the control of cell division and differentiation. The clonal theory of cancer postulates an induction of random alterations in the genes of some somatic cells (Fig. 1.1), giving growth advantages to the affected cell over its normal neighbours. Clonal expansion begins. Cellular markers such as the two isoenzymes of glucose-6-phosphate dehydrogenase (G-6-PD) have been used to demonstrate the high probability that most human tumours are of clonal origin. G-6-PD is an

X-linked enzyme. In women, one of the X-chromosomes is inactivated and therefore only one of the two G-6-PD activities is expressed per cell. This produces two cell populations, each expressing only one isoenzyme. When measured, only one type of G-6-PD was detectable in tumour cells. If a tumour had arisen from an event that affected many cells, the tumour would be a product of many clones and one would have expected both types of G-6-PD activities to be detected in the tumour. As initially envisioned, the clonal theory appeared to explain the effects of radiation, chemicals, and viruses in tumourigenesis, i.e. they produced mutations. Similarly, hereditary susceptibility to cancer was due to gene defects

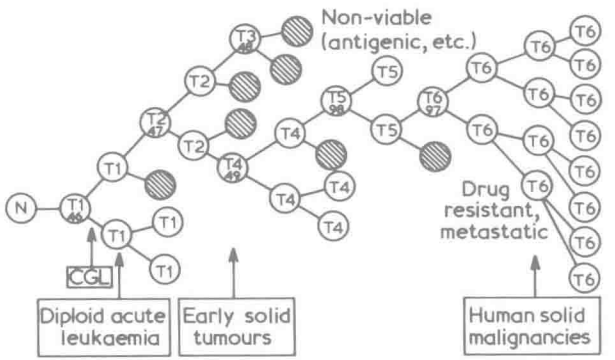

Fig. 1.1 'Model of clonal evolution in neoplasia. Carcinogen-induced change in progenitor normal cell (N) produces a diploid tumour cell (T1, 46 chromosomes) with growth advantage permitting clonal expansion to begin. Genetic instability of T1 cells leads to production of variants (illustrated by changes in chromosome number, T2 to T6). Most variants die, due to metabolic or immunologic disadvantage (hatched circles); occasionally one has an additional selective advantage (for example, T2, 47 chromosome), and its progeny become the predominant subpopulation until an even more favorable variant appears (for example, T4). The stepwise sequence in each tumour differs (being partially determined by environmental pressures on selection), and results in a different, aneuploid karyotype in each fully developed malignancy (T6). Biological characteristics of tumour progression (for example, morphological and metabolic loss of differentiation, invasion and metastasis, resistance to therapy) parallel the stages of genetic evolution. Human tumours with minimal chromosome change (diploid acute leukaemia, chronic granulocytic leukaemia) are considered to be early in clonal evolution; human solid cancers, typically highly aneuploid, are viewed as late in the developmental process.' (Reproduced with permission of the author: Nowel, P.C. (1976) [13].)