The book deals briefly with the normal structure, functioning and biochemistry of the esophagus and with the histological and genetic changes accompanying the development of esophageal cancer in humans and animals. Factors implicated in causing esophageal cancer are described in relation to its very dramatic epidemiology. Thus dietary deficiencies and consumption of foods contaminated by Fusaria mycotoxins are discussed in connection with the extremely high incidence of the disease in certain sharply demarcated regions in China and South Africa, and alcohol and tobacco use are discussed in relation to the epidemiology in Europe and USA. Other hazards mentioned include opium in Iran, betel nut in Asia and bracken in Japan.

The sole group of chemicals known to be very potent esophageal carcinogens in animal experiments, the nitrosamines, are described especially in terms of the widespread human exposure. The concept is put forward that these chemicals are responsible for initiation of the disease, but that promotion by the secondary risk factors is generally essential for symptomatic cancer to develop. This could explain why the epidemiology reflects exposure to secondary risk factors rather than levels of exposure to nitrosamines. The secondary risk factors increase cell replication but do not initiate cancer. The recent perturbing increase in adenocarcinoma is considered.
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Cancer of the esophagus
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Approaches to the etiology

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Preface

The surprising discovery that a small simple chemically inert compound, dimethylnitrosamine, was a potent carcinogen, was made by Barnes and Magee in 1956. A few years later I joined them in an attempt to find out how and why, in terms of metabolism of the carcinogen, and reactions with protein, RNA and DNA. From work carried out mainly in Heidelberg and in America, it was very soon found that many of the N-nitroso compounds were carcinogenic, they showed a surprising organospecificity, and that more than half of the 300 tested were carcinogenic for the esophagus. When it became apparent that human exposure to the compounds in the environment was widespread, and that no other chemically identified environmental compounds were potent esophageal carcinogens in animal experiments, the obvious possibility that they were a major cause of esophageal cancer was considered.

The problem in testing this concept was that human exposure was so widespread but difficult to quantify that epidemiological surveys could not associate the disease with exposure to nitrosamines. Instead incidence correlated with other risk factors, especially alcohol consumption and dietary deficiencies. A likely explanation seemed to me to be in the induction of cell replication. I had found that, while continuous feeding of dimethylnitrosamine induced liver cancer, one single injection of the compound was not carcinogenic unless given when the liver cells were dividing in response to partial hepatectomy. The secondary risk factors of alcohol, dietary deficiencies and mycotoxins were shown to stimulate basal cell replication in the esophagus. It therefore seemed highly probable that nitrosamines could initiate malignancy, but that in the esophagus promotion by an increase in cell replication was essential for clinical cancer to appear.

The incidence of esophageal cancer world-wide is one of the highest, in
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Preface

the UK, the incidence in women is the highest in Europe, and for men it is second only to France and Switzerland, and ranks among the ten most frequent cancers. The rate of liver cancer in the UK is very low. In spite of this, study of cancer of the liver receives infinitely more support than that of the esophagus. This book was written in the hope that an updated discussion of the problem might stimulate interest and research.

For one person to attempt to write a book considering such broad issues was a formidable prospect, and I have been helped by colleagues with expertise in certain aspects of the subject. The friends I would like to thank especially are the following: Dr Clifford Waters, formerly of Surrey University; Dr J.V. Frei, University of London, Ontario; Dr P. Grasso, formerly of British Industrial Biological Research Association; Dr R. Schoental, formerly of MRC Toxicology Unit; Dr M. Hill, European Cancer Prevention Chairman.

I would like to express my gratitude also to my secretary, Mrs Joan Nicholass, for her hard work and moral support, and to Mr Brian Street, without whose help in enabling me to work after a motor accident the writing of this book would have been very much delayed.

V.M.C.
Abbreviations

NOC  \( N \)-nitroso compounds

\textbf{Nitrosamines}

\begin{itemize}
  \item NDMA  \( N \)-nitroso-dimethylamine
  \item NDEA  \( N \)-nitroso-diethylamine
  \item NDPA  \( N \)-nitroso-dipropylamine
  \item NDBA  \( N \)-nitroso-dibutylamine
  \item NMEA  \( N \)-nitroso-methylethylamine
  \item NMBA  \( N \)-nitroso-methylbutylamine
  \item NMAA  \( N \)-nitroso-methylamylamine
  \item NMAIA  \( N \)-nitroso-methylallylamine
  \item N-SAR  \( N \)-nitroso-sarcosine
  \item NMBzA  \( N \)-nitroso-methylbenzylamine
  \item NMPHA  \( N \)-nitroso-methylphenylamine
  \item N-PIP  \( N \)-nitroso-piperidine
  \item N-PYR  \( N \)-nitroso-pyrrolidine
\end{itemize}

\textbf{Tobacco-specific nitrosamines}

\begin{itemize}
  \item TSN  Tobacco specific nitrosamines
  \item NNN  \( N \)-nitrosornornicotine
  \item NNK  4(methyl-nitroso-amino)-1-(3 pyridyl)-butanone
  \item NAB  \( N \)-nitrosoanabasine
  \item NAT  \( N \)-nitrosoanatabine
\end{itemize}

\textbf{Direct-acting nitroso compounds}

\begin{itemize}
  \item NMU  Nitrosomethyleneurea
  \item NEU  Nitrosoethyleneurea
  \item MNNG  Methylnitroso-soguanidine
\end{itemize}
xiv Abbreviations

ENNG Ethylnitronitrosoguanidine
NMUR Nitrosomethylurethane
NEUR Nitrosoethylurethane

DNA adducts
7MG 7-methylguanine
O\(^6\)MG \(O^6\)-methylguanine
3MA 3-methyladenine

Alcohols
EtOH Ethanol
3Mb 3-methylbutanol
2Mb 2-methylbutanol

Mycotoxins
DS Deoxyscirpenol