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CAUSES AND CONTROL OF COLORECTAL CANCER

A Model for Cancer Prevention

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Notice

The author has made every effort to provide current, complete and reliable information in this book, based on exhaustive research of the scientific data, as well as on wide consultation with colleagues. As the subject of colorectal cause and prevention is changing rapidly and as there is always the possibility of omission and of human error, the author and publishers are not responsible for any errors or omissions which may be present in this book. Before any action is taken by individuals, physicians or other health-care professionals, the author strongly recommends consultation with other authoritative sources such as colleagues, physicians, other health-care providers and other scientific publications.

Dedication

To Nicholas and Elizabeth Slezak, who long ago supported the vision that cancer will become a preventable condition.

CONTENTS

FOREWORD

It is an often stated maxim that we have it within our biological capabilities not to have to die from disease. There is only one unavoidable cause of death – old age! In the industrialized nations, science and technology have enabled man to overcome many nutritional deficiencies and infectious diseases of the past. Unfortunately, we have also created a series of new diseases, largely due to our lifestyles. These diseases include cancer, which is the second largest cause of morbidity and mortality. The recent span of several decades of research has contributed much to our understanding of the origins of cancer, and more importantly, has enabled us to approach its prevention. This research, both in lifestyle medicine and in the laboratory sciences, has provided important concepts, namely that cancer is not an inevitable cause of aging, and that most human cancers are caused by environmental or lifestyle factors, such as use of tobacco, abuse of alcohol, and nutritional overload. Most of these factors cause a metabolic overload that is simply beyond the human body's capacity for compensation or detoxification. From these insights evolves our understanding that morbidity and mortality from cancer can be significantly reduced by modifying or eliminating the causative and contributing factors.

For example, the overload caused by high-fat diets and excessive intake of food calories that is seen in affluent societies, negatively affects our metabolism, cell membrane structures, colonic constituents, prostaglandin synthesis and our entire hormone system. The only remedy for such detrimental changes lies in modifying food and food habits. Clearly, practicing primary prevention medicine by motivating such changes is more than overdue.

Large bowel cancer is one of the most common and persistent human malignancies in the Western world and has a greater than 50% mortality. Studies which have focussed on the epidemiology of large bowel cancer, as well as

laboratory studies, strongly support the role of dietary components in the etiology of this disease. Despite many recent advances, large bowel cancer continues to challenge epidemiologists, nutritionists, biochemists, pathologists, molecular biologists, and gastroenterologists.

In presenting a global view of large bowel cancer, Dr. Gabriel Kune MD comprehensively reviews not only the key studies performed worldwide by experts in the fields named above, but also discusses the opportunities for change and its impact on society. This volume covers all the advances made in our understanding of the etiology, biology and genetics underlying this disease, and applies this knowledge to early diagnosis, screening and primary prevention. This book presents a multidisciplinary approach to the subject and provides a means for those in biomedical sciences and related fields, and for physicians and other health professionals, to keep abreast of current progress in cancer prevention.

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PREFACE

All is flux, nothing stays still.
Nothing endures but change.

Heraclitus 540-580 BC

Over 700,000 men and women are found to have colorectal cancer globally each year, and as a result, over 400,000 of these individuals will die prematurely.

In the USA alone, 150,000 men and women are expected to be diagnosed with colorectal cancer during 1996. Colorectal cancer is one of the commonest malignant tumors and causes of cancer death in developed countries. About 30 years ago, little was known about the causes of this cancer, early diagnosis was only tentatively suggested, and prevention was not thought of. Within one generation, scientists drawn from a broad spectrum of disciplines have made important contributions towards explaining the causes and development of this cancer, and as a consequence, advances in the early diagnosis and prevention of colorectal tumors followed.

Over 1000 significant studies have been performed around the world during the past 30 years in relation to the causes, carcinogenesis and prevention of colorectal tumors. Cancer epidemiology has provided us with a multicausal explanation for both the development of, and protection from, colorectal tumors in relation to several environmental as well as inherited exposures. Pathology studies revealed a number of morphologic pathways which exist in the transformation of a normal colorectal epithelial cell into a cancer cell, in particular the adenoma–carcinoma sequence, including the time frame for these changes. Wedged between studies of causes and morphologic outcome, carcinogenesis research has provided increasingly sophisticated explanations of the mechanisms of action, whereby the several causal and protective exposures

alter the environment or "milieu" of the colorectal mucosa. More recently, molecular biology has revealed the presence of several mutations resulting from the altered environment of the large bowel mucosa, as well as inherited mutations, which are associated with the progression of morphologic change from a normal cell to colorectal cancer.

Close on the heels of this unprecedented volume of etiologic, carcinogenesis and morphologic research came several technical advances, and in particular effective fecal occult blood testing and fiberoptic endoscopy of the large bowel, as well as the endoscopic excision of colorectal polyps. These technical advances foreshadowed a major potential for the early diagnosis of colorectal cancer, as well as the ability to systematically and safely remove the major precursor lesion, colorectal adenomas, without resorting to abdominal surgery. Large controlled studies of screening for colorectal tumors were begun in the USA and Europe, the results of which are now making an impact on the secondary prevention of colorectal tumors, using various screening strategies, followed by regular surveillance. At present the main obstacle to secondary prevention with mass screening and surveillance is the vast expenditure of resources required.

In the past two decades, it appears that a significant proportion of the population in several Western countries, particularly the USA, UK, Scandinavia, Australia and New Zealand, were motivated to change their lifestyles in order to prevent or minimize the risks of cardiovascular disease, diabetes and other so-called "illnesses of our civilization". The dietary, alcohol, smoking and physical activity recommendations to prevent these illnesses happen to be almost identical to prudent advice for the primary prevention of colorectal tumors, as based on the findings of the vast etiologic research of the past 30 years. This fortunate situation in relation to primary prevention already appears to be having some impact on colorectal cancer incidence and mortality. Controlled intervention studies in primary prevention are also being conducted, some with reported findings, but most not yet completed. The results of these will add further impetus to the primary prevention of colorectal tumors. Primary prevention is likely to have enormous cost benefits for the community; however, it does involve large-scale behavioral changes in dietary habits, alcohol consumption, smoking and physical activity, changes which ideally are best commenced early in life.

All the data to explain the causes, development and control of colorectal tumors are certainly not yet to hand, and much more work needs to be done. However, this amazing breadth and depth of research of the last 30 years, which has reached across many disciplines, involving physicians, surgeons, endoscopists, cancer epidemiologists, biostatisticians, carcinogenesis researchers, behavioral scientists, public health workers, geneticists, molecular biologists, anthropologists, demographers and several other groups of scientists, has resulted in an important basic understanding of colorectal cancer etiology, carcinogenesis and prevention.

In assembling the current knowledge of colorectal tumor cause and control, the writer has optimism for the view that colorectal cancer will be the first common malignant tumor to be largely prevented or controlled in the first part of the 21st century. The results of this multidisciplinary approach to colorectal cancer etiology and control will also serve as an important model for the study of other common malignancies, such as cancers of the breast and prostate, the causes and prevention of which are less well understood.

Gabriel A. Kune, MD
University of Melbourne

ACKNOWLEDGMENTS

I am a part of all that I have met,
Yet all experience is an arch wherethrough
Gleams that untravel'd world.

Lord Tennyson 1809-1892
Ulysses

Many colleagues have contributed directly or indirectly to the data and views expressed in this book. The writings of Dr. Denis Burkitt, MD FRS, were inspirational, pointing to the scientific evidence that many common illnesses of Western cultures, including colorectal cancer, are related to lifestyle and therefore preventable. Denis Burkitt remained a friend, colleague and valued adviser until his death in 1993.

The author's focus on colorectal cancer prevention commenced in 1978 with the Melbourne Colorectal Cancer Study, which the author set up with Dr. Susan Kune PhD. We received invaluable advice from Dr. Bruce K. Armstrong MB DPhil, Director, Australian Institute of Health, Professor Robert MacLennan MD, University of Queensland and Queensland Institute of Medical Research, Professor John D. Mathews MD, Director, Menzies School of Health Research, Dr. Richard Rahe MD, University of Nevada, Dr. Claus B. Bahnson PhD, University of California, San Francisco, Professor Mark L. Wahlqvist MD, Monash University, Melbourne, and Dr. John H. Cummings MD, Dunn Nutrition Centre and University of Cambridge. Ms Lyn Watson MSc, Biostatistician, University of Melbourne, now Monash University, Dr. Nigel Gray President, International Union Against Cancer, Dr. Graham Giles PhD, Anti-Cancer Council of Victoria, Dr. John Hopper PhD, and Associate Professor Avni Sali MB PhD, University of Melbourne provided invaluable assistance during the

course of the investigation and subsequently. This study changed the author's research focus from clinical surgery to that of the causes and prevention of colorectal cancer, thereby coming into contact with an eminent group of scientists working in the area of cancer epidemiology, prevention, and carcinogenesis.

The views expressed in this book were influenced and shaped over the years by many leading figures in epidemiology, prevention, carcinogenesis, surgery, pathology, biostatistics and molecular biology, and I am grateful that they shared with me their experience and wisdom. In the USA I am grateful to Dr. Joseph F. Fraumeni Jr MD and Dr. Susan S. Devesa PhD of the National Cancer Institute, Dr. Michael J. Wargovich PhD, MD Anderson Cancer Center and University of Texas, Dr. John D. Potter MD, Fred Hutchinson Cancer Research Center, Seattle, Dr. Geoffrey R. Howe PhD, Columbia University, New York, Dr. Sidney J. Winawer MD, Memorial Sloan-Kettering Cancer Center, New York, Dr. Jerome J. De Cosse MD, Cornell University, Dr. Thomas M. Mack MD, University of Southern California, Mr. William Haenszel MSc and Dr. Richard L. Nelson MD of the University of Illinois in Chicago, and Dr. Michael J. O'Brien MD, Boston University.

In the United Kingdom Sir Richard Doll MD FRS, University of Oxford was and remains an inspiration for his scientific and balanced approach to cancer prevention. My visits with Professor Sir Roy Calne FRS, University of Cambridge, Professor John D. Hardcastle FRCS, University of Nottingham and Professor Sir Miles Irving FRCS, University of Salford, were most valuable.

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In Scandinavia, Professor Tor J. Eide MD, University of Tromsø, Norway, Professor Ole Kronborg MD, Odense University, Denmark and Professor Jan Kewenter MD, Göteborg University, Sweden have assisted me with various aspects of colorectal tumor morphology, screening and surveillance. Professor Paul Rozen MD, Tel Aviv University, a friend since undergraduate medical studies at the University of Melbourne, has provided valuable information and advice on several aspects of colorectal cancer etiology, screening and surveillance. I am most grateful for their help, advice and unselfish sharing of data and views.

My special thanks go to several colleagues who not only helped me over the years with various aspects of colorectal cancer etiology and prevention, but also gave their valuable time to read and offer constructive criticism on key chapters

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Professor Jeremy Jass MD, Professor of Pathology and Head of Department, Medical School, University of Auckland, New Zealand kindly contributed the chapter on the Molecular Evolution of Colorectal Neoplasms. He also read and gave me valuable advice and critique of the chapters on Heredity and the Morphology of Colorectal Neoplasia. His help and advice is much appreciated by the author.

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It is a special pleasure to acknowledge Dr. Ernst L. Wynder MD, President, American Health Foundation, truly a Founding Father of cancer prevention, for writing the Foreword. He was joined by Dr. Bandaru S. Reddy PhD, also of the American Health Foundation, a world figure in colorectal carcinogenesis research. Their contribution is a signal honor for the writer.

Gabriel A. Kune

1

PRINCIPLES OF CANCER CAUSATION

Only relatively recently have scientists engaged in cancer research begun to ask the question, "Why does a cancer develop?". Modern causal thinking in cancer could be said to have started in the late 1940s with the proposition that smoking is an important cause of lung cancer. In contrast, theories of carcinogenesis, that is, asking the question "How does a cancer develop?" have fascinated physicians and scientists since the time of Galen (Ballantyne 1988). The 20th century has seen major advances in understanding how the human body works in health and disease, and how a cancer develops, so that the understanding of carcinogenesis is well advanced in contrast to the understanding of cancer etiology. This chapter focusses on two aspects of cancer causation, namely, on the criteria of causality as they relate to cancer, and on the multicausal model of cancer etiology.

CRITERIA OF CANCER CAUSALITY

What aspects of an association should we especially consider before deciding that the most likely interpretation of it is causation?

Sir Austin Bradford Hill, FRS 1965

The cause and effect relationship has engaged the minds of philosophers and scientists since the time of Aristotle. In the health sciences there have been numerous significant publications illuminating various aspects of the cause and

effect relationship, and of these, the publications of Hill 1965, Susser 1973 and Rothman 1974, 1976 and 1982 are of particular importance regarding cancer.

Cause and effect relationships are of vital concern to those working in the field of cancer etiology and prevention, because judgements and decisions often have to be made in the absence of what would be called "complete proof" by physicists or mathematicians, or even by medical scientists working in pharmacology or aspects of pathogenesis. Apart from the philosophical consideration that complete proof is impossible in anything, the cancer epidemiologist is further faced with having to make judgements and decisions on human studies which, by their very nature, cannot be controlled to the same extent as can test tube or animal experiments. Of much greater utility for the cancer epidemiologist is to understand that there are a number of practical criteria which can be used in order to make a judgement on the degree to which a certain association, such as sunburn and skin cancer, smoking and lung cancer, a certain diet pattern and colorectal cancer, has been shown to be causal. It is like building a house, and making a judgement on how close one is to completion by the number of bricks which have been built, and how close this structure is to the architect's floor plan. The process in an individual case is certainly a brick-by-brick method. Ultimately, a conclusion regarding causality of a particular exposure in relation to cancer, whilst based on the criteria about to be described, is to some extent, also a personal judgement.

The time sequence of events is a basic criterion, in that the cause must always precede the effect. The practical criteria of causality upon which to make a judgement of the degree to which there is likely to be a cause and effect relationship between a particular cancer and a previous exposure, includes the consistency and strength of the association, the presence of a dose-response effect, the elimination of confounding factors, the biological plausibility and coherence of the association, and least importantly, confirmatory animal experimental studies.

CONSISTENCY OF THE ASSOCIATION

Internal consistency of the association being examined in one study, as well as external consistency observed in different populations and under different circumstances in several studies, is an important indicator of causality. In this regard, it is also of comfort to know that consistency has been obtained by several different methodologies, such as correlational studies, retrospective case-control studies and prospective cohort studies, and that these all show similar effects. The use of different populations, different sets of investigators and different methodologies helps to negate "consensus error", that is, similar studies having similar biases and for this reason, consistently coming to similar, albeit not necessarily correct conclusions.

STRENGTH OF THE ASSOCIATION

Relative Risk, Odds Ratio

This concept refers to the magnitude of the ratio of the two groups being compared, and this is usually expressed in population-based or cohort studies as a relative risk, or as an odds ratio in non population-based studies. Strong associations, such as those for example with relative risks of 5 or more are likely to be causal, since in well conducted studies any biases that may be inherent in the study are unlikely to be as strong as a relative risk of 5. Weaker associations such as those with relative risks of 1.5 or 2, whilst they may be explained by biases, do not necessarily mean that a causal association does not exist. A weak association may simply mean that the effect is weak, or that the effect is indirect, or that the effect is mainly on a precursor lesion such as a colorectal adenoma, removed in time from the diagnosis of colorectal cancer, and only a small proportion of these precursor lesions become malignant.

Confidence in a weak association increases if the 95% confidence interval excludes the null value of one and also if the actual interval is close. However, even if a weak association is not statistically significant, it should not be dismissed as not being causal if other criteria of causality are satisfied, and particularly so if sound methodology has been used in that particular study.

Meta Analysis, Pooled Analysis

Meta-analysis of data from several studies has been used to evaluate drug effects and has also been used in recent years in cancer epidemiology to express the strength of association of a particular exposure. Although this method of studying cancer etiology is attractive and comfortable for statisticians, and the results are numerically precise, the inferences drawn can be misleading (Chalmers 1991; Felson 1992; Boden 1992). Meta-analyses of the same exposure but using different criteria can have opposite results. Furthermore, meta-analysis which ignores well-known clinical biases, such as over-exposure of the control group by using hospital controls for associations such as smoking or alcohol consumption, can lead to a result showing no association or at best a very weak association (Kune and Vitetta 1992; Wynder and Stellman 1992). In contrast to meta-analysis, pooled analysis of data combining studies with similar methodology such as case-control studies, and performed to a similar degree of sophistication, will yield large study numbers and a high statistical power by combining studies using different populations and different sets of investigators. Considerable confidence can usually be placed in pooled analysis of data.

DOSE-RESPONSE EFFECT OF THE EXPOSURE

An increasing gradient of relative risk with increasing levels of exposure of the agent under examination, intuitively add a degree of confidence to the hypothesis

that an association is causal. Dose-response effects with agents such as smoking and lung cancer, alcohol and oral, pharyngeal or gullet cancer, or the cumulative effect of sunlight and skin cancer, are examples of this dose-response effect. In some situations the dose-response may be a threshold effect, such as has been found with vitamin C consumption and protection from colorectal cancer, or a J-shaped effect with low risk at low exposure rates, no or little risk at middle levels of exposure, and an increasing level of risk with high exposure, such as has been noted in relation to milk consumption and colorectal cancer, or alcohol consumption and overall mortality.

Cessation of the exposure, such as quitting smoking or drinking alcohol, may result in a decrease in risk over time. This effect, for example, has been shown with cessation of smoking and decreasing risk of lung cancer over time. The ultimate test is a controlled intervention trial in which an agent of protection is introduced, say a nutritional item, and this is shown to alter tumor incidence.

CORRECTION FOR CONFOUNDING CAUSES

Correction for confounding etiologies and for effect modification of covariates is an important aspect in the design and interpretation of cancer etiology studies (Miettinen 1974a; Rothman 1976). If in a particular study, known or putative confounding risk factors have been corrected for, and the association remains largely unchanged, or remains elevated in keeping with the expected change caused by the confounding factor, then this gives one further confidence that the association is causal. If however, after correction for a confounding effect, the association disappears and a null result is obtained, then there would be serious doubt that the association is causal. For example, chronic constipation was a risk in the univariate analysis of one colorectal cancer study, but when simultaneously corrected for several dietary factors, the association disappeared, indicating that it was the diet rather than the constipation that was the real risk factor (Kune et al 1988). The ability to use computer-generated "modelling" of several variables, such as multiple logistic regression equations, has been an invaluable advance in understanding not only confounding, but also the multicausal nature of cancer.

A major problem in many epidemiologic studies is that currently most studies are still conducted in such a way that the investigators do not obtain data to be able to simultaneously correct for other known or putative confounding etiologic factors. Future etiologic studies of cancer should be so designed that all major putative etiologic factors are included in the same data set.

PLAUSIBILITY AND COHERENCE OF THE ASSOCIATION

There is a subtle distinction between plausibility and coherence. However, both refer to a cause and effect hypothesis being in keeping with what is known of the natural history and biology of the particular illness under study, and also that

there are biologically sound mechanisms explaining how cancer might develop in relation to the exposure under study. Evidence of the agent producing premalignant changes in the cell under study adds to the biologic plausibility. For example, hyperplastic and dysplastic bronchial cells following tobacco exposure were confirmatory data for the biologic plausibility of smoking and lung cancer. Too much should not be made of this criterion of causality, as comforting as it may be for those seeking an explanation of the mechanism, because the natural history of a particular disease is often not well known and because a biologically plausible mechanism for the effect under study has often not been proposed or studied.

CONFIRMATORY ANIMAL EXPERIMENTAL STUDIES

Confirmation that models of animal carcinogenesis are augmented by the exposure under study, such as alcohol consumption or dietary factors in chemically produced colorectal cancer in rats, is probably the least important criterion of causality. This is because there are usually major differences in exposure levels between human and animal studies, because there are species differences in anatomy and histopathology, and because there are differences in the nature and biologic behavior of tumors produced experimentally when compared with similar human tumors.

THE MULTICAUSAL MODEL OF NEOPLASIA

It is not the diversity of the evidence, but rather
the many-sided nature of truth which is amazing.

Anonymous

The literature is silent on a general model of neoplasia that incorporates etiology, mechanisms of action, and morphologic change from a normal to a malignant cell. Cancer epidemiologists studying cancer etiology, scientists studying carcinogenesis, molecular biologists studying cell mutations, and histopathologists studying malignant transformation of a normal cell into a cancer cell, have until recently been largely working in isolation, hence a unified model of neoplasia has never been developed. The following model of neoplasia is not original. It is derived from several isolated sources, given a unified form, and used to give utility to these isolated hypotheses from clinical, epidemiological and experimental observations about neoplasia. This model should not be regarded as a formal or rigid proof of cancer causation.

The dictum of William of Ockham (1300–1348), usually referred to as "Ockham's razor", states that "A plurality must not be asserted without necessity" (*Quodlibeta Septum* 1320). This was later put into the more familiar form in the 17th century by John Ponce of Cork: "Entities should not be multiplied beyond necessity". This concept of having an economy of hypotheses to explain certain biologic phenomena was further promoted by the discovery of specific causes of illness, particularly the discovery of micro-organisms such as the tubercle bacillus, the discovery of insulin and of vitamin B12. Although few may know of William of Ockham or John Ponce of Cork, the concept of using an economy of hypotheses has undoubtedly diffused widely into modern scientific thinking on causality. This appealing concept, whilst useful in relation to certain illnesses, has seriously retarded the understanding of the etiology of neoplasia, as it has placed too rigid a framework of reference on broader conceptualizations of cancer etiology, particularly as for most cancers, a specific causal agent has not been identified. The need to adopt a rigid conceptual framework is still echoed by scientists working in the fields of pathogenesis, who criticize multicausal models and their proponents, saying that such hypotheses "retreat into the soft options of multicausal explanations". In cancer etiology research, multicausal explanations have been very useful (Potter et al 1993; Kune 1995).

SUFFICIENT, NECESSARY AND COMPONENT CAUSES

The scientific community is indebted to Dr. Kenneth Rothman who in 1976 clearly outlined the concepts of "sufficient", "necessary" and "component" causes, thereby laying the foundations for a multicausal model of cancer causation (Greenland 1995). A "necessary" cause is one which is always necessary to produce a particular cancer. An example is exposure to female hormones in utero and the subsequent development of vaginal cancer in that exposed female adult. Regrettably, few other "necessary" causes of cancer can be quoted. A multicausal model of neoplasia allows the flexibility to include inherited and acquired causes, and allows for physiologic and pathologic changes in the person who develops cancer, such as changes in the state of immunity or of other functions, as well as for the effects of interrelationships among component causes.

Further, the concept of a "necessary and sufficient" cause means that this is a specific cause, that no other causes are necessary, and that this cause always results in the development of a malignant tumor. Such a very specific situation has so far not been found for malignant tumors. This means that in many cases, an important cause can be found, but it is not sufficient to cause a cancer. Most smokers, for example, do not develop lung cancer. Multiple causes of a tumor have been described as "components" of "sufficient" causes (Rothman 1976). It is known that more than one component cause is present for a particular cancer. For example, in lung cancer, smoking is the most important component cause.

However, exposure to asbestos is also an independent component cause. There are also a number of other causal associations of lung cancer which can occur in the absence of smoking or even of passive smoking. For most cancers we only know some of the component causes with a varying degree of certainty.

ATTRIBUTABLE RISK

An important corollary of the concept of component causes, is the estimation of the size of a component cause, and this has been variously described as attributable risk, attributable fraction, etiologic fraction, or population attributable risk (Cole and MacMahon 1971; Miettinen 1974b; Greenland and Robins 1988). The calculation of attributable risk is of major relevance in the primary prevention of cancer, and will be referred to in several sections of this book. Thus blocking one of the component causes in prevention may lower the incidence of a particular cancer to a degree which reflects the attributable risk of that component cause in that population.

LATENT PERIOD AND PERIOD OF INDUCTION

The terms "latent period" and "induction period" are sometimes interchanged, though there is a distinction between the two. The induction period is the time during which a cause commences and is completed. When the induction period is completed, the latent period begins. During the latent period the cancer is not a clinical entity; it is symptomless and it may even be in its premalignant form, such as hyperplasia, dysplasia or a benign tumor such as an adenoma. The distinction between the so-called "induction period" and "latent period" is of some practical value because the induction period defines the time during which "primary prevention", that is, blocking a cause, applies. It is during the latent period that "secondary prevention", that is, the detection and treatment of premalignant lesions or of very early cancers such as carcinomas-in-situ, can be applied. Whilst the conceptual distinction between induction period and latent period is attractive for those interested in prevention, in practice there is usually difficulty in establishing this distinction.

INDEPENDENCE AND SYNERGY

Most etiologic factors in neoplastic processes appear to act independently of each other, and their effects, if there are multiple causes, are usually additive. However, in certain situations, the effect is "synergistic", meaning that the sum of the combined risk of the two exposures exceeds their additive value (Rothman 1974).

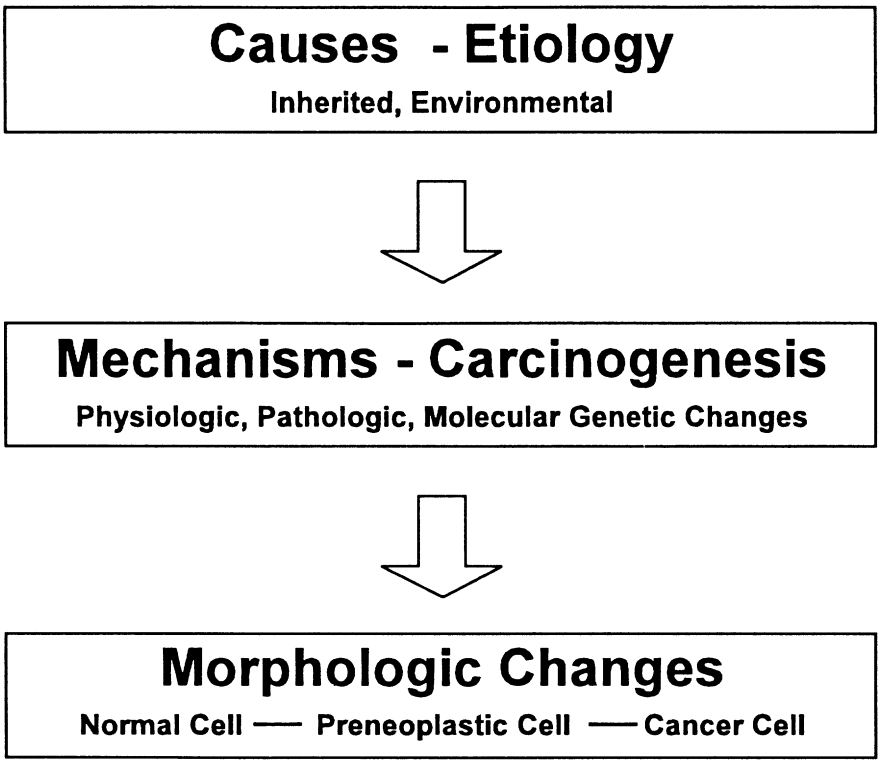

Figure 1.1 A general model of cancer causes, mechanisms of action and morphologic changes.

For example, smoking and alcohol consumption risks in oral cavity, pharynx and esophagus cancer exceed the additive value of each risk independently, although each factor can act as an independent causal agent (Rothman and Keller 1972; Tuyns et al 1977; Kune et al 1993). Similarly, asbestos exposure and ionizing radiation and exposure to smoking in relation to lung cancer also interact in a synergistic way, so that risk levels are very high for those who are exposed to both asbestos (or radiation) and to smoking (Saracci 1977, 1987).

MODEL OF CAUSES, MECHANISMS, MORPHOLOGIC CHANGES

Figure 1.1 shows this model in a simple form with several causes which act on one or more mechanisms of neoplasia, and these mechanisms are responsible for changing a normal cell into a malignant cell.

Causes – Etiology

The causes can be divided into inherited causes and causes acquired during life. The inherited causes are genetically expressed and are therefore both a cause and a mechanism of action. The acquired causes are environmental factors such as smoking, alcohol consumption, exposure to asbestos, radiation, dietary factors, drugs, chemicals, and others (Figure 1.2).

Mechanisms of Action – Carcinogenesis

The various causal factors can be depicted as being responsible for several pathophysiologic alterations in the environment of the target cell. This altered milieu is then responsible for a series of distinct genetic changes or mutations of the dividing cell, which results in progression from a normal cell to a malignant cell (Figure 1.2). The recent demonstration of mutations in the tumor-suppressor gene p53 among tobacco users who develop oral cancer and oral precancer is an exciting development, which for the first time connects a cause with a tumor gene mutation (Kaur et al 1994; Lazarus et al 1995; Brennan et al 1995).

Morphologic Changes

An increase in the number of cells, and an increase in the rate of cell division has been postulated to be positively related to carcinogenesis in general (Bullough 1950; Albanes and Winick 1988; Preston-Martin et al 1990). Morphologic changes have been well related to a series of mutations in a number of cancers, and in particular, in colorectal cancer (Chapter 3). Morphologic changes imply a sequence of events from a normal cell to a hyperplastic cell, to a dysplastic cell, to a carcinoma, and then to invasion and metastasis (Figure 1.2).

A second pathway of changes may be from a normal cell to a benign tumor, such as an adenoma, and then to a carcinoma (Figure 1.2). It is becoming clear, at least in colorectal neoplasia, that there are probably several morphologic pathways (Chapters 3 and 4).

MULTICAUSAL CANCER RESEARCH

At present, a multicausal model incorporating morphologic changes, causes and mechanisms probably best explains the development of malignant tumors. For the testing of the multicausal nature of various cancers, a study which examines simultaneously all putative etiologic factors in one data set, should be the blueprint for the future. Such studies need to be population-based and if performed meticulously, are time-consuming and expensive. However, they can be of immense value in understanding the multicausal nature of cancer etiology. Such a study design is also valuable in apportioning risk attributable to each putative etiologic factor in a particular population, and therefore will provide an indication of the extent of the reduction in incidence and mortality which may be achievable using effective primary intervention in relation to a particular cause.

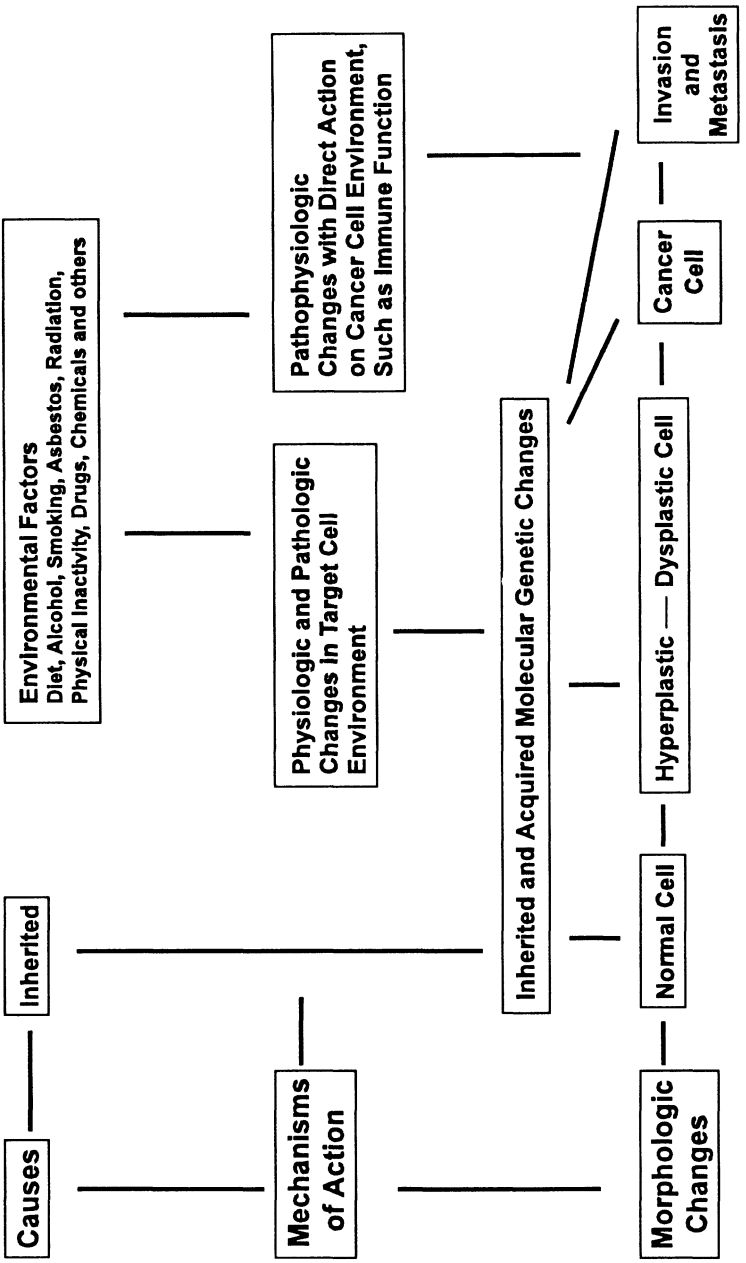

Figure 1.2 A more detailed illustration of the multicausal model of cancer causation, various mechanisms of carcinogenesis, and morphologic changes.

Multicausal cancer research requires major resources, considerable expertise, and such projects are of necessity not expedient with their results, and therefore few have been realized. In reviewing over 200 large epidemiological studies concerned with the causes of colorectal tumors, 4 have a multicausal design, namely the US Nurses' Health Study commenced in 1976, the Melbourne Colorectal Cancer Study commenced in 1979, the US Health Professionals' Follow-up Study and the Iowa Women's Health Study, both commenced in 1986. As noted in several sections of this book, these 4 studies have already contributed significantly to a "global" understanding of colorectal tumor etiology. Similar studies in relation to other cancers, particularly breast cancer and prostate cancer, are awaited.

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2

BASIC STRUCTURE AND FUNCTION OF THE LARGE BOWEL

A brief and basic description is given of the structure, contents, and function of the large bowel, particularly as it may relate to the causes and prevention of colorectal tumors. The chapter may be particularly useful to those who are not medically trained, and also to those who may be medically trained but are not engaged on a regular basis in dealing with the clinical aspects of large bowel tumors. This chapter is unreferenced, and for further detailed information, the reader is referred to standard texts, such as Gray's Anatomy and Bockus Gastroenterology.

THE STRUCTURE OF THE LARGE BOWEL

The large bowel is essentially a tubular structure and forms the terminal portion of the gastrointestinal tract. The large bowel and its several named parts, as it lies in the abdomen and pelvis, is shown in Figure 2.1.

MACROSCOPIC ANATOMY

The large bowel commences at the terminal ileum, which is the last portion of the small bowel, as the cecum, from which opens the blindly ending appendix. The right colon, or proximal colon, consists of the cecum, ascending colon, hepatic flexure and transverse colon, whilst the distal colon consists of the splenic flexure, descending colon and sigmoid colon. The sigmoid colon continues into the rectosigmoid junction, which is usually located about 15–18 cm from the anal verge, and then it continues into the rectum itself, terminating at the anal canal which ends as the anus (Figure 2.1). The rectum is

about 15 cm long when measured endoscopically from the anal verge. It is important to note that the rectum is sometimes misclassified as the colon in death certificates and in some epidemiologic studies.

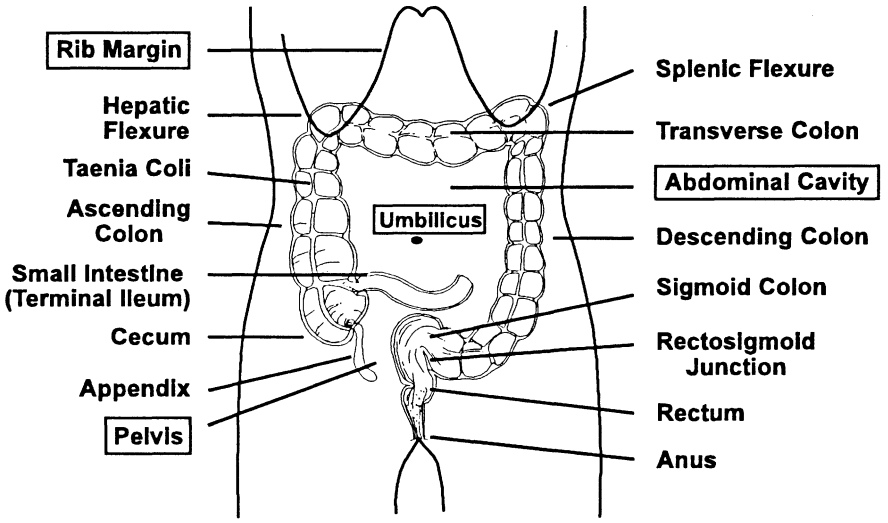

Figure 2.1 The named parts of the large bowel and its superimposed surface relations in the abdomen and pelvis.

The large bowel can be represented as a convoluted tube-like structure which has four layers, named from inside out, the mucosa, which is the lining of columnar epithelial cells from which colorectal tumors of the "adeno" type arise, the submucosa, the muscle layer, also called the muscularis layer, and the outer connective tissue layer, the serosa. The muscle layer of the colon differs from that of the rectum. Both the colon and rectum have a complete investment of circular muscle and the rectum also has an investment of longitudinal muscle, although in the colon the longitudinal muscle is very thin in most parts, and is concentrated in three longitudinal bands called taenia coli.

The rectum contains two or three valves of Houston, which are not true valves in the mechanical sense, but are spiral mucosal folds within the rectum, which, unless care is taken, may hide small tumours from the endoscopist's view. Other parts of the large bowel which are so-called "blind spots" and may cause endoscopic difficulties, are the rectosigmoid junction where the rectum is angulated and at times contracted also, as well as the junction of the sigmoid colon with the descending colon, the splenic flexure and the hepatic flexure (Figure 2.1).

MICROSCOPIC ANATOMY OF THE MUCOSA

The microscopic structure of the colorectal mucosa is of particular interest because almost all tumors of the large bowel are tumors of the columnar epithelium. The colorectal mucosa consists of a single layer of columnar epithelial cells, including goblet cells which secrete mucus. The mucosa is relatively flat and it is punctuated by blindly ending tubular structures called the glands or crypts of Lieberkühn, now usually referred to simply as "crypts" (Figure 2.2).

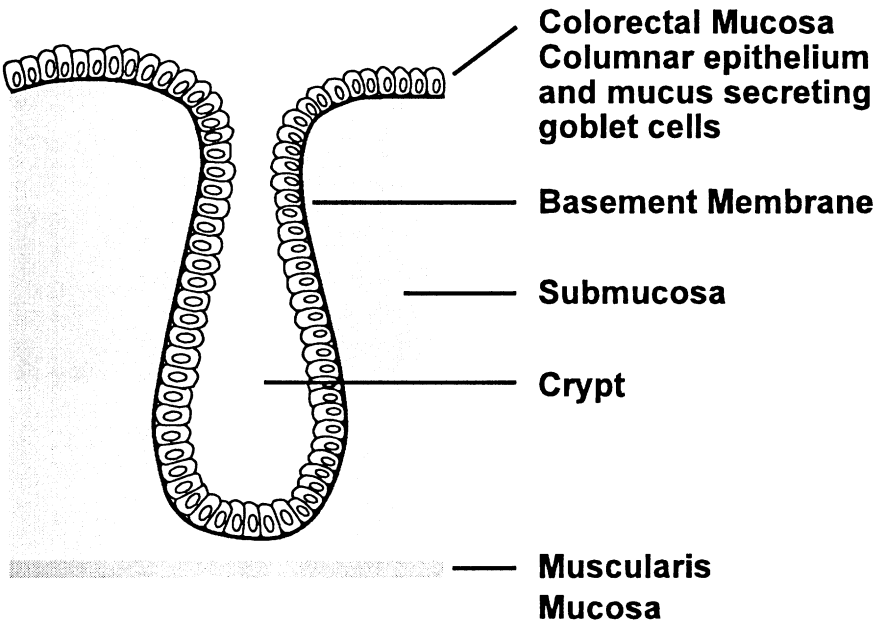

Figure 2.2 Microscopic anatomy of the mucosal and submucosal layers of the large bowel.

Proliferative activity and replacement of surface cells occurs from the bottom of these crypts, which then move upwards towards the surface. Emerging data from histopathology and molecular genetics indicate that abnormal proliferative activity, probably commencing in these crypts and probably usually associated with genetic change, forms the basis as well as the beginning of the epithelial tumors of the large bowel, which are the subject of this book. The columnar epithelium lies on a basement membrane, deep to which is found a thin layer of connective tissue, separated from the proper muscular layer by a thin layer of smooth muscle, the muscularis mucosa (Figure 2.2).

CONTENTS OF THE LARGE BOWEL

Large bowel contents is fluid in the cecum and proximal colon and then with progressive absorption of water it becomes semi-solid and solid in the distal colon. With respect to colorectal tumors, the important aspects of large bowel content include undigested residue, dietary fiber, bacteria, fecal bile salts and fat.

Dietary fiber is a complex of substances playing an important role in the prevention of colorectal tumors (Chapter 6). Between 200 mg and 600 mg of fecal bile salts are excreted in the feces each day, representing about one-fifth of the total bile salt pool. Bacteria in the feces deconjugate bile salts and only secondary bile salts are found in the feces in the form of deoxycholic acid and lithocholic acid. An excess of these bile salts appears to be one of the important mechanisms which can damage the colorectal mucosa and may lead to the development of colorectal tumors.

The large bowel is sterile at birth but becomes colonized soon after, and bacteria form an important part of the fecal content. It has been estimated that about one-third of the dry weight of feces consists of bacteria, and there is on average about 1.5 kg of bacteria in the large bowel. It has also been estimated that the number of bacteria in the large bowel equals or exceeds the total number of body cells. Fecal bacteria take part in numerous physiologic and pathologic processes in the large bowel and as will be noted subsequently, they are important in both the protection from and in the causation of colorectal tumors.

Approximately 10% of dietary fat is not absorbed and passes into the large bowel. On a diet of 70–100 g of fat per day, about 7 g of fat are excreted in the feces. Excessive amounts of fat in the colon appear to play a part in the development of colorectal tumors, in association with certain types of large bowel bacteria (Chapter 6).

FUNCTIONS OF THE LARGE BOWEL

The large bowel is the end storage organ for undigested food, in particular for dietary fiber and a small proportion of the fat intake before these undigested dietary components are excreted in the feces. The large bowel absorbs water and electrolytes, thereby firming up the feces; however, this function is not essential as a fairly normal life can be kept up after surgical excision of the large bowel.

The large bowel eliminates fecal contents regularly through coordinated muscular activity that is slow, complex and subject to change, making it difficult to define abnormal motility. However, this action leads to reasonably regular bowel movements. Intestinal, and particularly large bowel transit times, are inversely related to the development of colorectal tumors, with slow transit times being generally a risk and fast transit times protective. As will be noted later, dietary habits and physical activity affect the motility and transit time in the large bowel, and this may have an effect on the development of colorectal tumors.

3

MOLECULAR EVOLUTION OF COLORECTAL NEOPLASMS

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Strategies for preventing colorectal cancer will be more effective if they are based upon a thorough understanding of the evolutionary pathway leading from normality through to malignancy. Fundamental insights into the process of colorectal carcinogenesis have been achieved through the advent of molecular technologies. DNA technology also offers the promise of powerful and highly specific tests for detection of cancer and precancerous lesions (Smith-Ravin et al 1995). This chapter will review the major molecular breakthroughs of the last decade, integrating genetic changes with their morphologic counterparts.

NEOPLASIA: A GENETIC DISORDER

One of the foremost conceptual advances in the field of cancer research has been appreciation of the genetic nature of cancer. This is not to imply that cancer is necessarily hereditary, but rather that mutated genes are fundamentally responsible for neoplastic change. The demonstration of a specific cancer gene mutation within the entire cellular population of a malignant tumor also establishes the clonal nature of a neoplasm, that is, all the cells within a cancer are the descendants of a single normal cell. This also establishes the fact that neoplasia is essentially a focal process and not the result of a field change. However the passage of a normal cell to a malignant clone does not occur as a

single step. From the initial neoplastic clone, a subclone emerges and from this subclone another subclone. Each of these steps is governed by a mutation within a cancer gene. The mutation gives the subclone a selective growth advantage so that it outgrows or destroys the parent clone. The well-documented progression from normal through adenoma to colorectal carcinoma is the morphologic expression of this evolutionary process.

In one sense it is a travesty to speak of the 'evolution' of cancer. Neoplasia in fact represents a reversal of the Darwinian process that has allowed the more specialized to develop from the less specialized. Genes that have evolved to maintain growth, differentiation and intercellular communication are successively rendered dysfunctional by randomly occurring mutations. Interestingly, evolution could not take place without random mutational change and it has been suggested that cancer is a by-product of a natural genetic instability that is essential for the evolutionary process (Sommer 1994).

NATURE OF ADENOMA

Benign epithelial neoplasms of the colorectum are grouped together as adenomas. An adenoma is a focal, circumscribed and usually polypoid lesion that shows progressive growth as a result of uncontrolled crypt division. Adenomatous epithelium is characterized by a failure to switch from a proliferative state and for its constituent cell lineages (mainly columnar and goblet cell) to achieve full differentiation and cytoplasmic maturation. The clonal nature of an adenoma (origin from a single transformed cell) has been firmly established (Vogelstein et al 1988). Adenomatous progression is achieved by crypt division and through the generation of subclones with enhanced growth potential. Each subclone arises through a new mutation that adds to the accumulated mutational burden (Shibata et al 1993). Ultimately a subclone with the ability to invade and with potential to metastasize may appear, although only a small proportion of adenomas transforms into carcinoma.

The World Health Organization classification of intestinal tumors emphasizes the similarities rather than the differences between colorectal adenomas (Jass and Sobin 1989). However, there is considerable variability in the morphogenesis of the normal–adenoma–cancer sequence. A sessile villous adenoma and a pedunculated tubular adenoma vary in their behavior as well as in their gross and microscopic appearances. Flat adenomas are now well recognized and clinicopathologic studies have shown these to be associated with an increased potential for malignant change (Kuramoto et al 1990; Muto et al 1985). Flat adenomas and macroscopically invisible microadenomas may account for the phenomenon of "de novo" carcinoma (Minamoto et al 1994).

NATURE OF CANCER GENES

Two main types of cancer genes are recognized, namely oncogenes and tumor suppressor (oncosuppressor) genes. Oncogenes act dominantly insofar as mutation in a single allele will lead to a measurable oncogenic effect. An oncogene known to be activated by point mutation in colorectal adenomas is K-ras (Vogelstein et al 1988). Other oncogenes such as c-myc, c-myb and bcl-2 may be merely upregulated on a reactive basis (Smith et al 1993; Sugio et al 1988). Oncosuppressor genes act recessively. Both alleles need to be inactivated before a full oncogenic effect occurs. The first allele is inactivated by somatic mutation (or through a germline mutation in hereditary cancer syndromes). Loss of the second allele may also be due to somatic mutation or be the result of a mitotic error leading to loss of the chromosome (or part of the chromosome) carrying the second allele. The involvement of multiple oncosuppressor genes in the evolution of colorectal cancer was inferred by the demonstration within tumors of consistent loss of heterozygosity (LOH) for chromosomes 1 (Leister et al 1990), 5 (Rees et al 1989; Solomon et al 1987), 8 (Cunningham et al 1994), 17 (Vogelstein et al 1988) and 18 (Vogelstein et al 1988). The most well-characterized oncosuppressor genes are the adenomatous polyposis coli (APC) gene on 5q (Bodmer et al 1987; Rees et al 1989) and the p53 gene on 17p (Vogelstein et al 1988). 5q LOH occurs as an early event whereas 17p LOH is detected at an advanced stage of neoplastic progression (Vogelstein et al 1988). In each case, the first allele will have been inactivated previously through a somatic mutation (or an inherited germline mutation in the case of APC). Loss of function of the p53 gene may in fact herald the conversion of adenoma to carcinoma (Kikuchi-Yanoshita et al 1992).

IMPORTANCE OF APC GENE AND POLYPOSIS AS A MODEL FOR NEOPLASTIC PROGRESSION

The importance of the hereditary disorder familial adenomatous polyposis (FAP) as a model for the evolution of colorectal cancer has been long recognized. Subjects with a germline APC mutation develop innumerable adenomas at an early age. The earliest recognizable lesion in FAP is a unicryptal adenoma. This does not appear to form through the repopulation of a normal crypt by transformed cells. Microreconstruction studies indicate that a bud of adenomatous cells develops from the side of a normal crypt (Nakamura and Kino 1984). The bud advances up the crypt along with the normal epithelium and grows out into the lamina propria to form a neoplastic tubule. The opening of the neoplastic crypt finally reaches the epithelial surface and further branching and budding produces a superficial, cap-like mass of neoplastic epithelium. When sections are stained immunohistochemically for nuclear proliferative markers (PCNA or Ki-67), the neoplastic epithelium is highlighted within its superficial

location whereas the proliferation compartment of normal epithelium is restricted to the lower half of the crypt. It is not known whether an inherited APC mutation is sufficient on its own to initiate microadenomatous development as described above, or whether a second "hit" is required (either somatic mutation or loss of the second normal APC allele or some other mutation). Certainly LOH for 5q may occur as an early event (Rees et al 1989). 5q LOH was found in 10 of 15 small adenomas (some less than 3 mm) obtained from a patient with FAP. However, no LOH was found in 60 adenomas from 6 additional subjects with FAP (Ichii et al 1992). Yet, when the second allele was screened for somatic mutation, this was detected in 32 (42.7%) of the total of 75 adenomas (Ichii et al 1992). The frequency of somatic mutations was not influenced by either size of adenoma or grade of dysplasia (Ichii et al 1992). These findings indicate that a second hit involving the APC gene occurs at a very early stage in the evolution of adenoma. They do not prove that the second hit actually underlies the initiation of the unicryptal adenoma.

In 5 FAP subjects with a mean age of 27 years, the mean frequency of microadenomas was 40 per 10^4 normal crypts (assuming 5000 crypts per cm^2) (Roncucci et al 1991). The relatively high incidence of microadenomas speaks against the requirement for a second hit to bring about microadenomatous initiation. In subjects with an APC germline mutation, the simultaneous development of many thousands of adenomas around puberty could reflect a threshold effect in which the APC gene product falls below a critical concentration, perhaps in relation to an altered hormonal milieu (Bodmer et al 1987). However, the findings in an experimental mouse (Min) model for FAP support an obligatory two-hit mechanism for the initiation of adenomas (Levy et al 1994). All microadenomas, including one comprising only two crypts, showed evidence of a second mutation. It could still be argued that the second hit is not required for the initiation of a unicryptal adenoma, but is necessary for subsequent cryptal division. An alternative explanation for the high frequency of microadenomas in FAP could be the fact that several generations of daughter cells (as well as stem cells) serve as targets for the second hit. The resulting adenomas may be relatively evanescent, thereby accounting for the peculiar proneness of FAP adenomas to regress following surgery or Sulindac treatment. Whilst early involvement of the wild-type APC gene may be the preferred molecular route for the early genesis of adenomas in FAP, as noted below, the nature and order of early mutations may differ in the majority of individuals who are not primed with an APC germline mutation.

Recent observations go some way towards explaining the fundamental role of the APC gene in colorectal carcinogenesis. The cytoskeleton is not a static structure, but participates in the orchestration of multiple intracellular functions. Furthermore, the cytoskeleton of one cell is linked indirectly to the cytoskeleton of adjacent cells through a family of cell adhesion molecules and cytoplasmic proteins found at specialized points of contact along the cell membrane. The

APC gene product is one of the proteins involved within the chain of communication between the cytoskeleton and the cell adhesion molecule cadherin. The APC protein binds to both the microtubular system (Smith et al 1994) and to the intracellular protein β-catenin (Rubinfield et al 1993; Su et al 1993) which is in turn associated with the cytoplasmic domain of cadherin. Antibodies to the mutant gene product fail to bind to microtubules (Smith et al 1994). An insufficient concentration of wild-type APC protein presumably undermines not only cytoskeletal integrity, but also influences indirectly cell to cell interactions and structural relationships at the tissue level.

SPORADIC MICROADENOMAS AND ABERRANT CRYPT FOCI (ACF)

Low power light microscopic examination of methylene blue stained colorectal surface epithelium en face allows aberrant crypt foci (ACF) to be visualized on the basis of their altered staining, size and shape (Roncucci et al 1991). Routine histology of 30 ACF from subjects with colorectal disease other than FAP showed 21 to be microadenomas (Roncucci et al 1991). The remainder were either hyperplastic crypts or had no diagnostic morphologic features. In a series of 12 subjects with sporadic colorectal cancer, the mean number of ACF was 0.37 per cm^2. If the surface area of the entire colorectum is estimated as 1000 cm^2 and 21 of 30 (70%) ACF are microadenomas, then the mean number of colorectal microadenomas per subject is around 240 (Roncucci et al 1991). Others have found the proportion of microadenomas to be lower (5%), giving an estimated 20 microadenomas per subject with colorectal cancer (Jen et al 1994).

It is reasonable to assume that somatic mutations of the APC gene are implicated in the initiation of sporadic microadenomas (as in FAP). As argued in the case of FAP however, the high frequency of sporadic microadenomas casts doubt on the requirement for a second hit. Out of this surprisingly large number of focal microneoplasms, perhaps only one or two will develop into macroscopically visible adenomas. Of clinically diagnosable adenomas, only 5% are thought to proceed to malignancy. Thus, for every sporadic colorectal cancer there may be between 400 and 5000 microadenomas. Inactivation of the second APC allele, whilst not a prerequisite for microadenomatous initiation, may be a key step in furthering neoplastic evolution. In a series of sporadic colorectal adenomas, APC mutations were found more frequently in adenomas that were large, showed high grade dysplasia and displayed a villous architecture (De Benedetti et al 1994). Thus, whereas inactivation of the second APC allele is a very early event in polyposis, this step appears to occur at a relatively late stage in sporadic adenomas.

HYPERPROLIFERATION

Does a stage of hyperproliferation precede neoplastic initiation? Hyperproliferation is included in the model of Fearon and Vogelstein (Fearon and Vogelstein 1990), but illustrations reveal a focal lesion composed of dysplastic tubules (Fearon and Jones 1992). Focal hyperproliferation may therefore be synonymous with microadenoma. Diffuse and minor expansion of the proliferative compartment within otherwise normal colorectal mucosa is also described as hyperproliferation. This is a non-specific response to a variety of luminal factors and its relevance to carcinogenesis remains controversial (Jass 1993).

K-RAS AND NEOPLASTIC PROGRESSION

The K-ras oncogene located on chromosome 12p codes for a 21 kD cell membrane bound protein with intrinsic GTPase activity and involved in signal transduction. Mutation of K-ras has been implicated as a relatively early event in the morphogenesis of colorectal adenoma (Vogelstein et al 1988). However, this observation applies primarily to sporadically occurring polypoid adenomas (McLellan et al 1993), less so to adenomas in FAP (Ando et al 1992) and rarely to flat adenomas (Minamoto et al 1994; Yamagata et al 1994). Eleven of 15 sporadically occurring microadenomas (aberrant crypt foci) had codon 12 mutations (Pretlow et al 1993). This does not prove that the K-ras mutation initiated development of the microadenoma, although it is conceivable that microadenomatous initiation could be brought about by K-ras as well as by APC mutations. Given the high frequency of sporadic adenomas, as described above, it would appear that the early acquisition of a K-ras mutation does not herald the onset of an especially aggressive neoplastic pathway. Recently, K-ras mutations have been linked specifically with the initiation of non-neoplastic aberrant crypt foci (Jen et al 1994; Minamoto et al 1994), emphasizing the relative unimportance of this oncogene at the stage of initiation of neoplasia. The low incidence of K-ras mutations in flat adenomas indicates the more aggressive nature of an alternative, but as yet undefined molecular pathway. Clearly this is an area necessitating further research that may lead to the discovery of additional, important cancer genes.

p53 GENE

Whereas K-ras and APC gene mutations show a relatively selective association with colorectal neoplasia, p53 is implicated in the evolution of a variety of tumors (Lane 1993). Inherited mutations of this gene are responsible for the Li-Fraumeni cancer family syndrome (Srivastava et al 1990). The protein product binds to complexes of G1 cyclin and Cdk2 protein. These normally drive the

proliferating cell beyond the G1 checkpoint of the cell cycle. By blocking the kinase activity of these complexes, p53 protein prevents the cell from entering into the phase of DNA synthesis and replicating its DNA. Normal p53 function is required only in occasional circumstances, for example when DNA is damaged by ultraviolet light. Under these circumstances the normal rapid degradation of the molecule is retarded and cells are prevented from entering the S phase of the cycle until the DNA is repaired. Mutations of the p53 gene are associated with the development of chromosomal instability and aneuploidy (Auer et al 1994). Inactivation of both alleles (the first by mutation and the second by allele loss), not only removes a mechanism for blocking proliferation but facilitates the development of additional oncogenic mutations.

Loss of the second p53 allele occurs at a late stage in the evolution of the adenoma and may even underlie the transition from adenoma to carcinoma (Purdie et al 1991). Affected cells not only appear to be relieved of their remaining growth inhibitions, but the effects of earlier mutations may be more fully expressed. Mutation or loss of p53 may occur at a relatively early stage in particular circumstances, for example in the evolution of dysplasia in ulcerative colitis (Brentnall et al 1994). It is also conceivable that early involvement of the p53 gene is linked to the development of the relatively aggressive flat adenoma.

BCL-2 GENE

This oncogene blocks programmed cell death or apoptosis, and its overexpression therefore exerts a survival advantage. Overexpression of BCL-2 appears to occur in adenomas (Hague et al 1994) and in more poorly differentiated carcinomas (Ayhan et al 1994). Conversely, LOH for BCL-2 is observed in well differentiated carcinomas (Ayhan et al 1994).

DNA MISMATCH REPAIR GENES

Hereditary non-polyposis colorectal cancer (HNPCC) is now known to be caused by a germline mutation in one of a family of at least four DNA mismatch repair genes (Bronner et al 1994; Fishel et al 1993; Leach et al 1993; Nicolaides et al 1994; Papadopoulos et al 1994). They are regarded as oncosuppressor genes, the second copy being inactivated either by mutation or loss (Hemminki et al 1994). The subsequent breakdown of the DNA repair mechanism leads to an accelerated pathway of neoplastic evolution in which gene inactivation is preferentially mediated by somatic mutation as opposed to allele loss (Leach et al 1993). Aneuploidy is rarely encountered in HNPCC neoplasms (Kouri et al 1990). It has been suggested that an adenoma needs to develop on a sporadic basis in HNPCC to provide a substrate for defective DNA mismatch repair (Leach et al 1993). Hypomethylation of DNA, documented to occur within adenomas (Goelz et al 1985), may be the key that unlocks the potential defect in DNA repair

proficiency (Leach et al 1993). This would explain why adenomas are not especially frequent in HNPCC and show an anatomic distribution identical to sporadic adenoma, but are more likely to be of large size with villous change (Jass et al 1994). This fits with a recently suggested specific role for HNPCC genes in tumor progression, namely the failure of TGF-β to down-regulate proliferation as a result of mutational inactivation of the type II TGF-β receptor. Type II TGF-β receptor mutations have been demonstrated in human colon cancer cell lines showing microsatellite instability (Markowitz et al 1995). DNA mismatch repair genes are implicated in about 15% of sporadic colorectal cancers (Aaltonen et al 1993), presumably through somatic mutational inactivation.

Table 3.1 Summary of ordering of genetic events in adenoma progression according to clinicopathologic context

Adenoma	APC inactiv-ation of first allele	APC inactiv-ation of second allele	K-ras mutation	p53 loss or inactiv-ation	Mode of onco-suppressor gene inactiv-ation	Aneu-ploidy
Sporadic	? Initiating mutation	Common – intermediate to late	Common – early	Late	Mutation or loss	Late
FAP	Germline	Common – early	Common – intermediate	Late	Mutation or loss	Late
HNPCC	? Initiating mutation	Common – intermediate to late	? Common – early	? at all	Mutation only	Rare
Flat	?	?	Rare	? early	? Mutation or loss	?

CONCLUSION

Neoplasia occurs through the stepwise breakdown of genetic control systems that govern cellular replication and differentiation. Gene function is modified either by mutation (change in DNA structure) or by loss of the gene through a mitotic error. A summary of the ordering of genetic events in adenoma progression according to the type of adenoma, that is, sporadic, FAP, HNPCC or flat is shown in Table 3.1. Many of the genes implicated in the process of neoplasia are now well characterized. Most have an ancient evolutionary heritage such as the

DNA mismatch repair genes responsible for the condition HNPCC. Homologues of these genes are found in yeasts and bacteria. The undoing of the work of millions of years of evolution may be completed in the relatively short time frame of one lifespan. This anti-evolutionary process is highly focal, beginning in a single cell. Why should one cell be compelled to accommodate a multiplicity of genetic alterations when most cells would not show evidence of any mutations? It is clear that the occurrence of one mutation must increase the probability that additional mutations will occur. This may be a property of the mutation itself. For example, p53 protein provides a cell with time to repair mutations; inactivation of the p53 gene will have the opposite effect.

A second mechanism is clonal expansion. This will increase the pool of target cells, thereby increasing the probability of additional "hits". In the colorectum, such clonal expansion, that is, the formation of an adenoma, is accompanied by the spatial reorganization of the proliferative compartment. In normal crypts, proliferative cells are sequestered within the crypt base. In adenomas proliferative cells are located superficially and are thereby exposed directly to mutagenic factors within the bowel lumen.

In FAP, several thousands of adenomas may have formed within the colorectum by the second decade. Each adenoma represents a clonal population containing at least two genetic alterations (a germline APC mutation and mutation or loss of the second APC gene). The scene would hence appear to be set for the development of multiple cancers. Yet, within the span of two or three further decades, only one or two of the many thousand of adenomas may have transformed into cancers. This observation indicates that the order in which genetic changes occur influences the probability of subsequent genetic change. Genes that exert a direct permissive effect in this respect, such as the p53 and the HNPCC genes, will greatly accelerate the rate of the subsequent mutational cascade. More "benign" genes such as APC take the neoplastic process as far as the adenoma, but not beyond.

The molecular genetic model of colorectal neoplasia formulated by Fearon and Vogelstein in 1990, though useful at the time, would now with such rapid expansion in knowledge, be regarded as rather misleading. This is particularly evident when it is appreciated that their class I adenomas were derived exclusively from subjects with FAP. New genetic models are needed that are able to accommodate several neoplastic pathways. These will range from the slow, "classic" pathway with a long adenomatous phase, through to rapid or "de novo" transformation implicating foci of intra-epithelial neoplasia that are small, flat and highly unstable.

* * * * *

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4

MORPHOLOGY OF COLORECTAL NEOPLASIA

The aspects of morphology which are relevant to the understanding of colorectal tumor etiology and prevention are discussed in this chapter. Up to the mid-1980s histopathologists were comfortable in the belief that most colorectal cancers commenced in an adenoma, that only a few adenomas became malignant, and that in a few instances a colorectal tumor develops "de novo". In the 1980s the recognition of aberrant crypt foci, microadenomas and flat adenomas together with associated molecular genetic changes, however, has necessitated a major re-examination of the morphologic pathways to colorectal cancer.

PRECURSOR AND ASSOCIATED LESIONS OF COLORECTAL CANCER

Hyperproliferative lesions, aberrant crypt foci, hyperplastic polyps and adenomas are all biomarkers of abnormal proliferative activity of the entire colorectal mucosa. The various precursor and associated lesions which differ morphologically from the normal colorectal mucosa are shown diagramatically in Figure 4.1.

ABERRANT CRYPT FOCI AND HYPERPROLIFERATION

Increased colorectal crypt cell proliferation, as well as a shift of the proliferative zone in the direction of the crypt apex, are increasingly regarded as the early indicators of future risk for the development of colorectal tumors (Friedman 1985; Lipkin 1988). Aberrant crypt foci (ACF) were first described in 1987, 1988 in chemically induced rodent models of colon tumors, when the mucosa

was stained with methylene blue and examined under low power (Bird 1987; McLellan and Bird 1988). These lesions were then also identified in macroscopically normal human colonic mucosa (Pretlow et al 1991; Roncucci et al 1991b). ACF are described as usually having larger than normal crypts, have larger cells elevated microscopically above the surface mucosa, and often show increased branching and proliferation (Figure 4.1), but can also show other features from almost normal to dysplasia with a variety of changes in mucin production and goblet cells, suggesting heterogeneity even at this early stage (McLellan et al 1991; Caderni et al 1995; Pretlow 1995). Hyperproliferative lesions of the colorectal mucosa described in the past, may well have been instances of ACF, or at least included ACF. K-ras mutations, present in many colorectal tumors, have also been frequently noted in human ACF (Pretlow et al 1993; Smith et al 1994; Yamashita et al 1995). Apart from K-ras mutations and APC mutations, some p53 mutations have also been noted in chemically induced ACF in experimental animals (Stopera and Bird 1993; Vivona et al 1993; Smith et al 1994). Carcinoembryonic antigen is also over-expressed in human ACF (Pretlow et al 1994). ACF are more common in those at an increased risk for large bowel cancer (Pretlow 1995). Recent studies have shown stimulation of ACF with secondary bile acids, suppression with primary bile acids, and suppression of ACF in rodent models of chemically induced colon cancer, with the use of dietary fiber, beta-carotene, and other retinoids, calcium, aspirin and other non-steroidal anti-inflammatories—all of these agents are known to also inhibit colorectal tumor formation in humans (Rao et al 1992; Sutherland and Bird 1994; Thorup et al 1994; Alabaster et al 1995; Wargovich et al 1995a, 1995b; Bird 1995). Crypt cell proliferation was reduced in a controlled study of individuals with a family history of colorectal cancer by the administration of wheat fiber (Rooney et al 1994). ACF are more common in the distal than proximal large bowel (Pretlow 1995a), in keeping with the concept that environmental factors have a greater influence on the distal large bowel, and that hereditary factors have a greater influence on the proximal large bowel (Chapter 5).

Although direct evidence is so far lacking for a transition from ACF to microadenoma, adenoma or carcinoma, it is difficult to escape the conclusion that ACF are likely to represent an early morphologic change in colorectal neoplasia. However, as noted later, only those ACF with microadenomas and APC mutations are likely to progress (Jen et al 1994). ACF appear to represent genetic changes in response of the colorectal mucosa to certain environmental agents such as dietary factors, alcohol and smoking, which in some individuals produce non-neoplastic hyperproliferative lesions such as hyperplastic polyps, and in others produce a colorectal tumor, depending on the nature of the mutations which occur. A better understanding of the morphologic and molecular heterogeneity of ACF will help to elucidate the early phases of colorectal neoplasia (Bird 1995b). ACF are likely early lesions in, or at least

early biomarkers of, colorectal neoplasia, and will be used increasingly in the future as biomarkers in both colorectal tumor etiology research, and in interventional studies for the primary prevention of colorectal tumors.

COLORECTAL MICROADENOMAS

These were first recognized in 1991 by Roncucci and co-workers when ACF were examined microscopically (Figure 4.1). At present the relationship between these microscopic adenomas and ACF is not known. It is possible that a minority of ACF, perhaps 5%, change to a microadenoma, or are microadenomas at the time of onset, and that some of these then grow to become endoscopically recognizable adenomas. The nature of the genetic change in ACF may be an important determinant of progression to neoplasia, in that K-ras mutations alone may promote progress to non-neoplastic hyperplastic foci, some of which perhaps develop into hyperplastic polyps, whilst those which also have APC mutations are more likely to develop into microadenomas, and some of these then progress to macroadenomas (Jen et al 1994). Microadenomas are likely to become an important link in the morphology of colorectal neoplasia. They may also explain the concept of "de novo" colorectal cancer, in which a microadenoma changes into an invasive tumor without becoming a visible "macroadenoma" first (Figure 4.1).

HYPERPLASTIC POLYPS

Hyperplastic polyps (earlier termed "metaplastic polyps") are common in the large bowel of Western populations, and have a frequency distribution similar to colorectal cancer, that is, they are most frequent in the left colon and rectum. These polyps endoscopically look similar to adenomatous polyps; however, they have a distinct histology and are uncommonly larger than 5 mm in diameter. The view that hyperplastic polyps of the colorectum bear no relationship to adenomas nor to colorectal cancer was strongly espoused by Morson and co-workers at St. Mark's Hospital (Muto et al 1975; Morson 1976). There is however evidence of an indirect relationship, probably due to overlapping etiology. The distribution of hyperplastic polyps and colorectal cancer is similar (Bech et al 1991; Isbister 1993); mixed hyperplastic polyps and adenomas as well as hyperplastic polyps and invasive cancer have been found together (Fenoglio-Preiser et al 1985; Teoh et al 1989). Furthermore, hyperplastic polyps in the distal large bowel have been found to be "markers" for colorectal adenomas in the proximal large bowel, although not as powerful markers as are adenomas in the distal large bowel (Provenzale et al 1988, 1990; Ansher et al 1989; Foutch et al 1991; Jergas et al 1993; Pennazio et al 1993; Nusko et al 1994; Van Stalk et al 1994).

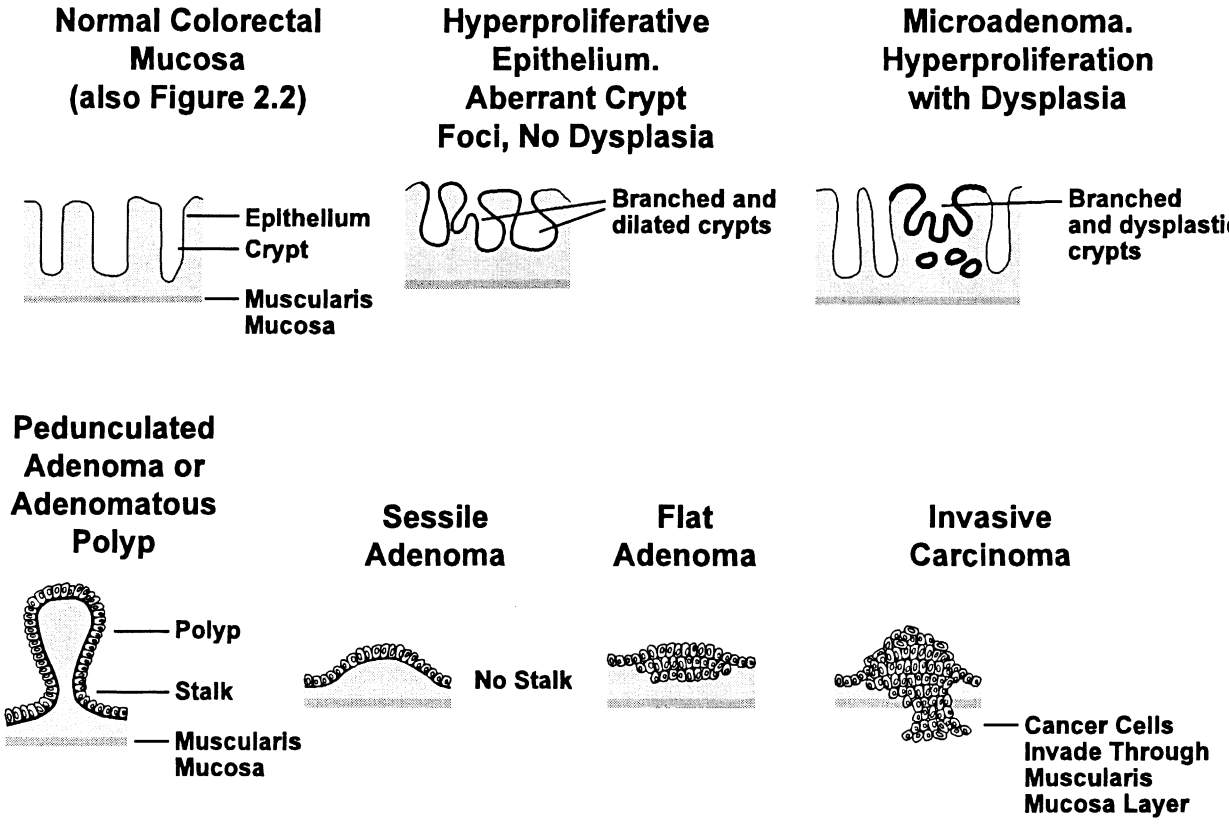

Figure 4.1 Diagrammatic representation of normal colorectal mucosa, several preneoplastic lesions including adenomas, and an early invasive colorectal cancer.

Cellular biochemical markers such as absence of IgA secretory activity and an increased expression of carcino-embryonic antigen has been found with hyperplastic polyps, dysplastic adenomas and carcinomas, but not in normal colorectal epithelial cells (Jass 1983). Hyperplastic colorectal polyps have been shown to express both gastric and colorectal differentiation antigens, suggesting that the term metaplasia may well apply to these lesions (Borchard and Donner 1994).

Clues regarding the causes of hyperplastic polyps would be most valuable, as intuitively one feels that these causal factors are likely to be similar to the environmental causes of colorectal adenomas, namely dietary habits, alcohol consumption and smoking. Hereditary factors seem unimportant in the cause of hyperplastic polyps and had a similar frequency in 2 studies, irrespective of a family history of colorectal tumors (Burt et al 1985; Cannon-Albright et al 1988). In a recent publication from the 2 well-conducted large US cohorts of the Nurses' Health Study and the Health Professionals' Follow-up Study, a statistically significant positive association was in fact found between alcohol consumption and smoking and hyperplastic polyps, as well as a statistically non-significant positive association for animal fat intake (Kearney et al 1995).

Thus at present, the evidence suggests that while there is no morphologic transition from hyperplastic polyps to colorectal tumors, the lifestyle causal associations of hyperplastic polyps, especially dietary factors, alcohol consumption and smoking, are similar to those for both colorectal adenomas and colorectal cancer, and therefore the presence of hyperplastic polyps is a potentially useful biomarker of colorectal tumors in individuals and in populations.

ADENOMAS

These are benign tumors of the large bowel, and in Western populations are the major precursors of colorectal cancer. The evolution of colorectal adenomas is discussed by Jass under the molecular evolution of colorectal tumors (Chapter 3). The natural history of adenomas is discussed in detail subsequently in this chapter, while the several putative causes of adenoma formation are dealt with in Chapters 5–10. The monoclonal origin of adenomas, that is, their commencement from one stem cell, is established (Fearon et al 1987). Current evidence makes it likely that adenomas commence in a subset of proliferative lesions such as ACF, becoming first a microadenoma and then a visible adenoma. As only a small proportion of adenomas become malignant, there must be an enormous number of hyperproliferative lesions, ACF, microadenomas and macroadenomas in the large bowel which are unaltered or regress during life (Figure 4.2).

Adenomas are classified according to their appearance as protuberant or polypoid, (sessile or pedunculated), or as flat adenomas (Figure 4.1).

Microscopically, adenomas are classified as tubular, villous or mixed tubulovillous. Most adenomas are tubular in structure.

Polypoid Adenomas

These are the common type of adenoma in Western populations (Figure 4.1). Their evolution appears to be associated with both p53 and ras mutations (Fujimori et al 1994; Yukawa et al 1994).

Flat Adenomas

Macroscopically flat adenomas (Figure 4.1) were first recognized in 1985 by Muto and co-workers and most of the data on this tumor have since emanated from Japan (Muto et al 1985; Adachi et al 1988; Minamoto et al 1994). Flat adenomas, as well as the flat adenoma-carcinoma sequence have been documented in chemically induced colon tumors in rats (Rubio and Shetye 1994). A flat "serrated" adenoma has also been described, and this can also develop into an invasive carcinoma, and has a proliferation pattern that is different from a flat tubular adenoma (Rubio and Rodensjö 1995).

In Western populations flat adenomas are much less frequent than polypoid adenomas, although their frequency is uncertain as they can be difficult to identify during colonoscopy (Matsumoto et al 1992). They are probably more common in the distal than in the proximal colon, suggesting environmental exposures to be important in their etiology. There is increasing evidence that flat adenomas are different in their biologic behavior to polypoid adenomas. Flat adenomas tend to occur at an earlier age than polypoid adenomas and are probably more aggressive, both histologically and clinically, regarding malignant potential (Muto et al 1985; Lanspa et al 1992; Teixeira et al 1994; Matsumoto et al 1994; Tada et al 1994). Furthermore, ras mutations are not expressed in flat adenomas (Fujimori et al 1994; Yukawa et al 1994). An epidemiologic overview of these biologic differences suggests that quantitative rather than qualitative differences of inherited and environmental exposures are responsible for the different frequency of flat compared to polypoid adenomas in Japan versus Western populations.

DYSPLASIA, CARCINOMA IN-SITU

Histologic changes intermediate between a normal colorectal mucosal cell and a cancer cell are termed "dysplasia", and these changes have been graded arbitrarily into mild, moderate and severe, or into low-grade and high-grade (Morson 1976; O'Brien et al 1990). The terms "severe dysplasia" or "high-grade dysplasia" are often preferred to the terms "carcinoma in-situ" or "intramucosal carcinoma" because these lesions probably lack the ability to invade and metastasize, since this ability very likely requires further genetic and possibly immunologic changes.

"DE-NOVO" CARCINOMA

The term "de novo" colorectal carcinoma has an obscure origin, is somewhat misleading, has led to unnecessary and circular arguments regarding its evolution, and refers to a colorectal cancer which is not polypoid and in which there is no evidence of a contiguous adenoma. Such small non-polypoid cancers have certainly been documented and their frequency and evolution have been debated (Shamsuddin et al 1985; Jass 1989; Kuramoto and Oohara 1989, 1995; Shimoda et al 1989; Bedenne et al 1992; Minamoto et al 1994). In Western populations, non-polypoid/non-adenoma related cancers probably account for one-third of the incident cases, whilst in Japan three-quarters of incident cases belong to this group (Bedenne et al 1992; Kuramoto and Oohara 1995). Some believe these cancers to originate from normal colorectal mucosal cells ("de novo"); however, others believe that these cancers evolve from flat adenomas. The flat adenoma-adenocarcinoma sequence has recently also been documented in chemically induced colon tumors in rats, and interestingly, about one-third of all neoplasms were of the flat variety, a proportion similar to so-called "de novo" cancers in Western populations (Rubio and Shetye 1994).

INVASIVE COLORECTAL CANCER

When cancer cells penetrate the mucosal layer (Figure 4.1), they are regarded as invasive cancers which are able to spread, metastasize and cause premature death. The ability to become invasive and then metastasize appears to involve further somatic mutations and possibly also other host-defense mechanisms, which at present are poorly understood.

NATURAL HISTORY OF COLORECTAL ADENOMAS

In different populations the prevalence of colorectal adenomas correlates reasonably well with the prevalence of colorectal carcinomas, so that colorectal adenomas are prevalent in developed countries. Their prevalence and their tendency to be multiple increases with age in both sexes. A wide range of prevalence rates has been arrived at in different studies. Prospective studies suggest that about one-third of the adult population over the age of 50 years in a Western culture bears one or more colorectal adenomas (Williams et al 1982; O'Brien et al 1990; Eide 1991; Peipins and Sandler 1994). There is a long time frame for the development of an adenoma and its progression to a carcinoma, which is quite variable, with a range of 5–30 years and a median period of about 10 years, from a clean colorectum to an invasive cancer (Kozuka et al 1975; Morson 1976; Hoff et al 1986; Stryker et al 1987; Winawer et al 1987).

ADENOMA–CARCINOMA SEQUENCE

The important issues in the consideration of the adenoma–carcinoma sequence are the morphologic aspects of this change, the evidence that adenomas are a precursor lesion for colorectal cancer, the risk factors which are predictors that an adenoma will develop into a carcinoma, together with estimates of the magnitude of the adenoma–carcinoma sequence.

Historical Aspects

The first scientific studies which described the adenoma–carcinoma sequence were published in 1926 by Schmieden of Frankfurt, followed up by Schmieden and Westhues in 1927. A generation later, English speaking pathologists and clinicians began to acknowledge and study this relationship, commencing with Jackman and Mayo in 1951 who coined the phrase "adenoma–carcinoma sequence" (Jackman and Mayo 1951; Grinnell and Lane 1958; Helwig 1960; Bockus et al 1961).

In the 1960s Morson and his colleagues at St. Mark's Hospital in London, as a result of intensive pathology research, put this adenoma–carcinoma sequence on a firm footing in the English-speaking world, (Morson 1966; Muto, Bussey and Morson 1975). This group was the first to produce a useful model for the adenoma–carcinoma sequence, incorporating genetic susceptibility and unspecified environmental agents as etiologic factors (Hill et al 1978). There were also several scientists such as Eide, Fenoglio-Preiser, Jass and others, who have made important contributions to the understanding of this adenoma–carcinoma change since that time. Japanese scientists, commencing with Muto in 1985, first recognized flat adenomas, thereby adding a new dimension to the adenoma–carcinoma change.

Evidence for Adenoma–Carcinoma Sequence

There is both circumstantial and direct evidence that a high proportion of colorectal adenomas are precursor lesions for colorectal carcinoma.

Circumstantial Evidence

Burkitt noted in a survey of world literature in 1975 that colorectal adenomas are common in the Western world and uncommon in developing countries, and that this corresponded to the incidence of colorectal cancer in these countries. Subsequently, several other studies confirmed this and a multicenter autopsy study of colorectal adenomas noted that the highest proportion of adenomas were observed in the population with the highest incidence of colorectal cancer, the lowest in the population with a very low incidence of colorectal cancer, and intermediate figures were present for areas with an intermediate incidence of colorectal cancer (Clark et al 1985). Although adenomas are reported as fairly evenly distributed, larger adenomas are more frequent in the distal large bowel,

in keeping with the etiologic evidence that lifestyle causes influence the distal large bowel relatively more than its proximal portion.

There is also a particularly high percentage of colorectal adenomas present synchronously with colorectal cancer. A study from the USA showed a rate of 36% synchronous polyps in the presence of colorectal carcinomas (Chu et al 1986). In the population-based Melbourne Colorectal Cancer Study, where the resection rate of colorectal cancer was about 90%, one or more colorectal adenomas were present in 21% of the resected specimens (Kune et al 1987b). A careful comparison of the prevalence of colorectal adenomas with and without a synchronous colorectal cancer has not been made so far. The prevalence of both adenoma and carcinoma increases with increasing age in both males and females. Further evidence for the adenoma–carcinoma sequence is that the accumulating incidence of adenomas precedes the incidence curve of colorectal cancer by about 5 years, as does the frequency distribution by age (Morson 1976; Eide 1991).

Epithelial dysplasia in colorectal adenomas has been shown to be of various grades from mild to severe (Morson 1976). In general carcinogenesis theory it is agreed that carcinomas arising from an epithelial surface pass through stages of mild to severe epithelial dysplasia before becoming an invasive cancer. These stages of increasing severity of epithelial dysplasia in colorectal adenomas have been well correlated to the level of risk for colorectal cancer, and this forms further strong circumstantial support for the concept of the adenoma–carcinoma change (O'Brien et al 1990; Atkin et al 1992). Several studies have shown that those with a past history of colorectal adenomas are at a significantly elevated risk for the later development of colorectal cancer (Kune et al 1987a; Stryker et al 1987; Atkin et al 1992). Crucial evidence for the adenoma–carcinoma sequence has been derived from recently reported large prospective randomized controlled screening and surveillance studies in which the incidence of colorectal cancer had been significantly reduced with the systematic excision of all colorectal adenomas discovered during screening (Mandel et al 1993; Winawer et al 1993; Kewenter et al 1994; Kronborg and Fenger 1994).

Direct Evidence

The frequent demonstration of small foci of invasive cancer in adenomas provides strong direct evidence that they are a precursor lesion (Grinnell and Lane 1958; Muto et al 1975; Shinya and Wolff 1979). Remnants of adenomas in colorectal cancer have been found in about 60% of carcinomas which have not spread further than the submucosal layer of the bowel, and in over 80% of small exophytic cancers smaller than 2 cm (Muto et al 1975; Eide 1983; Bedenne et al 1992). Follow-up of untreated adenomas has shown the development of cancer at the site of the adenoma some years later (Morson 1976; Stryker et al 1987). Contiguous adenoma–carcinoma change has been much less well documented in flat adenomas than in polypoid adenomas.

The evidence is therefore very strong that colorectal adenoma is an important precursor of colorectal cancer.

Risk of Adenoma–Carcinoma Change

Proportion of Adenomas Becoming Carcinomatous

It has been estimated that about 5% of colorectal adenomas undergo the adenoma–carcinoma sequence (Morson 1976; Jass 1989). The careful work of Morson and colleagues from St. Mark's Hospital in London established several morphologic criteria of the probability for the adenoma–carcinoma change, namely an increasing size of the adenoma, increasing villous component, and an increasing degree of dysplasia and multiplicity (Muto et al 1975; Morson 1976). Eide in 1986 made an important contribution in establishing conversion rates of adenoma–carcinoma in a defined population, based on size and histologic characteristics, and he estimated the annual conversion rate to be 1 in 400 (0.25%), but this overall rate was 3% for large adenomas, 17% for villous adenomas and 37% for severely dysplastic adenomas (Eide 1986). A recent study by flow cytometry of DNA contents suggests that DNA aneuploidy may be an additional indicator of malignant transformation of colorectal adenomas (Suzuki et al 1995).

It has however been pointed out that small adenomas can also be pre-malignant, and that a significant number of the flat tubular adenomas, first described by Muto and co-workers in 1985, will show high grades of epithelial dysplasia (Muto et al 1985; Jass 1989; Matsumoto et al 1994; Teixeira et al 1994).

Adenoma Regression

Of interest is that not all colorectal adenomas increase in size over time and not all become more dysplastic, as some regress and can disappear completely (Knoernschild 1963; Hoff et al 1986a; Eide 1991). Mechanical factors may lead to adenoma disappearance in some cases, caused by torsion of the pedicle and sloughing, as witnessed by disappearance being more common in pedunculated than in sessile adenomas, and more common in the distal large bowel and rectum where there is a higher mechanical force of the fecal bulk (Eide 1991). Whether regression of adenomas is also in part a response to environmental changes such as dietary changes, cessation of smoking or changes in alcohol consumption, would form an important research project. As noted in Chapter 18 dealing with primary prevention, up to the present the Australian Polyp Prevention Project is the only interventional study which has shown that dietary intervention reduces large adenoma development (Macrae et al 1995).

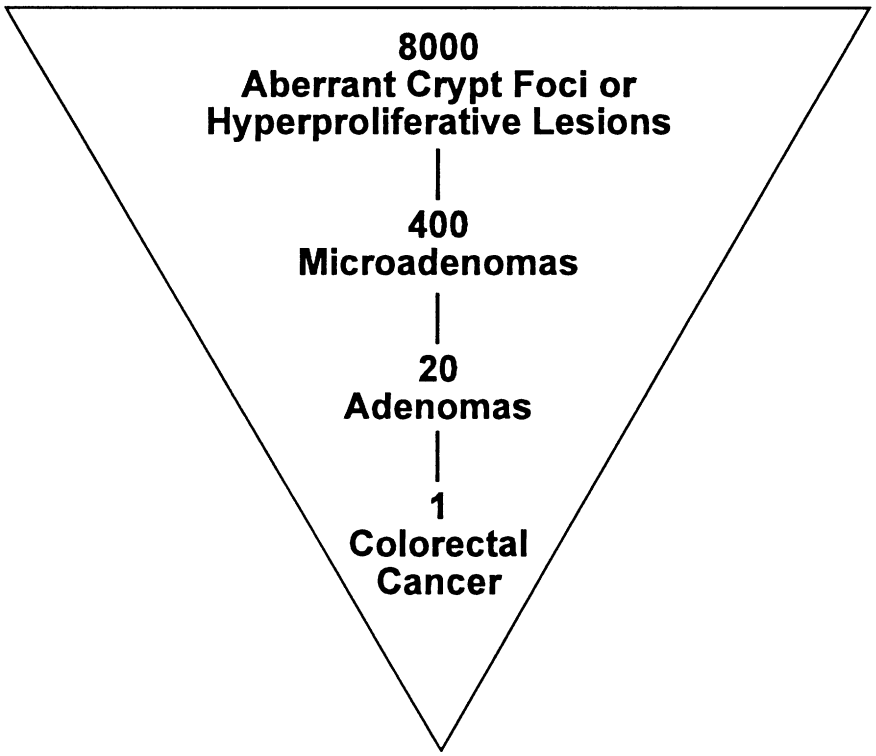

Figure 4.2 The likely frequency of precursor lesions which result in just one colorectal cancer.

MORPHOLOGIC PATHWAYS TO COLORECTAL CANCER

It is now evident that there are several morphologic pathways from a normal colorectal mucosal cell to an invasive colorectal cancer (Figure 4.3). It is also clear that one invasive colorectal cancer represents the apex of a very broad inverted "pyramid" of precursor lesions, say, that for any one invasive cancer there may be 20 adenomas, 400 microadenomas and 8000 aberrant crypt foci or hyperproliferative lesions (Figure 4.2).

Cells in crypts which are histologically hyperproliferative and phenotypically and genetically different from normal crypt cells, and when in groups are called aberrant crypt foci (ACF), will probably be shown to be present in large numbers in adults, in response to various environmental exposures that are causing mutations. ACFs will probably also be regarded in the future as the earliest preneoplastic lesion. A subset of ACF or other similar hyperproliferative lesions, will probably be shown to progress to microadenoma formation, as a

consequence of further environmental exposures and further mutations (Figure 4.3). Some ACF, probably a small number in Western populations, may develop increasing degrees of dysplasia without undergoing adenoma formation, and develop into an invasive colorectal cancer directly from severely dysplastic epithelium (Figure 4.3).

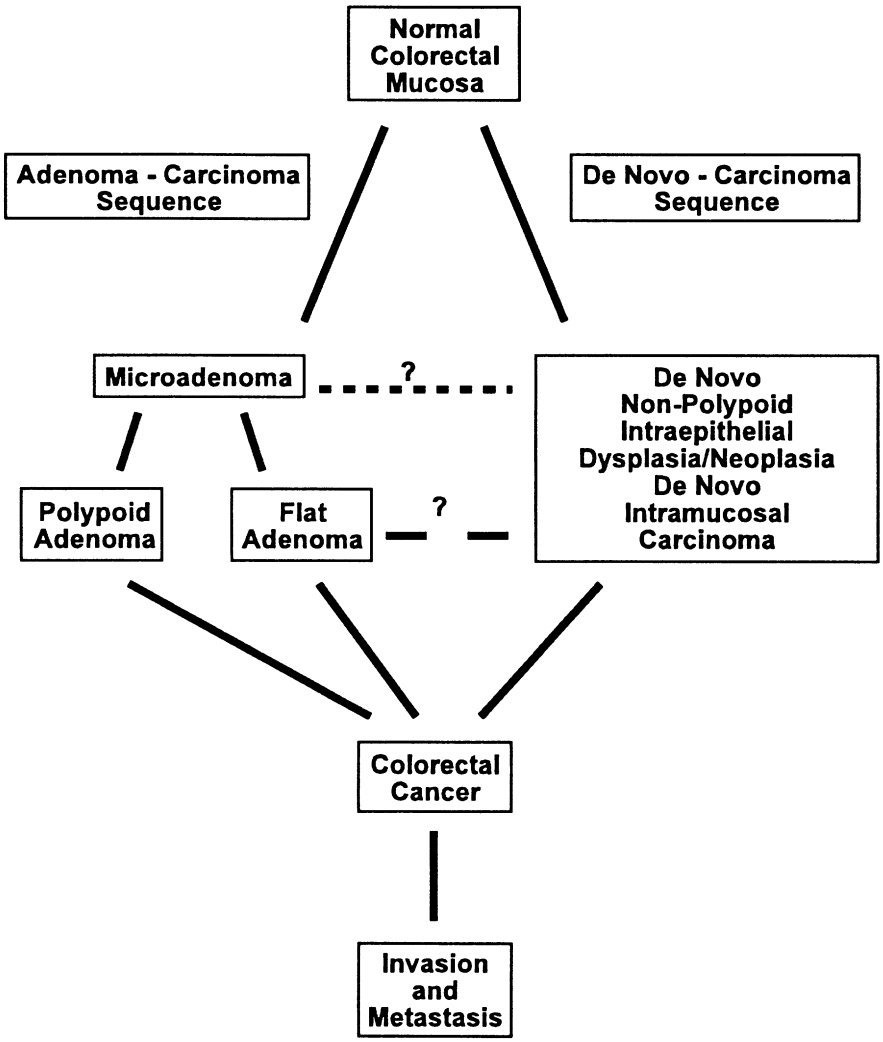

Figure 4.3 The several putative morphologic pathways from normal colorectal epithelium to an invasive colorectal cancer.

Microadenomas, probably in response to further environmental stimuli, result in genetic changes and enlarge to form macroscopically and endoscopically detectable adenomas. Most adenomas in Western populations are polypoid and only a small number are flat, whereas in certain populations such as Japan, a significant proportion are flat adenomas. Quantitatively different inherited and environmental exposures in different populations are likely to be the explanation for this difference in the frequency of polypoid versus flat adenomas. Different genetic pathways are the likely determinants of whether a flat or a polypoid adenoma develops.

In Western populations about 5% of adenomas become malignant, and about two-thirds of incident colorectal cancers arise in a pre-existing adenoma. In these populations, perhaps one-third of all colorectal cancers do not arise in a pre-existing macroscopic adenoma, and in these it is suggested that they arise either by increasing dysplastic change in ACF or from a microadenoma (or a small flat adenoma), which is completely destroyed at an early stage by the invasive cancer (Figure 4.3). In Japan, the only non-Western country where the morphology of colorectal tumors has been extensively studied, the proportion of colorectal cancers arising either from flat adenomas or directly from ACF through dysplastic change is apparently high, when compared to Western populations.

Further genetic and possibly other host-defense changes are necessary to transform a focus of severely dysplastic cells into an invasive colorectal cancer, which is then able to grow and metastasize (Figure 4.3).

* * * * *

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5

HEREDITY

A geneticist with a sense of humour was once asked whether insanity is inherited, and she replied, "Yes, you get it from your children!"

The inherited aspects of ordinary (sporadic) colorectal adenomas and ordinary (sporadic) colorectal cancer, familial adenomatous polyposis syndromes (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), will be discussed in this chapter. About 95% of all colorectal cancers are in the category of "ordinary" colorectal cancers, and FAP and HNPCC form about 5%. Those with a family history of colorectal cancer are known to be at a higher risk of developing this cancer than those who do not have a family history, and this has been assumed to be the main evidence for an inherited susceptibility to colorectal cancer.

FAP is a rare, inherited, autosomal dominant condition, very different in its behavior from ordinary colorectal cancer. FAP has been well reviewed in recent publications (Jass 1993). HNPCC is also inherited as an autosomal dominant condition. HNPCC is probably more common than familial adenomatous polyposis. It is currently being characterized both clinically and by molecular genetics, and it will be described in more detail, so that its epidemiologic and genetic aspects can be distinguished from ordinary colorectal cancer.

Current research indicates that this hereditary predisposition to colorectal adenomas and cancer can appear in one of two main ways, namely as inherited mutations which result in an abnormal control of colorectal mucosal cell proliferation, or as an inherited abnormality of enzyme action affecting the production or neutralization of compounds which cause neoplasia (Fettman et al 1991).

production or neutralization of compounds which cause neoplasia (Fettman et al 1991).

MOLECULAR GENETICS OF COLORECTAL CANCER

The original concept of Knudson of two steps in the development of a particular cancer will need to be considerably modified to a multistep and multipathway genetic phenomenon involving tumor suppressor genes, oncogenes, DNA mismatch repair genes, as well as other genetic events of gene expression; some of these are largely inherited as germline mutations, and some are largely or entirely acquired as somatic mutations (Knudson et al 1976; Knudson 1985; Scott and Müller 1993). Both the accumulation of genetic changes and the order of these changes are important in the development and progression of colorectal neoplasia.

An important breakthrough in the investigation of the molecular genetic events in colorectal cancer was first made by geneticists investigating a man with Gardner's Syndrome and in whom a constitutional deletion on the long arm of chromosome 5q was found (Herrera et al 1986). Close on the heels of the publication of this finding was an explosion of molecular genetic studies describing the occurrence of several genetic events in colorectal neoplasia, both inherited and acquired, so that within less than a decade the genetic events occurring in the transformation of a normal colorectal cell to a carcinoma could be charted with some confidence (Scott and Müller 1993). The germline molecular genetic changes in FAP and HNPCC have been well studied, particularly in FAP. In ordinary colorectal tumors the genetic changes indicate that there may be several pathways, that some of the genetic changes are similar to those seen in FAP and HNPCC; however, to what extent these changes are due to germline mutations and to what extent they are acquired somatic changes, is not known at present. Most genetic changes in ordinary colorectal tumors are regarded as acquired during life in response to various environmental exposures such as diet, alcohol and smoking, and a small fraction, perhaps 10–15%, are inherited as germline mutations.

In this section, a description only will be given of the genetic changes. For an analysis of the molecular evolution of colorectal cancer, which integrates the various genetic changes with their morphologic equivalents, and which takes a comprehensive view of the genetics of colorectal neoplasia, the reader is referred to Chapter 3 written by Jass.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

FAP is an autosomal dominantly inherited disease, which was first described in detail by Bussey in 1975. There is a 50% chance of inheriting the gene and after this, the gene penetration is very high, so that almost 100% of those with the

gene develop hundreds to thousands of colorectal adenomas by the age of 40 years; these then progress to one or more colorectal cancers, usually at a relatively young age for this cancer (Bisgaard et al 1994). FAP is responsible for less than 1% of all colorectal cancers and it has a prevalence of about 1 in 10,000 (Bulow 1987; Bishop and Thomas 1990; Bisgaard et al 1994).

The gene responsible for FAP was shown to be present on chromosome 5 (Bodmer et al 1987; Leppert et al 1987). This gene was later identified and cloned, and is now referred to as the APC or Adenomatous Polyposis Coli gene (Groden et al 1991; Kinzler et al 1991a, 1991b; Nishisho et al 1991). The germline mutation of the APC gene is sufficient for the development of multiple adenomas of the colon. The APC gene appears to operate early in the process of colorectal neoplasia. The accurate presymptomatic diagnosis of FAP using linkage studies close to the APC gene and mutational assays is now a practical possibility (Powell et al 1993; Park et al 1994; van der Luijt et al 1994; Walpole et al 1995).

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

HNPCC is also an autosomal dominantly inherited condition with a high degree of gene penetrance. Recently, a family of 4 DNA mismatch repair genes have been identified, which appear to be responsible for the development of HNPCC (Papadopoulos et al 1994; Aaltonen et al 1994a; Nikolaides et al 1994). Genetic testing using mutational analysis has been started in some centers with encouraging early results (van-de-Water et al 1994; Kohonen-Corish et al 1995). Although most large families with HNPCC will have mutations in hMSH2 or hMLH1 (Froggatt et al 1995), each HNPCC family is likely to have its own mutation pattern, which makes the task of genetic testing much more complex and therefore more costly than that for FAP. The role of DNA mismatch repair genes in HNPCC is discussed in more detail by Jass in Chapter 3.

ORDINARY COLORECTAL CANCER

The inherited aspects of ordinary colorectal cancer are much less well defined than is the case for FAP and HNPCC. In ordinary colorectal cancer, the APC gene, the DNA mismatch repair genes, as well as phenotypes associated with methylation and acetylation are seen, but to what extent they are inherited as germline mutations is not known.

Mandibular Osteomas

Mandibular osteomas found in FAP were also noted in ordinary colorectal cancers. The possibility that these may be simple markers of an inherited suceptibility deserves further study (Sondergaard et al 1993).

histocompatibility antigens (Terasaki et al 1977; Kune and Serjeantson 1984). Thus the chromosomes carrying the HLA histocompatibility antigens are unlikely to be concerned with the inherited tendency to colorectal neoplasia. However, presumably what is a somatic selective loss of the HLA-A,B,C locus products has been reported in colorectal adenocarcinoma (Smith et al 1988).

Changes on Chromosome 5

Adenomas examined in those without a familial predisposition to colorectal cancer have shown allele loss on chromosome 5q in one-third to over half of all cases (Vogelstein et al 1988; Ashton-Rickart 1989). Also, Solomon and co-workers in 1987 found that 20% of 45 colorectal cancers examined had allelic loss on chromosome 5. To what extent these changes are inherited and to what extent they represent somatic changes acquired during life is at present unknown, since the evidence for germline mutation is known to occur only in the context of FAP. On present evidence, chromosome 5 changes in ordinary colorectal tumors are regarded as somatic changes.

DNA Mismatch Repair Genes

These mutations are now regarded as associated with and an essential component of HNPCC. It is of interest that the effects of these genes were first noted in instances of ordinary colorectal cancer (Ionov et al 1993; Thibodeau et al 1993; Aaltonen et al 1993). In a recent study, only 3% of 33 ordinary colorectal adenomas had this replication error noted (Aaltonen et al 1994a). Replication error in ordinary colorectal cancer in a collected series was 12%, while this figure was 86% in HNPCC (Aaltonen et al 1994a). It is not known to what extent those with ordinary colorectal cancer have germline mutations and to what extent they are acquired somatic mutations (Kim et al 1994).

Inherited Fast Acetylator Activity

A group of compounds which have been shown to have the ability to damage DNA are arylamines, and these are formed in significant quantities in cooked meat and other cooked protein (Weisburger and Jones 1990; Minchin et al 1993; Bailey and Williams 1993). It was noted in relation to diet that the frequent consumption of heavily grilled or browned meat, especially red meat, is a risk for colorectal cancer. This process involves acetylation, and its rate appears to be under genetic control (Large et al 1986; Ilett et al 1987; Fettman et al 1991; Turesky et al 1991; Minchin et al 1993; Lang et al 1994; Bell et al 1995). Fast acetylators appear to be at higher risk for colorectal cancer compared to slow acetylators and slow oxidizers (Kadlubar et al 1992; Minchin et al 1993; Lang et al 1994; Bell et al 1995). Inherited fast acetylator status and the carcinogenic potential of grilled and fried meat provides an interesting and potentially important link between genetic and dietary etiologic factors (Lang et al 1994).

Acetylator status may have racial differences, as it does not appear to be important in the Japanese population (Shibuta et al 1994).

Hypomethylation

Hypomethylation has been shown to be an early event in colorectal neoplasia, probably occurring during the stage of hyperplasia to early adenoma formation, and this appears to be under genetic control (Feinberg and Vogelstein 1983). Hypomethylation was however also noted in a lung metastasis from a colon cancer (Feinberg and Vogelstein 1983). It is unknown at present whether the genetic expression of hypomethylation is inherited or an acquired somatic change, in relationship to both dietary folate deficiency and alcohol consumption (Potter et al 1993; Giovannucci et al 1995). Folate-deficient diets lead to DNA hypomethylation, and hypomethylation appears to be associated with overexpression of oncogenes and inactivation of tumor suppressor genes (Wainfen et al 1989; Feinberg et al 1988; Goelz et al 1985; Cravo et al 1992).

Mutated in Colorectal Cancer Gene (MCC)

In addition to the APC gene, the chromosome 5q region also contains a somatic mutation called "mutated in colorectal cancer" gene, or MCC, and as this gene is lost in colorectal cancer cases, it is thought to be a tumor suppressor gene (Kinzler et al 1991). It seems that this genetic change is an early event in colorectal neoplasia during adenoma formation. However, how this gene operates is at present not known, though recent evidence indicates that it probably does not operate as an independent tumor suppressor (Curtis et al 1994).

K-ras Gene Mutation

Mutations of the K-ras oncogene found on chromosome 12 have been noted in only a small proportion of adenomas which are smaller than 1 cm, but in about 90% of adenomas greater than 1 cm and in about half of the ordinary type of colorectal cancer (Bos et al 1987; Forrester et al 1987; Vogelstein et al 1988). This is regarded as a somatic change.

Deleted in Colorectal Cancer Gene (DCC)

It appears that the APC mutation and the K-ras gene mutation are insufficient to initiate the change from early colorectal adenomas to highly dysplastic adenomas and then to carcinoma, and that other mutations are also required. This appears to primarily involve the "deleted in colorectal cancer" gene or DCC found on chromosome 18, and the p53 gene found on chromosome 17, to be described in more detail below (Vogelstein et al 1989; Fearon et al 1990; Müller and Scott 1992).

p53 Mutation

Genetic changes in the tumor suppressor p53 gene are the most commonly noted mutations in human cancers and also in numerous premalignant lesions, including colorectal tumors (Harris and Hollstein 1993; Lazarus et al 1995). This gene apparently inhibits cell division by the production of a blocking protein (Marx 1993). The current evidence indicates that the allelic loss of DCC on chromosome 18 precedes the allelic loss of p53 on chromosome 17 (Baker et al 1990; Goyette et al 1992). p53 mutations are regarded as somatic changes in response to environmental factors, and recent data have linked p53 mutations to smoking (Kaur et al 1994; Brennan et al 1995; Lazarus et al 1995). This finding is most significant given that p53 mutations are also present in many tumors and premalignant lesions, and given that smoking is almost a universal carcinogen in humans. As smoking appears to have an effect early in the process of colorectal neoplasia (Chapter 8), p53 gene mutations are probably an early event, whatever the morphologic pathway, a conclusion also reached by a recent study from Japan (Hasegawa et al 1995). In a small study of 42 patients with Dukes C colorectal cancer, a statistically significant overexpression of p53 was noted in those with a family history of colorectal cancer in two or more first-degree relatives, and those with an increased body weight; however, no association was noted with smoking, alcohol, physical activity and parity (Zhang et al 1995). Most of the evidence suggests that the second allele of p53 on chromosome 17p is lost late in the process of colorectal neoplasia, and is associated with advanced colorectal cancers, including those with lymph node metastases and hepatic metatases (Vogelstein et al 1988; Baker et al 1990; Goh et al 1994; Kastrinakis et al 1995; Longo et al 1995).

Glutathione S-transferase Genotype (GST)

Glutathione S-transferases are a family of enzymes which protect the large bowel mucosa by conjugating dietary carcinogens with glutathione, and these enzymes are under genetic control. One member of this family, at the GSTM1 locus, is nulled in about half of caucasians, and those with the GSTM1 null phentotype are susceptible to smoking-related lung cancer and also to colorectal cancer, particularly of the proximal colon (Seidegård et al 1990; Zhong et al 1993). Moreover, the GSTT1 null genotype has been associated with an earlier age of onset of colorectal cancer (Chenovix-Trench et al 1995).

Chromosome 17q Allele Loss

Chromosome 17 harbors tumor suppressor genes other than p53. Loss of heterozygosity on chromosome 17q was recently reported in association with invasive and metastatic colorectal cancer, and particularly Dukes C stage, that is, cancers with lymph node metastases (Purdie et al 1995).

invasive and metastatic colorectal cancer, and particularly Dukes C stage, that is, cancers with lymph node metastases (Purdie et al 1995).

BCL-2 Proto Oncogene and Apoptosis

This oncogene apparently encodes a protein which prevents programmed cell death (apoptosis) present in normal basal crypt cells, but not in more differentiated cells migrating up the crypts, and is present in high levels in colorectal cancer cells including in Dukes C cancers, suggesting its importance in progression and metastasis (Sinicrope et al 1994). This is regarded as a somatic change. However, a recent report indicates that this oncoprotein is expressed in adenomas, carcinomas as well as metastases, suggesting that BCL-2 deregulation may also be a relatively early event in carcinogenesis (Hague et al 1994).

Whilst molecular biology research has focussed mainly on the genetic changes which affect cell proliferation, more recently attention has also been paid to a process called apoptosis, which is under genetic control and which regulates autonomous cell death. Colorectal carcinogenesis from a normal cell to a colorectal cancer has been found to be associated with a progressive inhibition of apoptosis, an effect that is likely to be related not only to neoplastic progression, but also to tumor growth (Bedi et al 1995).

Stromelysin-3 and BM-40 SPARC Genes

A recent study from France suggests that colorectal cancer invasion and metastasis is associated with the overexpression of two genes, stromelysin-3 and BM-40 SPARC, which influence collagen matrix degradation (Porte et al 1995).

EPIDEMIOLOGIC EVIDENCE OF INHERITED SUSCEPTIBILITY

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC)

This was first described by Dr. Aldred Warthin, pathologist of the University of Michigan at Ann Arbor in 1913, in a family now known as "Family G", members of which have been studied now for almost a century. Two extended families were later studied, called "The Cancer Family Syndrome" by Lynch and co-workers in 1966. The untiring efforts of Dr. Henry Lynch, his family, and their co-workers spearheaded the characterization of what is now called "Hereditary Non-polyposis Colorectal Cancer", or HNPCC, most recently reviewed by Lynch and co-workers in 1993, and by Mecklin and co-workers in 1994. The Lynch family and their collaborators have also named two syndromes, the "Lynch Syndrome I" when the cancer in a family is limited to the large bowel, and "Lynch Syndrome II" with the cancer occurring in a family in the

as HNPCC and noting that it includes a tendency also for extracolorectal benign and malignant tumors (Mecklin and Järvinen 1991; Jass 1993).

To facilitate international comparisons, an International Collaborative Group has established certain criteria for the recognition of HNPCC (Vasen et al 1991a, 1991b). These criteria are that three or more relatives with histologically confirmed colorectal cancer are present and one of those is a first-degree relative of the other two, that colorectal cancer involves at least two successive generations, and that at least one of the cases is diagnosed before the age of 50 years. To these criteria one may add the occasional presence of extracolorectal tumors and more recently also, the presence of DNA mismatch repair gene mutations. It has been argued that in the absence of genetic testing the above criteria are too strict, especially for the purposes of screening for HNPCC (Jass et al 1992; Percesepe et al 1994).

Some further characteristics of HNPCC are its tendency for the tumors to be multiple, both synchronous and metachronous, to be more often situated in the right colon than expected, and for about one-fifth of the cancers to show abundant mucus secretion (Bufill 1990; Jass 1993). HNPCC differs from FAP in that it does not have hundreds of adenomas. However, the adenomas which are present often occur at a young age, are large, often have a villous component and high grades of dysplasia, suggesting an aggressive and unstable natural history of these adenomas towards cancer formation (Jass and Stewart 1992; Jass et al 1992). However, the cancers which do develop seem relatively non-aggressive in terms of spread and metastasis, with only one-third found in Dukes C stage (Jass et al 1994). Although these pathologic characteristics of HNPCC cases such as abundant mucus, synchronous and metachronous tumors, and right-sided preponderance, may not be greatly different from frequencies observed in population-based studies, the presence of these additional features would increase the clinical suspicion of HNPCC in a particular family.

There have been several epidemiological studies examining the frequency of HNPCC among populations of colorectal cancer cases when studied by various means and using various criteria for diagnosis. These studies show a frequency of HNPCC in the range of 3% to 6% (Mecklin 1987; Mecklin et al 1987; Ponz de Leon et al 1989, 1993; Lynch et al 1990; Kee and Collins 1991; Westlake et al 1991; Stephenson et al 1991; Centonze et al 1993). The study of Ponz de Leon and co-workers in 1989 was a population-based study with a frequency of 3.9%, and at a re-evaluation in 1993 of 3.4%, with two other studies, namely Mecklin and co-workers in 1987 a frequency of 3.8%, and Stephenson and colleagues in 1991 with a frequency of 4%, so that the likely frequency from these studies, keeping in mind under-reporting and over-reporting errors, is 4% of the total of colorectal cancer cases. If less strict criteria of inclusion are taken, such as the highly predictive "vertical transmission", plus one other predictive criterion, and in particular early onset and proximal colon tumors, a rate of almost 9% was noted in a recent study (Percesepe et al 1994).

colorectal cancer cases. If less strict criteria of inclusion are taken, such as the highly predictive "vertical transmission", plus one other predictive criterion, and in particular early onset and proximal colon tumors, a rate of almost 9% was noted in a recent study (Percesepe et al 1994).

In contrast to these reports, several studies show much lower frequencies for HNPCC. Three recent series, one from Switzerland and two from Southern Italy reported a rate of 1.3%, 1.7% and 0.8% respectively of HNPCC (Meier et al 1994; Riegler et al 1994, 1995). A re-examination of the data from the large population-based Melbourne Colorectal Cancer Study of 702 colorectal cancer cases and 710 age-sex matched population-based controls in whom careful enquiries were made regarding a history of colorectal cancer in both first degree and second degree relatives, showed that there were only 3 of 702 (0.4%) cases and none (0%) of 710 controls who had three or more relatives with colorectal cancer (Kune et al 1988). Similarly, in another Melbourne study reported by St. John and co-workers 1993, which also carefully examined colorectal cancer in relatives of a large number of colorectal patients and controls operated on by one surgeon, Sir Edward Hughes, a re-examination of the data showed that only 4 of 525 cases (0.8%) cases and none (0%) of 523 controls had three or more relatives with colorectal cancer (St. John et al 1993; St. John, personal communication 1995). Finally, 2 recently reported population-based studies from Finland estimate the frequency of HNPCC to be 0.5–0.9% in one, and 0.7–2.5% in the other (Aaltonen et al 1994b; Mecklin et al 1995). These data add considerable weight to the contention that the HNPCC burden is unlikely to be more than 4%, even permitting for a possible geographic variation in incidence. When genetic markers for HNPCC become generally available, genetic testing will elucidate the frequency of HNPCC in a community. In some centers, genetic testing using mutational analysis has already commenced, with encouraging early results (van-de-Water et al 1994).

ORDINARY OR SPORADIC COLORECTAL ADENOMAS

A strong body of epidemiologic evidence has emerged in the past decade indicating an important etiologic role for hereditary factors in ordinary colorectal adenomas. Three types of studies have investigated the inherited aspects of ordinary colorectal adenomas, namely retrospective case-control studies, prospective uncontrolled endoscopic studies, and prospective controlled endoscopic studies.

Case Control Studies

Indirect evidence of an inherited susceptibility to the development of colorectal adenomas is provided by retrospective case-control studies in which a family history of colorectal cancer was obtained from cases with histologically documented colorectal adenomas and from matched controls without adenomas

elevations were found for large adenomas, but not for small adenomas (Boutron et al 1995). The risk levels in the positive studies were of a similar order to those found in the prospective controlled studies about to be described.

Prospective Uncontrolled Endoscopic Studies

Since 1984 several uncontrolled endoscopic studies evaluated the prevalence of colorectal adenomas in asymptomatic individuals in whom a family member has had colorectal cancer (Gillin et al 1984; Gryska and Cohen 1987; Guillem et al 1988; Fisher and Armstrong 1989; McConnell et al 1990; Orrom et al 1990; Baker et al 1990; Stevenson and Hernandez 1991; Stephenson et al 1993; Bashir et al 1995). In these studies, which were performed using colonoscopy, adenoma rates were obtained between 12% and 59%, and in several, though not in all, this would be higher than expected in the general population. However in the absence of controls, no firm conclusions can be drawn from these studies. In one interesting study, both the adenoma rates and the proliferative activity of the colonic mucosa was increased with the increasing strength of the family history, and this is a reasonably good indicator of a family history being a marker of inherited susceptibility for adenomas (Gerdes et al 1993).

Prospective Controlled Endoscopic Studies

Study of a Large Utah Family

In 1985 Burt and co-workers reported a unique study in which members of a large Utah pedigree with multiple cases of colorectal cancer, probably not of the hereditary type, were examined with a 60 cm fiberoptic flexible sigmoidoscope, using spouse controls. Rectosigmoid adenomas were found in 41 of 191 family members but only in 12 of 132 spouse controls (RR = 2.4, 95% CI = 1.30–4.35, p = 0.003). In this study, hyperplastic polyps were found with a similar frequency in family members as in spouse controls. No data were available regarding dietary habits, alcohol consumption and smoking. This interesting and unique study is not generalizable, since the data pertain to one kindred only and since no data are available for other known risk factors in colorectal adenoma, such as diet, alcohol consumption and smoking. However, this prospective study adds weight to the contention that colorectal adenomas have an inherited aspect to their etiology.

Other Prospective Cohort Studies of Relatives

A further study by the Utah Group used a similar design to the Burt et al 1985 study, examining 670 persons in 34 kindreds in whose family there was a history of a non-inherited type of colorectal adenoma or colorectal cancer, also using spouse controls (Cannon-Albright et al 1988). In this study, the endoscopist did not know the status of the person being examined, that is, whether they were a case or a control. Unfortunately data were not available on other risk factors such

of a non-inherited type of colorectal adenoma or colorectal cancer, also using spouse controls (Cannon-Albright et al 1988). In this study, the endoscopist did not know the status of the person being examined, that is, whether they were a case or a control. Unfortunately data were not available on other risk factors such as dietary habit, alcohol consumption and smoking. Although the relative risk between cases and controls was only 1.58 ($p = 0.02$), these risk levels being of a similar magnitude to the previously described case-control studies and the other controlled studies about to be described, the group concluded that inherited susceptibility to colorectal adenomas is very common.

Several other prospective controlled studies in which patients were endoscoped and information was also available on family history of colorectal tumors in first degree relatives, has been published (Rozen et al 1987; Ponz de Leon et al 1987; Guillem et al 1992; Winawer et al 1993; Zauber et al 1994; Bazzoli et al 1995b). With one exception, a statistically significant elevation of risk, of the order of two to threefold was found in the relatives of those with a colorectal tumor. The study of Winawer and co-workers in 1993 also showed an elevated risk of 2.7, which however was not statistically significant, probably because of the relatively small study numbers.

ORDINARY OR SPORADIC COLORECTAL CANCER

In the past 15 years an increasing body of epidemiologic evidence consistently points to an important etiologic role for heredity in ordinary colorectal cancer. Most epidemiologic studies have relied on the respondent's report of the presence of a family history of colorectal cancer. Whilst this is not a problem in cohort studies, in case-control studies there was always the question of a positive "recall bias" differential among the respondents who had colorectal cancer. A recently reported careful examination of the accuracy of self-reported family history of colorectal cancer, had a sensitivity (true positives) of 87% among cases, and 82% among controls, and a specificity (true negatives) of 97% for both cases and controls, suggesting that recall bias is more a theoretical than a real reason in explaining case-control differences of family history of colorectal cancer (Aitken et al 1995).

Population Rates

In the large population-based Melbourne Colorectal Cancer Study in which a careful family history of colorectal cancer was obtained, the family history rate of colorectal cancer in first degree relatives was 10% among the population-based controls, and exactly this rate was obtained in the 2 large US cohorts, the Nurses' Health Study and the Health Professionals' Follow-up Study (Kune et al 1989; Fuchs et al 1994).

Armstrong 1989; Kato et al 1990; St. John et al 1993; Fuchs et al 1994; Goldgar et al 1994). In these 11 reported studies the relative risk or odds ratios ranged from 2 to 6, however in 8 studies the risk was between 2 and 3. In all large studies, the risk elevations were statistically significant.

When methodologies other than case-control or cohort studies were employed similar conclusions were reached. Thus in the US study of 9 colon cancer pedigrees using non-parametric methods, 8 showed a statistically significant aggregation of colon cancer, very suggestive of an inherited mechanism (Bale et al 1984). A Danish study, using the Danish Cancer Registry data, in which observed versus expected rates of colorectal cancer were calculated, a twofold risk was noted for those with a parental history of colorectal cancer (Sondergaard et al 1991).

Colon Versus Rectal Cancer Risk

In the population-based Melbourne Colorectal Cancer Study the relative risk was higher for colon cancer than for rectal cancer, higher for proximal than for distal colon cancer, and there was a statistically significant gradient of reducing risk from cecum to rectum (Kune et al 1987, 1989). Similar findings were noted in other studies also (Bufill 1990; Kato et al 1990; Sondergaard et al 1991; Fuchs et al 1994).

These findings are consistent with the predilection of HNPCC cases for the right colon indicating that the germline mutations in sporadic colorectal tumors may be similar to, and overlap with, those of HNPCC. Right-sided colon cancers have more inherited genetic defects than left-sided colon and rectal cancers, and therefore may require fewer acquired or somatic genetic changes to become malignant than might be the case for left-sided colon and rectal cancers (Melling et al 1994).

Number of First Degree Relatives Involved

The risk level rises if more than one near family member has had colorectal cancer (Rozen et al 1987; Guillam et al 1992; St. John et al 1993; Fuchs et al 1994). Thus, in the Melbourne Colorectal Cancer Study, the relative risk was 1.9 with one family member and 2.4 with 2 family members involved. In the US Nurses' and Professionals' cohorts the risk levels rose from 1.7 with one family member to 2.8 with 2 family members involved (Fuchs et al 1994). If 3 or more family members are involved, this is likely to be a family with HNPCC and therefore excluded from the present consideration.

Age of Onset of Colorectal Cancer

In several epidemiologic studies an earlier age of detection of colorectal cancer was present in those with a family history of this cancer, when compared with those without such a history (Kune et al 1989; St. John et al 1993; Fuchs et al

1994; Slattery and Kerber 1994). In the Melbourne Colorectal Cancer Study, the relative risk if colorectal cancer was diagnosed before age 45 was 5.0 and in the US Nurses' and Professionals' cohorts this was 5.4 (Kune et al 1989; Fuchs et al 1994). Early age of diagnosis of colorectal cancer appears to be an important indicator of inherited predisposition.

Correction for Confounding Factors

In the Melbourne study a model of dietary risk was created which included all dietary risk factors found in the study, and this risk model was highly statistically significantly associated with colorectal cancer (Kune et al 1987a). The risk factors were a low intake of dietary fiber, vegetables, dietary vitamin C, fish, high intake of fat and beef, and this model when statistically adjusted with the family history of colorectal cancer in near relatives showed little change with the risk, changing from 2.2 to 2.0 after adjustment (Kune et al 1989). Beer consumption was found to be a risk for rectal cancer in the Melbourne study, and when a statistical adjustment was made for this the relative risk of a family history of colorectal cancer remained unaltered (Kune et al 1987b; Kune et al 1989). It was concluded from this study that the family history effect is largely independent of the dietary and beer risk found in that study. In the 2 well-conducted US cohorts, the Nurses' Health Study and the Health Professionals' Follow-Up Study, and in which 463 subjects were identified with colorectal cancer, the relative risk in the presence of a positive family history was 1.7 and statistically significant after adjustment for age, dietary factors, alcohol consumption, smoking, body mass index, physical activity and aspirin use (Fuchs et al 1994).

Attributable Risk

The risk attributable to the inherited predisposition for colorectal cancer was shown to be about 10% in the one study which was able to measure the attributable etiologic fractions in one data set (Kune et al 1992). Of interest is that in that study the attributable risk for dietary factors was about 50%.

Summary for Ordinary Colorectal Cancer and Heredity

A comparison of the large population-based Melbourne case-control study and the US Nurses' and the Health Professionals' cohort studies is shown in Table 5.1, indicating very similar results (Kune et al 1989; Fuchs et al 1994). The family history rate of colorectal cancer is 10%. The relative risk is about twofold, and if more than one relative is affected, this risk rises. The risk is particularly high if the cancer is diagnosed before the age of 45, and the risk remains elevated and statistically significant after correction for major risk factors including diet, smoking and alcohol.

Table 5.1 Risk of colorectal cancer in the presence of a positive family history of colorectal cancer in first-degree relatives. Comparison of results from a representative population-based case-control study, and a representative cohort study.

Study	Method	No. in study	Family history rate of colorectal cancer	Relative risk of colorectal cancer (95% CI)	Relative risk if 2 or more relatives affected	Relative risk if colorectal cancer diagnosed before age 45	Risk present when confounding factors of diet, alcohol and smoking statistically corrected
MELBOURNE COLORECTAL CANCER STUDY (Australia) (Kune et al 1989)	Case-control	1,412	10%	2.1 (1.53–2.96)	2.4	5.0	Yes
NURSES' HEALTH STUDY AND HEALTH PROFESSIONALS FOLLOW-UP STUDY (USA) (Fuchs et al 1994)	Cohort	119,116	10%	1.7 (1.34–2.19)	2.8	5.4	Yes

The epidemiologic data point to an important inherited causal contribution in about 10% of individuals who develop colorectal cancer. This inherited contribution seems particularly important in those who are first diagnosed with this cancer under the age of 45 years, and in those in whom more than one family member has colorectal cancer.

CONCLUSION

Less than 1% of incident cases of colorectal cancer are due to familial adenomatous polyposis syndromes (FAP), up to about 4% of incident cases are due to hereditary non-polyposis colorectal cancer (HNPCC), whilst the remainder are ordinary colorectal cancer cases. Both FAP and HNPCC have an established inherited basis. About 10% of ordinary colorectal adenomas and colorectal cancers appear to have a significant inherited basis, so that an inherited susceptibility to colorectal cancer is present in about 15% of incident colorectal cancers. Early age of diagnosis, having more than one family member with a colorectal tumor, and possibly a colonic site, appear to point to an inherited susceptibility for ordinary colorectal tumors.

A succession of genetic changes seem to be the single most important mechanism of ordinary colorectal neoplasia, through a multistep and multipathway process. At present the proportion of germline mutations compared to acquired somatic mutations is uncertain; however, current evidence suggests that only a small fraction is likely to be due to inherited germline mutations. Progress in both genetic epidemiology and molecular genetics has been breathtakingly fast during the past decade, and if these two sciences can combine and collaborate to a greater extent with cancer epidemiologists, a well-developed understanding of the inherited etiology of colorectal neoplasia should be forthcoming within the next decade.

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6

DIET

When mighty roast beef was the Englishman's food,
It ennobled our hearts and enriched our blood
(With fat and heterocyclic amines - Author)

Richard Leveridge 1670-1758
The Roast Beef of England

Eating is a complex human function that undergoes several changes during a lifetime, and through which humans consume food, a combination of many thousands of substances, prepared and eaten in various ways. This is a somewhat simplified description of the dietary etiology of colorectal cancer, and one which will be undoubtedly greatly modified in the next few decades.

HISTORICAL BACKGROUND

In a fascinating anthropologic perspective on changing human nutritional habits, Eaton and Konner in 1985 describe the nutrition of the anatomically modern man of the paleolithic period. These populations obtained animal protein and fat from wild game (35% of diet by weight) with a very low fat content of 4%, a high content of polyunsaturated omega 3 fatty acids, ate a wide variety of wild plant species (65% of diet by weight), rarely ate cereals and consumed no dairy foods. Each day the diet had a very high fiber content of 45 g, high vitamin C content of almost 400 mg, high potassium to sodium ratio of 16, a high calcium intake of almost 1600 mg. It had a very high protein and a low saturated fat content. With the development of agriculture there was a drastic decline in meat eaten to 10% by weight, with an increase in vegetable foods including cereals, to 90% by weight, and accompanied by a decrease in stature (Eaton and Konner 1985).

However, since the industrial revolution, Western diets have increased their animal protein and saturated animal fat content from grazing animals that have largely replaced wild game, refined carbohydrates have appeared, and the total amount of foods of plant origin decreased. Modern Western diet differs markedly from that of the paleolithic period, and many, as early as at the beginning of the 20th century, have regarded this as an important contributory cause of illnesses of our civilization such as diabetes, heart disease, and some cancers (Rollo 1912, 1916).

The concept that diet may be a causal factor in colorectal cancer is very recent, hinted at by Oettle in 1964 and formally advanced in the late 1960s when Wynder and Shigematsu in 1967 suggested that luminal factors in the large bowel of dietary origin may be cancer producing, and then in 1969 and 1971 Burkitt suggested that a relative deficiency of dietary fiber with an excess of refined carbohydrate may be causal factors. Also in 1969, Gregor and colleagues suggested that animal protein may be an important causal factor. In 1972, Yudkin hypothesized that colorectal cancer, among many other illnesses, was related to a high sugar intake, and then in the early 1970s Wynder and others suggested that dietary fat may be a culprit in the dietary cause of colorectal cancer (Wynder 1975).

During the 1970s, support for the fat, meat and fiber hypotheses came from numerous quarters, giving a firm though indirect footing to the dietary etiology of colorectal cancer (Drasar and Irving 1973; Armstrong and Doll 1975; Howell 1975; Walker 1976). Since the 1980s, there has been nothing less than an explosion of research, and numerous major etiologic studies in humans as well as numerous experimental and animal studies regarding the likely mechanisms for the dietary etiology of colorectal cancer were performed. In less than a generation, the foundation for the dietary etiology of colorectal cancer had become established.

DIET AND COLORECTAL ADENOMAS

FOODS, FOOD GROUPS AND NUTRIENTS

A strong body of emerging data indicates that colorectal adenomas, the main precursor lesions for colorectal cancer in Western societies, have a very similar dietary etiology to colorectal cancer, so that most if not all dietary factors are important early in the process of colorectal neoplasia. This clearly has major implications for the dietary prevention of colorectal cancer.

The extensive research and publication of data on the morphology of colorectal adenomas, particularly in connection with the adenoma–carcinoma sequence has led to a stifling of "causal thinking" and of research which asked the question of why a colorectal adenoma might develop. Thus, data on the association between previous diet and colorectal adenomas is very recent, with

the first publication from Scandinavia by Hoff and co-workers in 1986. At the time of writing, 26 studies have been published consisting of 23 case-control studies and 3 cohort studies (Table 6.1). Up to the present a detailed quantitative intake of all foods eaten in the past has not been done and the methodology used was at best that of a semi-quantitative food frequency questionnaire. In only 2 of 26 studies were there no associations found between previous diet and colorectal adenomas (Stemmermann et al 1988; Kono et al 1991). In the other 24 studies the dietary risk and dietary protective factors were similar to those for colorectal cancer itself. In most studies, there were no gender differences in relation to the dietary effects; however, a quantitative difference was noted in 2 case-control studies, with stronger effects in women for meat, fruit and vegetables and for saturated fat, carbohydrates, fiber and folate than for men (Neugut et al 1993; Sandler et al 1993).

Meat consumption was a risk in most studies, while chicken and fish were protective (Table 6.1). Moreover, a high ratio of meat versus chicken and fish combined was a significant risk in both studies which examined this ratio (Giovannucci et al 1992; Neugut et al 1993). A high consumption of vegetables and a high consumption of fruit were uniformly and significantly protective (Table 6.1). A high consumption of coffee was associated with a significant protective effect in a Danish study (Olsen and Kronborg 1993) and had a protective effect in an Italian study also (Centonze et al 1995).

High consumption of dairy foods has generally shown a null result with the exception of one study in which a statistically non-significant risk elevation was noted (Table 6.1). Sugar-containing drinks or sweets were statistically significant risks for colorectal adenomas in both studies in which this assocation was examined (Table 6.1).

In relation to nutrients, the consumption of fat was either a risk factor or showed no association with the risk of colorectal adenomas (Table 6.1). Three studies indicate that fat is a risk over and above its energy content (Hoff et al 1988; Giovannucci et al 1992; Rozen et al 1994). In the US Health Professionals' Follow-up Study energy-adjusted fat intake remained a risk for colorectal adenomas (Giovannucci et al 1992). In another study the growth of small adenomas was positively related to fat consumption (Hoff et al 1988). Polyunsaturated fats were protective for colorectal adenomas, an effect also noted for colorectal cancer (Olsen et al 1994). Proteins generally showed a null effect. In a Japanese case-control study, low rice consumption was an independent risk for large adenomas (Kono et al 1993). A high fiber intake was protective in all 7 studies which examined this (Table 6.1), and in 6 it was statistically significant. A high body mass index was a risk for colorectal adenomas in both men and women in the 3 case-control studies which examined this association (Neugut et al 1991; Rozen et al 1994; Shinchi et al 1994).

Table 6.1 Diet factors and colorectal adenoma risk. Summary data of 26 epidemiologic studies (23 case-control and 3 cohort), showing association for a high consumption of diet item.

Diet factor		Number of studies	Risk elevation 50% or more	Protection 50% or more	No association with risk
Foods and food groups	Meat	5	4	0	1
	Chicken	1	0	1	0
	Fish	4	0	4	0
	Dairy Foods	4	1	0	3
	Vegetables	7	0	6	1
	Fruits	6	0	5	1
Nutrients	Fat	9	5	0	4
	Carbohydrate	4	0	1	3
	Protein	3	0	0	3
	Sugar	2	2	0	0
	Fiber	7	0	7	0
	Folate	4	0	4	0
Minerals	Calcium	2	0	0	2
	Zinc	1	0	1	0
	Potassium	1	0	1	0
	Magnesium	2	0	2	0
	Selenium	1	0	1	0
	Iron	3	1	2	0
Vitamins and Provitamins	A	4	0	3	1
	Beta-carotene	4	0	3	1
	B6	2	0	2	0
	C	5	0	4	1
	D	1	0	0	1
	E	4	0	3	1
Body mass index	High body mass index	3	3	0	0

Data Sources

This table was compiled from the following studies:
Hoff et al 1986, 1988; Macquart-Moulin et al 1987; Stemmermann et al 1988; Kato et al 1990; Kono et al 1991, 1993; Kune et al 1991; Little et al 1991; Giovannucci et al 1992; Benito et al 1993; Clark et al 1993; Neugut et al 1993; Olsen and Kronborg 1993; Sandler et al 1993; Kampman et al 1994; Kikendall et al 1994; Nelson et al 1994; Olsen et al 1994; Shinchi et al 1994; Paspatis et al 1995; Boutron et al 1995; Centonze et al 1995; Enger et al 1995; Tseng et al 1995; Almendingen et al 1995.

In a cohort study of men, body mass index was positively associated with large adenomas over 1 cm, but not with small adenomas (Giovannucci et al 1995a). Of interest is that in 2 large, well-conducted cohort studies no association was found for men or women between calcium, vitamin D and dairy foods, and colorectal adenomas (Giovannucci et al 1992; Kampman et al 1994). No association was noted between calcium intake and adenomas in a case-control study from Israel (Rozen et al 1994). Thus, if calcium and vitamin D have a protective effect, that effect probably operates late during the process of colorectal neoplasia, possibly after adenoma formation.

Dietary zinc and dietary magnesium were protective in studies which examined this association (Table 6.1). A high potassium intake which reflects vegetable consumption was protective. An inverse relationship was found between plasma selenium levels and colorectal adenomas in one case-control study (Clark et al 1993). The quantity of selenium in food is in part dependent on the type of soil, but in general it is found in foods of plant origin, especially wholegrain cereals, garlic and onions. It is also found in fish and eggs. In another case-control study, exposure to iron as indicated by serum ferritin levels was significantly positively associated with adenoma risk; however, in 2 recent case-control studies dietary iron was inversely related to adenoma risk in women (Nelson et al 1994; Almendingen at al 1995; Tseng et al 1995).

Dietary folate or serum or red blood cell folate levels were examined in 3 case-control studies and a protective effect was present with high levels of dietary folate or of serum folate (Giovannuci et al 1992; Paspatis et al 1995; Tseng et al 1995). The role of folate in colorectal neoplasia will be discussed in more detail when dealing with the dietary associations of colorectal cancer. A high consumption of foods containing the essential amino acid methionine was protective for colorectal adenomas in one cohort study (Giovannucci et al 1992).

Protective effects were reported for most vitamins and provitamins, with the exception of vitamin D (Table 6.1). Either protective effects or null results were noted for dietary vitamin A, beta-carotene, vitamin C and vitamin E. The protective effects of the antioxidant vitamins A, beta-carotene, C and E are discussed further in the section dealing with dietary effects on colorectal cancer. A protective effect was shown for vitamin B6 in both studies that examined this association. The explanation for this is unclear, but there is some evidence that vitamin B supplementation in older age groups stimulates immunocompetence (Talbot et al 1987). The difficulty with drawing inferences from dietary vitamin associations is that these vitamins are usually contained in foods of plant origin in which there are also numerous other compounds now known to be protective for cancer in general, and several for colorectal cancer also.

IMPLICATIONS OF DIET AND ADENOMA DATA

Firm conclusions cannot be drawn because a quantitative dietary study of all foods eaten prior to adenoma formation has not been conducted. However, the results of the 26 studies published since 1986 and summarized in Table 6.1 indicate that colorectal adenomas have dietary risk and protective factors which are very similar to those for colorectal cancer. The only difference is that for colorectal cancer, calcium-containing foods and dairy foods have been found to be a protective factor in several studies, whereas for colorectal adenomas, largely a null effect has been noted. For all other foods, food groups and nutrients examined, there was a similar risk or protective effect for colorectal adenomas as was found for colorectal cancer. This means that dietary factors are important early in the process of neoplasia, at least in those whose cancer begins as a colorectal adenoma, and this appears to be the case for the majority. This also means that dietary prevention of colorectal neoplasia needs to commence early and before adenomas form, as discussed in Chapter 18 dealing with primary prevention.

If dietary factors prove to be as important in the cause of colorectal adenoma as these factors are for colorectal cancer itself, then a quantitative study of all foods eaten prior to adenoma diagnosis needs to be conducted, since the dietary etiology of colorectal adenomas is likely to become an important stepping-stone in the primary prevention of colorectal neoplasia (Kune and Vitetta 1995).

INDIRECT EVIDENCE OF DIETARY ETIOLOGY

Indirect early clues to a dietary etiology of colorectal cancer have been gleaned from migrant studies, such as the observations that the incidence of colorectal cancer rises among first- and second-generation immigrants who migrate from a low-risk to a high-risk country; it was presumed (without much factual evidence) that these migrants make radical dietary changes, explaining, at least in part, the rise of colorectal cancer rates (Smith 1956; Haenszel 1961; Wynder and Shigematsu 1967; Haenszel et al 1973; Locke and King 1980; Kune et al 1986; McMichael and Giles 1988; Minami et al 1993). Other indirect clues have been time-trend studies such as the inclusion of more bran during war-time flour milling with a subsequent lowering of bowel cancer rates, as found by Powles and Williams in 1984. Further indirect evidence was that some subcultural groups such as Seventh-Day Adventists in California, experience low levels of colorectal cancer because of a vegetarian diet, as reported by Phillips in 1975.

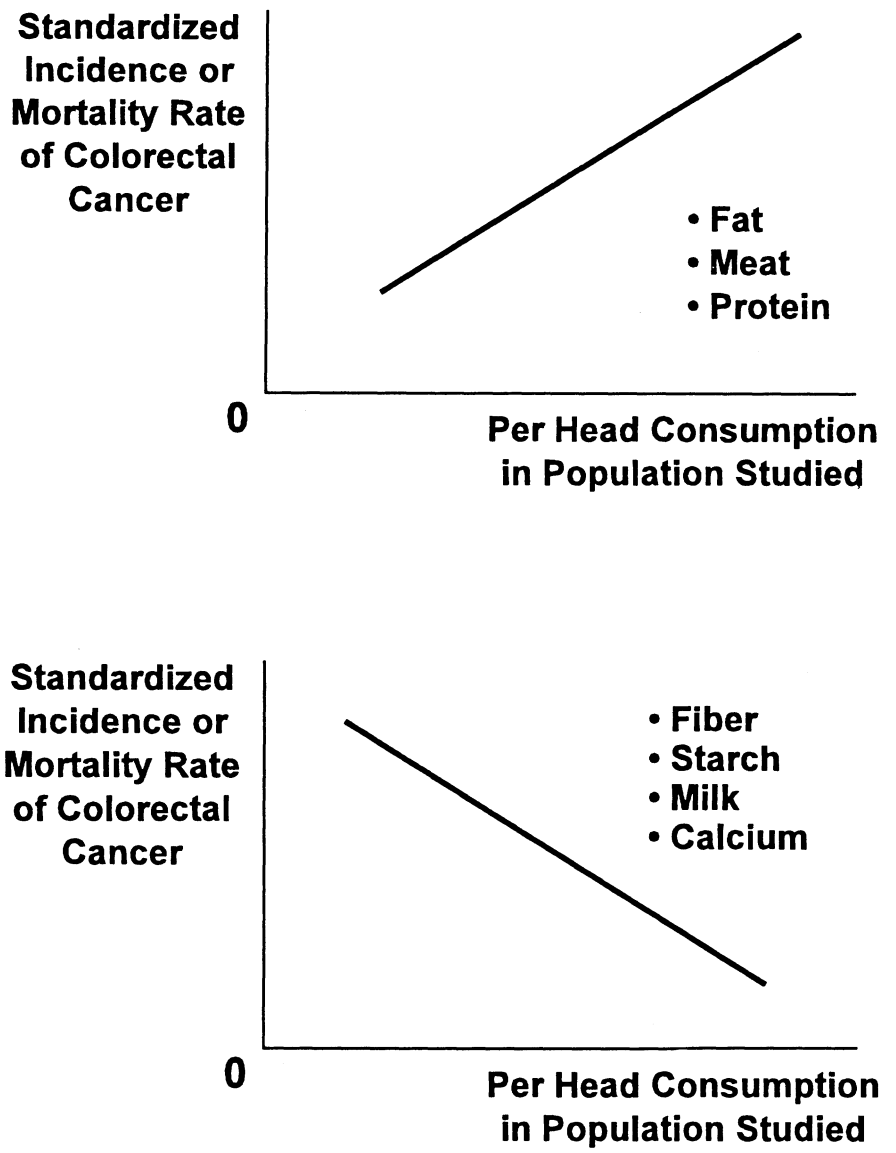

Figure 6.1 Correlation between per head consumption of various foods and nutrients in different populations, and standardized incidence or mortality rate of colorectal cancer in these populations.

Valuable indirect data have been derived from correlational studies, sometimes referred to as "ecologic" studies, which measure the per head consumption of certain food groups in various populations, and correlate them to standardized

incidence or mortality rates of colorectal cancer in those populations. Positive correlations between colorectal cancer and fat, protein and meat, as indicated in Figure 6.1, have been found in several studies (Drasar and Irving 1973; Armstrong and Doll 1975; Wynder 1975; Howell 1975; MacLennan et al 1977; Rose et al 1986). Inverse relationships between colorectal cancer and dietary fiber, starch, stool weight, milk consumption or calcium consumption as shown in Figure 6.1 have also been found in a number of studies (MacLennan et al 1977; McKeown-Eyssen and Bright-See 1984; Rose et al 1986; Sorenson et al 1988; Rosen et al 1988; Cummings et al 1992; Cassidy et al 1994). Although a significant component of vitamin D is sunlight-related, of interest is that an inverse correlation between solar radiation and colon cancer risk in the USA was found by Garland and Garland in 1980 and this is included here because of its relationship to dietary calcium and dietary vitamin D intake. Correlational studies have not been consistent with respect to dietary factors and colorectal cancer, and several studies have not found a correlation with food groups such as meat or fat or fiber. A recently reported correlation investigation from the Seven Countries Study did not show an association between the average intake of the antioxidant provitamins alpha carotene, beta-carotene, alpha tocopheral and vitamin C when examined in relation to colorectal cancer mortality rates (Ocke et al 1995). Correlational studies are indirect clues only, and require more precise and direct etiologic study.

DIETARY FACTORS IN COLORECTAL CANCER ETIOLOGY

The direct evidence that dietary factors are of importance in colorectal cancer causation can be inferred from 58 major case-control studies and 10 cohort studies which have examined this association, as well as from confirmatory experimental and laboratory studies of carcinogenesis that give biologic coherence and plausibility to the several foods and nutrients which may be causally involved. Foods, food groups and nutrients will be described individually, as assessed from a review of summarized findings in the case-control studies and from pooled analyses. Table 6.2 shows the summary findings of all the case-control studies which have examined the association between various foods and food groups, and it also indicates the summary findings of the 58 case-control studies which have examined the various nutrients, including minerals, vitamins and provitamins, and which have found statistically significant associations ($p \leq 0.05$). Table 6.3 shows the summary findings of the 10 cohort studies.

The foods and food groups described will include meat, fish, dairy products, eggs, vegetables (including various subgroups), fruit, cereals, tea, coffee and water. The nutrients examined will include fat, protein, carbohydrate, fiber, folate and methionine, vitamins (A, beta-carotene, B1, B2, B6, nicotinic acid, C,

D and E), minerals (calcium, potassium, salt, iron, zinc, magnesium and selenium). With each of these foods, food groups or nutrients, the relevant mechanisms of carcinogenesis will also be described. Cell proliferation abnormalities of the colorectal mucosa have been associated with the risk of colorectal tumor development, and several dietary factors have been found to enhance or inhibit the cellular changes that lead to tumor formation; this aspect will also be discussed.

FOODS AND FOOD GROUPS

Meat

Red meat, and in particular beef, is a risk factor for colorectal cancer (Tables 6.2 and 6.3). In a recently reported Dutch cohort, meat was not associated with the risk of colorectal cancer; however, follow-up was only 3.3 years (Goldbohm et al 1994). Most studies in which a statistical correction was made for fat, beef remained a risk. In general, white meat, rabbit and game showed inconsistent results and on present evidence, these meats probably do not have an important association with the risk of colorectal cancer. The mechanisms of action of meat is uncertain, but part of the process may involve acetylation in predisposed individuals, an increase in the fecal content of endogenously produced nitrosamines, the presence of metabolites of tryptophan, and other processes involved in meat preparation, such as grilling or frying have been suggested (Hill and Draser 1973; Suzuki and Mitsuoka 1981; Ames 1983; Weisburger and Jones 1990; Minchin et al 1993; McKinnon et al 1993). As described later, the iron content of meat may be a further risk. Methods of cooking, particularly grilling and frying have also been implicated, and will be discussed later in this chapter. However, the methionine content of meat is likely to be one of the few protective elements in meat (Giovannucci et al 1995b).

Fish

It was found in the 1970s that among Alaskan natives who have a high fish consumption, mortality from colorectal cancer was low (Blot et al 1975). Several case-control studies and one large cohort study found fish consumption associated with protective effects as shown in Tables 6.2 and 6.3. In the Melbourne Colorectal Cancer Study, eating fish was statistically significantly protective, it was independent of all other dietary risk and protective factors, independent of the beer risk found in the study, and there was also a suggestion of a dose-response effect (Kune et al 1987a; 1987b; Kune 1990). The protective effect of fish was confirmed in the Iowa Women's Study (Bostick et al 1994). In the large prospective US Nurses' Study regular fish and chicken consumption

was associated with a decreased risk of colon cancer (Willett et al 1990). Fish consumption has been found to be a protective factor for other cancers also, in particular for breast cancer, which has epidemiologic similarities with colorectal cancer (Kune 1990). The administration of fish oils or vegetable oils high in omega-3 polyunsaturated fatty acids has been shown to decrease the rate of colon tumors formed in chemically induced rodent models of colon carcinogenesis (Reddy et al 1986, 1988; Nelson et al 1988; Narisawa et al 1994). The polyunsaturated omega-3 fatty acids contained in fish have been implicated as the likely compounds connected with this protective effect (Kune 1990; Anti et al 1994). In humans, as well as in chemically induced colon neoplasia in rodents, the oral administration of fish oils has been shown to inhibit mucosal cell proliferative activity (Deschner et al 1990; Reddy et al 1991; Anti et al 1994; Hendrickse et al 1995). Fish consumption is therefore emerging as a protective factor for colorectal cancer.

Dairy Products

Inconsistent results of both risk and protection, as well as no association, have been found in the several case-control studies which examined the association between dairy products and colorectal cancer (Table 6.2). Non-significant protective effects were present in cohort studies (Table 6.3). Milk is a complex food and with respect to colorectal cancer etiology, it contains elements which are likely to be protective, in particular its calcium content, as well as elements which are likely to be risks, in particular its fat and energy content. Studies which were able to correct for fat and energy content of milk have found milk drinks protective (Kune et al 1987a). It will be of great interest to know what impact modified milks of low fat content will make in the future on fat- and energy-related illnesses such as colorectal cancer and coronary heart disease. Fermented milk products such as yoghurt and lactic bacterial cultures used in the fermentation of milk products, may be protective for colorectal tumors (Table 6.2) and deserve further investigation (Kulkarni and Reddy 1994). In a recent study, dairy proteins, in particular whey and casein diets were protective against chemically induced colon cancers in rats (McIntosh et al 1995).

Eggs

In a recently reported analysis of egg consumption and colorectal cancer risk, a positive association was present in many of the 15 studies reviewed (Steinmetz and Potter 1994). This was also found in the present analysis (Table 6.2). Eggs are a complex food and at present little that is specific can be said about this relationship.

Table 6.2 Summary data from 58 case-control studies showing statistically significant associations ($p < 0.05$) between high consumption of various diet factors and colorectal cancer.

Food or food group	Number of studies	Risk	Protection	No association
MEAT	33	21	3	9
Beef	17	8	0	9
Lamb	12	6	0	6
Pork	16	3	4	9
Chicken	14	5	3	6
Rabbit	2	2	0	0
Game	2	0	0	2
FISH/SEAFOOD	21	4	5	12
DAIRY FOODS	22	6	5	11
Milk drinks	20	4	2	14
Yoghurt	6	0	2	4
Cheese	13	1	1	11
Butter	12	2	2	8
EGGS	17	6	2 (raw)	9
VEGETABLES	33	3	23	7
Cruciferous	21	0	14	7
Alium (garlic, onion, chives)	5	0	4	1
Leafy	5	0	3	2
Lettuce	8	0	4	4
Peppers	6	0	2	4
Carrots	4	0	1	3
Potatoes	14	1	2	11
String beans	15	3	4	8
Fava beans	1	1	0	0
FRUIT	23	1	8	14
CEREALS	21	3	5	13
White bread	7	2	0	5
Wholemeal bread	5	0	2	3
Rice	9	4	1	4

Table 6.2 (Continued)

Nutrient	Number of studies	Risk	Protection	No association
FAT	35	15	7 (4 veg oil)	13
Saturated fat	15	8	1	6
Unsaturated fat	10	2	3	5
Cholesterol	8	2	1	5
PROTEIN	22	8	1	13
CARBOHYDRATE	17	5	0	12
Starchy foods	7	2	1	4
Oligosaccharides	9	4	0	5
FIBER	31	3	15	13
FOLATE	4	0	3	1
METHIONINE	1	0	1	0
VITAMINS and PROVITAMINS				
Vitamin A	15	1	1	13
Beta carotene	14	1	4	9
Vitamin C	17	0	7	10
Vitamin D	5	0	0	5
Vitamin E	5	0	1	4
Vitamin B1	3	0	1	2
Vitamin B2	3	1	1	1
Vitamin B6	2	0	2	0
Nicotinic acid	1	1	0	0
Vitamin suppl	1	0	1	0
MINERALS				
Calcium	14	0	6	8
Potassium	5	0	3	2
Salt	11	5	0	6
Iron	1	0	0	1
Zinc	1	0	0	1
Magnesium	1	0	1	0
HIGH FREQUENCY OF MEALS	7	6	0	1
HIGH ENERGY CONSUMPTION	17	12	0	5

Data Sources
First author and year of publication in chronologic order appear at end of chapter after the references.

Vegetables

There is very consistent evidence from numerous case-control studies that a high intake of vegetables is associated with statistically significant protection against colorectal cancer (Table 6.2). In 3 studies a risk for beans was found and in one for fava beans. The protective effect of a high vegetable intake in colorectal cancer etiology has been ignored until the past few years, while much more emphasis has been placed on other nutrients such as fat intake, where the evidence that fat is a risk is in fact much less convincing than the evidence for the protective effect of vegetables. The protective value of a high vegetable intake should have been noted long ago by the reported low rates of colorectal cancer in communities which eat vegetarian diets such as Seventh-Day Adventists, on whom data have been known since the early 1970s (Phillips 1975). It is therefore of interest that this review of the 33 case-control studies (Table 6.2), as well as a meta-analysis of 16 case-control studies, showed a highly protective effect of vegetable consumption with an odds ratio of 0.48, lower than that for fiber itself, which in that study had an odds ratio of 0.58 (Troc et al 1990). The cohort study which examined this effect in women found vegetable consumption to have a protective effect for colon cancer (Steinmetz et al 1994).

Of particular protective value for colorectal cancer appear to be the cruciferous vegetables, which are vegetables of the genus *Brassica*, and which include cabbage, cauliflower, broccoli, brussel sprouts, kohlrabi, swede, turnip and kale (Table 6.2). The finding of a protective effect of cruciferous vegetables over and above that afforded by high fiber and high vegetable intake is consistent with experimental observations that indoles present in cruciferous vegetables inhibit carcinogenesis produced by polycylic hydrocarbons and this they apparently do by increasing aryl hydrocarbon hydroxylase activity (Wattenberg and Loub 1978). A cauliflower extract containing S-methyl methane thiosulfonate was found to inhibit chemically induced intestinal tumors in rats (Kawamori et al 1995). Members of the allium vegetable family, namely onions, garlic and chives, have also been found to be protective in case-control studies (Table 6.2), and garlic in a cohort study (Steinmetz et al 1994). This family of vegetables has been shown to have anti-carcinogenic properties in several studies, and this may be relevant in their protective effect (Steinmetz et al 1994). Garlic inhibits chemically induced colon cancer in rats (Chang et al 1995). Leafy vegetables are also protective. Tomatoes, low in beta-carotene but high in the antioxidant lycopene, a great feature of Mediterranean diet, was found to be statistically significantly protective for gastrointestinal cancers, including colorectal cancer in an Italian study (Franceschi et al 1994). There is little evidence that potatoes have any protective value for colorectal cancer. Beans, and particularly fava beans, were the only vegetable noted to be risks for colorectal cancer. In an interesting study from New Zealand, where the Polynesian population has several colorectal cancer related risks compared to

Europeans, namely overweight, higher fat and energy intakes, yet have lower rates of colorectal cancer than Europeans, it was found that the Polynesian people consume certain plant foods significantly more often than Europeans, and this may be a factor in protection from this cancer (Ferguson et al 1995).

The study of anticarcinogenic "phytochemicals", the naturally occurring foods of plant origin which have anti-cancer properties, is a most exciting development. Over and above their fiber content, vegetables contain several substances which have been shown experimentally (including in chemically induced colorectal cancer) to have anti-cancer properties; these include carotenoids, vitamin C, vitamin E, folate, as well as indoles, phenols, flavinoids, isothiocyanates, allylic sulphides, monoterpenes, phenolic acids, linolenic acid, and very likely, several others not yet researched (Wattenberg 1977, 1985, 1987; Steinmetz and Potter 1991; Deschner et al 1993). These compounds in experimental situations have been shown to have protective effects through enzymes, antioxidant action, inhibition of nitrosamine formation, the blocking of hormone receptor sites, acting as cell differentiation agents, and regulating prostaglandin production. On present evidence, a varied and high vegetable intake appears to be the most important dietary protective factor for colorectal tumors. This highly protective effect of vegetables appears to have been the best kept secret in cancer prevention!

Fruit

A high fruit intake was a statistically significant protective factor in several case-contol studies (Table 6.2). The protective effect of fruit is in keeping with the inverse relationship between colorectal cancer and vitamin C consumption described subsequently. Different fruits also contain carotenoids, catechins, flavenoids, limonoids, monoterpenes and phenolic acids, compounds which in experimental settings have been shown to have anti-cancer properties. The protective effect of fruit is less strong and less consistent in human studies than that found for a high vegetable intake (Table 6.2).

Cereals

The case-control data on cereals do not consistently indicate a protective effect. A statistically significant protective effect of high cereal intake was only present in 5 of 21 case-control studies which examined this association (Table 6.2). The lack of a consistent protective effect for colorectal cancer for cereals in general, as well as components of cereals, is also lacking. In several studies, inconsistent effects for rice and pasta have been noted. Wholegrain cereals have linolenic acid, phenolic acids, and vitamin D precursors, compounds which experimentally have been shown to have protective effects in carcinogenesis.

Tea and Coffee

Case-control data on high intakes of tea and coffee have generally shown no association with the risk of colorectal cancer. Studies of mainly Mormon or Seventh-Day Adventist populations however, found a twofold risk for coffee drinking (Phillips and Snowdon 1985; Slattery et al 1990). In contrast, a recent Swedish study showed a statistically significant protective effect for colon cancer for high coffee consumers, and a significant protective effect for rectal cancer for tea drinkers, and a Danish study has shown a significant protective effect for heavy coffee drinkers also (Olsen and Kronborg 1993; Baron et al 1994). Interestingly, a low dose of green tea extract in water had a potent effect in reducing chemically induced colon cancer in rats (Narisawa and Fukaura 1993). The role of coffee and tea drinking in colorectal cancer etiology needs clarification in view of these conflicting data.

Water

Drinking water obtained from surface sources has been associated with elevated risks for colorectal cancer. This risk appears to be related to water chlorination and the resultant formation of hydrocarbons or other similar compounds present in drinking water, and derived from industrial waste contamination, and some of these compounds may be carcinogenic (Gottlieb et al 1981; Wigle et al 1986). So far, no association between water fluoridation and colorectal cancer risk has been found (Wigle et al 1986).

NUTRIENTS

The nutrients considered are fats, fiber, protein, carbohydrate, starch, oligosaccharides, calcium, potassium, salt, selenium, iron, folate, methionine, vitamins, provitamins and vitamin supplements.

Fiber

Denis Burkitt first suggested in 1969 and then in 1971 that a number of illnesses including colorectal cancer may be caused by a low intake of dietary fiber. Since that time an explosion of human, laboratory and experimental research has confirmed the protective role of fiber-containing foods for colorectal cancer.

Table 6.3 Summary data from 10 cohort studies of diet factors and colorectal cancer risk.

Food or Nutrient	Study	Findings
MEAT	Hirayama 1981 Willett et al 1900	Risk Risk (SS)
SUGAR	Bostick et al 1994	Risk (SS)
MILK	Ursin et al 1990 Martinez et al 1995	Protection (NS) No assoc (colon) Protection (NS rectum)
FISH	Bostick et al 1994	Protection (NS)
FISH+CHICKEN MEAT	Willett et al 1990	Protection (SS)
EGGS	Phillips & Snowdon 1985	Risk (SS)
VEGETABLES	Steinmetz et al 1994	Protection (NS)
GARLIC	Steinmetz et al 1994	Protection (almost SS)
COFFEE	Phillips & Snowdon 1985	Risk (SS)
FAT	Stemmerman et al 1984 Willett et al 1990	Risk (SS) Risk (SS)
UNSATURATED FAT	Willett et al 1990 Bostick et al 1994	No association Protection (NS)
OMEGA-3 FATTY ACIDS	Bostick et al 1994	Protection (NS)
FIBER	Willett et al 1990 Steinmetz et al 1994	Protection (meat intake dependent) Protection (NS)
CALCIUM/ VITAMIN D	Garland et al 1985 Phillips & Snowdon 1985 Wu et al 1987 Stemmermann et al 1990 Willett et al 1990 Bostick et al 1993 Martinez et al 1995	Protection (SS) Protection (NS) Protection (NS) Protection (SS) No association Protection (NS) No assoc calcium Protection Vit D (SS)
FOLATE	Giovannucci et al 1995b	Protection (SS)

SS = Statistically significant $p \leq 0.05$
NS = Risk elevated 50% or more, result not statistically significant $p > 0.05$

Results of Epidemiologic Studies

Both prospective cohort studies which examined this association found an inverse association (Table 6.3). Of 31 case-control studies, 15 found a statistically significant protection for colorectal cancer in those who consume a diet high in fiber (Tables 6.2). Two recently published studies, a meta-analysis by Troc and co-workers in 1992, and a combined analysis of 13 high quality case-control studies by Howe and co-workers in 1992, strongly supported the view that fiber-rich foods are protective for colorectal cancer and that the level of protection increases as the fiber intake is increased. This protective effect was similar for different age groups, for colon and rectal cancer, and for both men and women (Howe et al 1992).

Mechanisms of Action of Fiber

There is substantial animal experimental and laboratory evidence, as well as evidence from human studies, that the group of substances referred to as "dietary fiber" act as a protective factor in colorectal neoplasia by several direct and indirect mechanisms (Harris and Ferguson 1993). Undegradable dietary fiber may bind and render carcinogenic substances inactive, fiber absorbs water, dilutes the concentration of carcinogenic substances, and increases fecal bulk, thereby shortening bowel transit time, decreasing contact time. Also, the degradation of fiber lowers colonic pH, reduces conversion of primary bile acids to secondary bile acids and products of bacterial fermentation of fiber, especially short chain fatty acids and butyrate in particular, are produced which have an inhibitory effect on colorectal carcinogenesis (Stephen and Cummings 1980; Thornton 1981; Cummings and Branch 1982; Cummings 1983; Davies et al 1986; Weisburger and Wynder 1987; Cummings and Macfarlane 1991; Cummings et al 1992: Harris and Ferguson 1993; Nagengast et al 1993; Nordgaard et al 1995; Probert et al 1995).

Among all these mechanisms of action, recent evidence increasingly suggests that the bacterial fermentation of dietary fiber and the production of short chain fatty acids, in particular butyrate, has a major protective effect on colonic epithelial cell division, arresting growth, inducing differentiation and acting in this way even on preneoplastic cells, thereby forming an important mechanism in the prevention of large bowel cancer (Cummings 1995). Butyrate has also been shown to alter gene expression and growth of colon cancer cell lines (Whitehead et al 1986; Dang et al 1995).

Rectal mucosal cell proliferation has been inhibited in a controlled study of individuals with a family history of colorectal cancer with the use of wheat bran (Rooney et al 1994). Furthermore, the use of bran, and particularly wheat bran, decreases epithelial proliferation in the rectal mucosa, increases fecal fat excretion and decreases the stool level of diacylglycerols, compounds which are likely to be involved in colon carcinogenesis (Alberts et al 1990; Reddy et al

1994). Dietary fiber has also been shown to suppress the formation of aberrant crypt foci, a likely early preneoplastic lesion, in chemically induced colorectal tumors in rats (Thorup et al 1994; Alabaster et al 1995).

It is a gross over-simplification to discuss "dietary fiber" as if it were a single substance, since it is made up of a large number of compounds which may give different levels of protection against colorectal cancer. At present it has not been clearly established to what extent it is the fiber itself and to what extent the other components of fiber-rich foods are responsible for this protective effect. The two case-control studies which have been able to examine this important distinction in some detail have found that fiber from vegetables, less importantly from fruits and least from grain cereals, is most consistently associated with protective effects for colorectal cancer, and this fits in well with the other epidemiologic data summarized in Table 6.2 (Kune et al 1987a; Slattery et al 1988b).

Fats

Results of Epidemiologic Studies

Statistically significant elevated risk levels have been found for a high fat intake in a number of case-control studies as well as in both of the cohort studies which examined this association (Tables 6.2 and 6.3). However, several case-control studies found no association and a number found statistically significant protective effects (Table 6.2). Most of the case-control studies in which a statistically significant protective effect of fat was noted, emanated from populations which use a lot of vegetable oil. In this regard, the separation of saturated fatty acids have generally shown elevated risk levels, whilst unsaturated fat and/or fats of vegetable origin have been associated with protective effects or no association with the risk (Table 6.2). In the US Nurses' study, fats of animal origin were a risk, while fats of plant origin had no association with the risk of colon cancer (Willett et al 1990).

Saturated fats and fats of animal origin appear to be a risk, whereas unsaturated fats of vegetable origin are not a risk, and may have a protective effect. The use of vegetable oils amongst vegetarian populations and in certain countries such as in Southern Europe, may be a part explanation of the relatively low colorectal cancer rates in these populations. Furthermore, the fats derived from fish also appear to have a protective effect (Kune 1990).

Although early indirect correlational studies, such as the one reported by Liu and colleagues in 1979, showed a positive association between dietary cholesterol and colorectal cancer, case-control studies showed conflicting results (Table 6.2). Serum cholesterol levels are not correlates of dietary cholesterol intake. Early studies indicated an inverse relationship between serum cholesterol and colorectal cancer. However later studies showed no association or an inverse association only with advanced tumors, which was regarded to be a tumor effect rather than an etiologic effect (Millar et al 1981; Sidney et al 1986). On present

evidence, dietary or serum cholesterol is unlikely to be related causally to colorectal cancer.

Several case-control studies found a statistically significant positive association between total energy consumption and colorectal cancer risk (Table 6.2). A preliminary combined analysis of 13 high quality case-control studies suggests that energy intake is positively associated with the risk of colorectal cancer, and that fat consumption probably does not make a significant contribution to this risk beyond its energy content (Howe 1995, personal communication).

Mechanism of Action of Fat

At present there are more questions than answers in relation to the fat hypothesis. What is emerging is that we need to distinguish between fats of different types and origins, namely fats derived from animal food, plant food and fish, and we also need to distinguish any specific effect that fat may have as a causal factor in colorectal cancer, over and above its energy content.

Although the strength of the fat hypothesis is diminishing, it would be unwise to abandon it especially with respect to saturated fats of animal origin, because there are coherent and plausible hypotheses and experimental data on how fat may influence the mechanism of colorectal carcinogenesis. The work of Reddy, Hill and several other scientists working in the field of carcinogenesis have shown that a high consumption of saturated fat increases the rate of chemically induced colon cancer in experimental animals, and that both in humans and in laboratory animals high fat diets increase the excretion of bile acids and these bile acids in turn are altered by bacteria in the large bowel, resulting in the development of compounds regarded as carcinogenic (Reddy et al 1976; Reddy et al 1977; Hill 1977; Reddy 1981). A high fat intake, particularly if given as a bolus, increases the rate of proliferation of the colorectal mucosa in humans (Stadler et al 1988). A high fat intake in chemically induced colon tumor models increases the number of aberrant crypt foci, a likely preneoplastic lesion (Lasko and Bird 1995). Furthermore, increased fecal bile acids have been found in populations with high rates of colorectal cancer, as well as in individuals with colorectal cancer and adenomatous polyps, and the capacity of the colonic flora for enzymatic transformation of bile acids is reduced in vegetarians, compared to meat eaters, as well as being decreased by reducing fat content and by manipulation of the colonic flora (Hill et al 1975; Reddy and Wynder 1977; Goldin et al 1980; Reddy et al 1980; Reddy 1981; Reddy 1986; Moorhead et al 1987). However, the experimental data designed to test the mechanisms involved in the fat hypothesis of colorectal cancer have been inconsistent. The fat hypothesis of colorectal cancer etiology has been weakened, particularly by recent epidemiologic data, but should not be abandoned and particularly not for saturated fats of animal origin.

Protein

Of 22 case-control studies 13 found no statistically significant association between high protein consumption and colorectal cancer and 8 found a risk (Table 6.2). In Western populations, meat forms a large proportion of the protein nutrient and this may explain the positive effects, as may the energy content of protein. As with fiber, fat and carbohydrate, it is a gross oversimplication to group all proteins together, since different types of protein from different sources and from different protein molecules may have different effects on the risk of colorectal cancer. Whilst protein from meat is a risk, the methionine content of meat is protective, and recently dairy proteins and whey proteins have also been shown to be protective in experimental colorectal tumors (Kune et al 1987a, Giovannucci et al 1992, 1995b; McIntosh et al 1995).

Carbohydrate

Most case-control studies have not found an association between total carbohydrate intake and colorectal cancer (Table 6.2). A recent report from the Iowa Women's Health Study cohort found a statistically significant elevated risk for sugar (sucrose) and sugar-containing foods in colon cancer (Bostick et al 1994). Statistically significant risk elevation for sugar was also noted in 4 of 9 case-control studies which examined this association (Table 6.2). A high sugar diet increases both intestinal transit time and fecal output of secondary bile acids, and both of these factors are regarded as mechanisms involved in colonic neoplasia (Kruis et al 1991). Furthermore, both natural sugar and cooked sugar increases the proliferation and aberrant crypt formation in colonic mucosa, as well as increasing microadenoma formation in rodent models of colonic carcinogenesis (Corpet et al 1990; Archer et al 1992; Stamp et al 1993; Bruce et al 1993). These experimental data indicate that if sucrose is an etiologic factor, it operates early in the process of neoplasia. The idea of Yudkin expressed in 1972 that sugar is "pure, white and deadly" is gaining some ground in colorectal neoplasia.

Starch

Starchy foods have been estimated in a number of case-control studies and showed inconsistent results (Table 6.2); however, a strict measurement of starch itself has not been made, nor of so-called "resistant starch" in these studies. In a recently reported correlational study, a strong inverse relationship has been shown between starch intake and colorectal cancer incidence in 12 populations worldwide, and similar inverse relationships were also noted when non-starch polysaccharide was combined with resistant starch, a relationship which remained unchanged after adjusting for fat and protein consumption (Cassidy et al 1994). These data add support to the hypothesis that fermentation of these nutrients in the colon and the production of short chain fatty acids, particularly butyrate, as discussed previously in the section dealing with dietary fiber, is an

important mechanism of protection against colorectal cancer (Cummings and Branch 1982; Cummings et al 1983; Whitehead et al 1986; Caderni et al 1989; Cummings et al 1992b; Dolara et al 1993; van Munster et al 1994; Cummings 1995).

Calcium

Calcium intake in the evolutionary perspective is interesting because at the end of the Stone Age humans consumed twice as much calcium as humans in the 20th century, and this was sourced from vegetables rather than dairy foods (Eaton and Nelson 1991). An inverse relationship between calcium consumption and colorectal cancer risk has been established in 6 of 14 case-control studies (Table 6.2). In prospective cohort studies which have examined this effect, with two exceptions, protective effects were seen (Table 6.3). A review of Sorensen and colleagues in 1988 also supports a protective role for high dietary calcium intake. This nutrient probably needs to be examined in conjunction with vitamin D, as both seem to work together in order to produce a protective effect (Garland et al 1985).

A decrease in the proliferation of rectal epithelial cells has been shown to occur in humans who have taken supplements of calcium carbonate, and similar changes have also been found with the addition of calcium and vitamin D in human colon tumor cell lines, as well as in mouse colon epithelial proliferation (Lipkin and Newmark 1985; Wargovich and Lointier 1987; Rozen et al 1989; Wargovich et al 1992; Kleibeuker et al 1994; Nobre-Leitao et al 1995; Wargovich et al 1995). This evidence suggests that calcium has an effect early in the neoplastic process; however, it is inconsistent with the epidemiologic data discussed earlier, in which dietary calcium intake was not shown to have an association with colorectal adenoma risk (Table 6.1). It is also inconsistent with 2 recent randomized double-blind placebo-controlled studies in which calcium supplementation did not affect colorectal mucosal proliferative activity of patients who previously had colorectal adenomas removed (Baron et al 1995; Bostick et al 1995). However, there is reasonably consistent evidence supporting the original hypothesis of Newmark and co-workers 1984, that calcium binds fatty acids and bile acids in the lumen of the large bowel, rendering these compounds harmless to the mucosa. One study which specifically examined this last hypothesis found no reduction in fecal bile acid levels with calcium supplementation (Alder et al 1993; Kleibeuker et al 1994). However, other inhibitory effects of calcium, namely modulation of protein kinase C and of K-ras mutations, and the inhibition of cholic acid promoted experimental colonic carcinogesis are also supportive of the calcium hypothesis (Pence 1993; Pence et al 1995).

The current evidence justifies the conclusion that there may be a modest protective role for a high intake of calcium/vitamin D-containing foods (and vitamin D exposure); however, a major protective effect for colorectal tumors for

calcium/vitamin D should not be expected (Bostick et al 1993; Kleibeuker et al 1994). If there is a protective effect of calcium, it may not occur early in the neoplastic process.

Potassium

A statistically significant protective effect has been found in 3 of 5 case-control studies which examined the relationship between potassium intake and colorectal cancer risk (Table 6.2). The potassium effect is thought to be largely explained by a high vegetable intake, which is known to be the most important protective food group for colorectal cancer, as vegetables contain considerable quantities of the potassium ion (Kune et al 1989).

Salt

A statistically significant positive association between salt intake and colorectal cancer risk was found in 5 of 11 studies which examined this effect (Table 6.2). In studies which were able to correct for other dietary factors, the risk remained unchanged (Kune et al 1989). Of importance is that in none of the studies was a protective effect found. There have been no suggested mechanisms of how salt may produce its effect in colorectal neoplasia.

Selenium

An inverse relationship between dietary selenium and colorectal cancer risk has been proposed (Stampfer et al 1987). The amount of selenium in foods is in part dependent on the type of soil the food is grown in, and in part dependent on the type of food consumed; however, in general selenium is found in foods of plant origin, particularly whole grain cereals, garlic, onions, as well as in fish and eggs. In the section dealing with colorectal adenomas, an inverse relationship was found between plasma selenium levels and colorectal adenomas. However, in the US Nurses' Health Study cohort, an inverse relationship between toenail selenium levels (regarded as reflecting selenium intake) and cancer was not found, and in fact a non-significant positive association was noted for colorectal cancer (Garland et al 1995).

In rat models, colonic cell division was reduced when a fairly high concentration of selenium was administered (Salbe et al 1990). Selenium administration was found to inhibit chemically induced distal colon tumors in rats which were fed a fiber-free diet (McGarrity and Peiffer 1993). A careful well-designed study of the role of dietary selenium in colorectal neoplasia has so far not been made.

Iron

There is some, though not consistent, clinical and experimental evidence that ingested iron and high body iron stores are positively associated with both

colorectal adenomas and colorectal cancer (Stevens et al 1988; Freudenheim et al 1990; Nelson 1992; Knekt et al 1994; Nelson et al 1994; Tseng et al 1995).

Methionine

The essential amino acid methionine is found in red meat, fish, poultry, milk protein and some vegetable proteins, and has been found to be a protective factor in both colorectal adenomas and colorectal cancer. A low methionine intake when associated with regular beer consumption appears to be a risk for both men and women, especially for rectal cancer (Giovannucci et al 1993, 1995b; Martinez et al 1995). The mechanism involved is discussed below in relation to folate consumption.

Folate

The micronutrient folate, which is sometimes referred to as folic acid or folacin, is found in abundance in cereals especially wheat bran, in baker's yeast, cruciferous vegetables, spinach and some nuts. Low folate diets have been found to be a consistent risk for both colorectal adenomas and colorectal cancer in both cohort and case-control studies (Tables 6.1, 6.2 and 6.3), and especially so in habitual alcohol consumers (Benito et al 1991; Freudenheim et al 1991; Giovannucci et al 1993, 1995b; Ferraroni et al 1994). This appears to be an independent effect that remains after adjustment for energy, body mass index, diet factors, physical activity and smoking. Moreover, folate deficiency enhances chemically induced colon cancers, and folate supplementation protects against the development of these tumors (Cravo et al 1992; Kim et al 1995).

The mechanism whereby folate deficiency contributes to the risk of colorectal neoplasia is unclear; however, folate is involved in DNA synthesis, and in DNA methylation, and with folate-deficient DNA hypomethylation there is an over-expression of oncogenes and inactivation of tumor suppressor genes (Goelz et al 1985; Feinberg et al 1988; Cravo et al 1992). Hypomethylation appears to be an early event in colorectal neoplasia and can be started by low cell levels of the methyl donor S-adenosylmethionine (Cooper 1983; Feinberg and Vogelstein 1983). The production of this compound is dependent on both methionine and folate intake. Hypomethylation effects are probably reversible in the short term; however, with long-term hypomethylation, morphologic changes occur including the development of malignant tumors (Pascale et al 1991; Newberne and Rogers 1991; Cravo et al 1992). This is a good example of how dietary factors can influence genetic change. The relationship between a low folate/methionine diet, habitual alcohol consumption and colorectal tumor risk is discussed further in Chapter 7 dealing with alcohol consumption.

Vitamins and Provitamins

Most vitamins and provitamins are contained in foods of plant origin which are now known to possess antineoplastic activity because of numerous compounds,

other than vitamins, which they also contain. Thus inferences regarding the role of vitamins and provitamins in colorectal neoplasia need to be made cautiously, since vitamin supplementation may not have the same effect as the consumption of the foods in which they are found.

Vitamin A

In general no associations have been found between vitamin A consumption and colorectal cancer risk (Table 6.2).

Beta-Carotene

No association between beta-carotene consumption and colorectal cancer risk was found in 9 of 14 case-control studies; however, 4 studies found a statistically significant protective effect (Table 6.2). In the study which was able to simultaneously correct for other dietary variables, a protective effect of beta-carotene found in the univariate analysis was largely explained by the protective effect of vegetables, indicating that in that study beta-carotene probably did not have an important independent association with colorectal cancer risk, although the question of collinearity was not completely answered (Kune et al 1987a). There is, however, both human and experimental evidence that beta-carotene is protective in the early stages of colorectal neoplasia, and this includes a protective effect for colorectal adenomas (Table 6.1). In support of this early effect is the finding that beta-carotene administration suppresses aberrant crypt foci, a likely early preneoplastic lesion, in chemically induced colon cancer in rats (Alabaster et al 1995). A significant suppressiosn of rectal epithelial kinetics was also found in the Australian Polyp Prevention Project, in the group randomized to beta-carotene (Kilias et al 1993). These data all point to beta-carotene having an effect mainly early in the process of colorectal neoplasia.

Vitamin C

A statistically significant inverse relationship was noted in 7 of 17 case-control studies which examined this association (Table 6.2). An important finding is that of the 17 studies none have shown vitamin C to be a risk. Furthermore, the study, which was able to simultaneously correct statistically for all other dietary risk factors, found that the inverse relationship with vitamin C was an independent effect (Kune et al 1987a). A quantitative estimation of the protective effect in that study showed that vitamin C was protective only for dietary intakes greater than 230 mg of vitamin C per day. This may mean that only very high levels of dietary vitamin C are protective, hence the absence of an inverse relationship in a number of case-control studies.

Vitamin C is known to block the synthesis of N-nitrosocarcinogens by destroying the nitrite molecule, and it may be in this way that it has a protective effect. Nitroso compounds, particularly in relation to red meat and beer

consumption, have been implicated as possible mechanisms of risk in relation to meat and beer (Suzuki and Mitsuoka 1981; Kune and Vitetta 1992).

Vitamin B1 B2 B6 and Nicotinic Acid

No consistent effects have been noted with vitamin B1, B2, or nicotinic acid in relation to colorectal cancer risk. Of interest and so far unexplained, is the protective effect of vitamin B6 in both studies which examined this association for both colorectal adenomas and colorectal cancer (Tables 6.1 and 6.2). There is some evidence that vitamin B6 supplementation in those over 65 years stimulates immunocompetence, and this may be a partial explanation of the protective effect (Talbot et al 1987).

Vitamin D

No association has been found in any of the 5 case-control studies which examined the association between dietary vitamin D and colorectal cancer (Table 6.2). Moreover, in a large cohort, serum vitamin D metabolite levels did not affect the subsequent risk of colon cancer (Braun at al 1995). Apart from dietary sources, sunlight is a most important source of vitamin D. As indicated previously, Vitamin D works with calcium intake and appears to be responsible for a modest protective effect in colorectal cancer (Garland and Garland 1980; Lipkin, Newmark and Kelloff 1991; Martinez et al 1995).

Vitamin E

No association between vitamin E and colorectal cancer risk has been found in 4 of 5 case-control studies which examined this effect (Table 6.2). In one case-control study a protective effect was found for vitamin E containing foods (Ferraroni et al 1994). A recent pooled analysis of well-conducted cohort studies showed that serum alpha tocopherol levels were inversely related to colorectal cancer risk, implying that vitamin E may have a modest protective effect in colorectal neoplasia (Longnecker et al 1992).

Vitamin Supplements

The only study which was able to examine the association between vitamin supplements containing vitamin A and vitamin C, found a highly statistically significant protective effect with the regular use of these supplements and this effect was independent of other dietary risks found in the study (Kune et al 1987a). The use of vitamin supplements in the prevention of colorectal neoplasia is discussed in more detail in Chapter 18 dealing with primary prevention.

OTHER DIET RELATED FACTORS

Energy

It was first emphasized by Lyon and co-workers in 1987, that there is a positive association between energy intake and colon cancer risk. A statistically significant positive association was found between energy intake and colorectal cancer risk in 12 of 17 case-control studies which examined this effect (Table 6.2). In a preliminary analysis of pooled data from 13 case-control studies, energy intake was statistically significantly positively associated with the risk of colorectal cancer (Howe 1995, personal communication). These observations suggest that all future epidemiological nutritional studies of colorectal cancer need to be corrected for energy intake. It appears important in the analysis of both dietary and alcohol data to adjust statistically for energy intake in order to separate the effect of energy from that of the non-energy aspects of the dietary components, fat, protein or carbohydrate. Indeed, it is possible that the inconsistent findings of case-control studies in relation to fat, protein and carbohydrate consumption are in part due to the unadjusted energy factor.

Importantly, a high energy intake is emerging as a possible independent risk factor for colorectal cancer, a factor which is also often associated with other risks, namely an increased body weight and lack of physical activity. A mechanism for this effect has so far not been suggested. However, it has been postulated since 1950 that increased cell stimulation leading to an increased number and rate of cell division is an important mechanism in the development of any malignant tumor (Bullough 1950; Albanes and Winick 1988; Preston-Martin et al 1990). Thus a high food/energy intake may lead to increased mucosal activity of the entire gastrointestinal tract including the colon and rectum, resulting in an increase in the rate of cell division and hence an increased risk of colorectal cancer. A restriction of energy intake in animal models decreases the rate of cell division and inhibits the formation of tumors, including those in the colon (Winick and Noble 1966; Goettler et al 1987; Albanes and Winick 1988; Lasko and Bird 1995). Furthermore, a recent study of obese humans showed that a one-third reduction of energy intake led to a statistically significant reduction in rectal cell proliferation, an investigation increasingly regarded as a valid biomarker of colorectal carcinogenesis (Steinback et al 1994).

Body Weight, Body Mass Index

Several cohort and case-control studies have indicated that being overweight is a risk for colorectal cancer, especially in males (Lew and Garfinkel 1979; Garland et al 1985; Nomura et al 1985; Phillips and Snowdon 1985; Wu et al 1987; Graham et al 1988; West et al 1989; Kato et al 1990; Gerhardsson de Verdier et al 1990; Kune et al 1990; Bostick et al 1994; Chyou et al 1994; Dietz et al 1995; Giovannucci et al 1995a).

The mechanisms involved are largely unknown; however, they are likely to be similar to those in relation to a high energy intake, and both these risks are also often associated with another risk, namely a lack of physical activity (Lee and Paffenbarger 1994). Intestinal transit time is positively associated with colon cancer risk, and in a recent population-based study, an increase in body mass index was associated with an increased transit time in both men and women (Probert et al 1995). In an interesting and provocative recent review, it has been hypothesized that hyperinsulinemia may be an explanation of the mechanism whereby obesity, high energy intake, high saturated fat, sugar, low soluble fiber intake, and physical inactivity, are all risks for cancer of the large bowel (Giovannucci 1995). Certainly insulin is an important growth factor for cells, including colorectal epithelial cells, and in vitro it is a promoter of tumor cell growth.

Frequency of Meals and Food Diversity

In 6 of 7 case-control studies a high frequency of meals was a risk, particularly for colon cancer (Table 6.2). The explanation for this finding is likely to be complex. It may be that a high meal frequency correlates with a high energy intake, a likely risk for colorectal cancer. Eating also activates the gastroileal reflex delivering substrate into the right colon, it increases bile secretion into the bowel, and increases segmentation but not the propulsive activity of the colon, and all of these factors have been hypothesized to promote the development of colon cancer (Gerhardsson de Verdier and Longnecker 1992). It may also be hypothesized that a high frequency of meals brings into operation an increase in gastrointestinal mucosal cell activity in general, resulting in a degree of hyperplasia of the mucosa which may be a factor in elevating the risk, as discussed previously in connection with a high energy intake (Albanes and Winick 1988; Preston-Martin et al 1990). Decreasing meal frequency, and particularly the avoidance of "snack" meals, may be one simple means of lowering colon cancer risk.

A recent study has also found a significant association in men for food diversity and colon cancer (McCann et al 1994). When the data were adjusted for body mass index, vegetable dietary fiber, energy and total number of servings of food, the elevated risks become statistically non-significant, suggesting that meal frequency may be the important component of the food diversity risk.

Method of Cooking – Fried and Grilled Meat

Elevated risks for colorectal cancer have been found for fried and grilled meat in most, though not all, epidemiologic studies which examined this effect (Phillips 1975; Lyon 1988; Young and Wolf 1988; Peters et al 1989; Schiffman and Felton 1990; Gerhardsson de Verdier et al 1991; Knekt et al 1994; Muscat and Wynder 1994). Data on fried and grilled vegetables are not available.

It has been recently hypothesized that heterocyclic amines and other compounds such as hydroxymethyl-formaldehyde produced by high temperature frying, broiling or grilling of meat are the compounds involved, and this is in keeping with laboratory and animal model data showing these compounds to be carcinogenic (Sugimura et al 1977; Sugimura and Sato 1983; Corpet et al 1990; Weisburger and Jones 1990; Overvik and Gustafsson 1990; Schiffman and Felton 1990; Ito et al 1991; Minchin et al 1993; Bailey and Williams 1993). As discussed in Chapter 5, dealing with inherited predisposition, this process involves acetylation and oxidation, the rate of which is under genetic control (Bell et al 1995). It appears that fast acetylators and fast oxidizers, who also regularly eat fried, broiled and grilled meat, are under an increased risk for colorectal cancer (Minchin et al 1993; Lang et al 1994). This provides an interesting link between diet and heredity. A careful study examining the effect of frying, broiling and grilling of food, especially meat, independent of the food being cooked, is needed, in view of these methods of cooking being widely practised in many societies. An identification of the genetically predisposed individuals by genetic testing could also be valuable.

DIETARY INTERRELATIONSHIPS

Foods are complex substances eaten in varying proportions and in varying relationships to each other, as well as eaten raw, cooked or prepared in various ways. Up to the present time, insufficient research has been focussed on food interrelationships and their possible role in colorectal cancer etiology, hence the dietary etiology of colorectal neoplasia, whilst resting on a solid foundation, remains somewhat unsophisticated.

Fiber and Vegetable Relationship

In the Melbourne Colorectal Cancer Study, which had a quantitative assessment of all foods eaten in the past, one important dietary finding was that a concurrent high intake of fiber from any source, and of vegetables, seemed necessary before either had its maximum protective effect (Kune et al 1987a). In only one other study was both fiber and vegetables examined but an interaction was not analyzed in that study, yet this important finding does merit further research.

Fiber/Vegetables and Fat

The combination of a high fat and low fiber/vegetable consumption in relation to a low fat and high fiber/vegetable consumption was associated with a statistically highly significant relative risk of 3.0 in the Melbourne Colorectal Cancer Study (Kune et al 1987a). Unfortunately, in that study a distinction between fat of animal origin and of plant origin was not made. Although the relationship between animal fat and foods of plant origin is likely to be complex, there is experimental data from rat models of colorectal carcinogenesis and also data

from human studies of groups at various levels of risk in relation to their type of diet (non-vegetarian versus vegetarian), which suggest that foods of plant origin including plant sterols and plant fats attenuate the risk of a high animal fat diet (Bull et al 1979; Raicht et al 1980; Nair et al 1984).

Red Meat and Fish

In the Melbourne Colorectal Cancer Study the highest risk was associated with a low intake of fish and a high intake of beef (Kune et al 1987a). Similarly, in the Nurses' Health Study, the ratio of the consumption of red meat to the consumption of fish and chicken was strongly associated with an increased incidence of colon cancer (Willett et al 1990).

Beef, Fiber, Vitamin C

In a large population-based case-control study, the highest risk levels were found in the presence of a low fiber/vegetable intake and a high beef intake (Kune et al 1987a). Similarly, in a Greek study there was an eightfold difference between a high meat/low vegetable versus a low meat/high vegetable intake (Manoussos et al 1983). Furthermore, in the Melbourne study, the highest risk levels were found in relation to a low dietary vitamin C and a high beef consumption, and similarly in the US Nurses' Study low fruit-fiber intake added to the risk, and this effect was partly dependent on meat consumption (Kune et al 1987a; Willett et al 1990). The relationship between vitamin C and nitrosamine metabolism, and the relationship between meat intake, nitrosamines and colorectal cancer risk has already been discussed, and this may be one of the keys for the explanation of these effects between meat/beef, dietary fiber and vitamin C containing foods.

Folate, Methionine and Alcohol Consumption

High alcohol and low folate consumption has been associated with a particularly high risk of colon cancer in the US Health Professionals' Follow-up Study; however, those with a high folate or methionine intake were protected from the alcohol risk (Giovannucci et al 1995b). Similar interrelationships were noted in that study for colorectal adenomas (Giovannucci et al 1993).

Dietary Habits of Smokers

Smokers as a group have lower intakes of fruit, vegetables and the corresponding nutrients of fiber, vitamin C and beta-carotene, and they have a higher consumption of fats than non-smokers, though the differences, while statistically significant, have been relatively small (Subar et al 1990; Cade and Margetts 1991; Subar and Harlan 1993). Nevertheless, as discussed in Chapter 8, several studies found statistically significant associations between smoking and adenomas and smoking and colorectal cancer even after statistical corrections were made for dietary factors.

ATTRIBUTABLE RISK FOR DIET IN COLORECTAL CANCER

The calculation of attributable risk of a particular etiologic factor, by whatever method used, is based on several assumptions, so that any figure arrived at in a particular population is by necessity an oversimplification. Thus, if several dietary factors have been determined to be relevant, in most calculations equal weighting is given to each dietary factor, yet this may not be realistic. For example, the risk associated with a low plant food diet may be more important than that associated with a high fat/meat diet. Furthermore, the dichotomization of dietary risk factors is made in an arbitrary manner, such as at a median score, and this appears to be a further oversimplification of a complex situation. For example, in the Melbourne Colorectal Cancer Study, 11 dietary risk factors were identified and if the risk score was dichotomized at 5 or more of these risk factors, then the attributable risk for diet was 46%, but if the division was made at 4 or more factors, then the attributable risk for diet rose to 68% (Kune et al 1992b).

Estimates of attributable risk of diet have been made quasi intuitively by epidemiologists, with estimates ranging from 70% to 90% (Doll and Peto 1981; Wahrendorf 1987). In the Melbourne Colorectal Cancer Study in which equal weighting was given to each of 11 dietary risk factors and when dichotomization was made at a risk score of 5 or more of the 11 dietary risk factors found in the study, the risk attributable to previous diet was 46% (Kune et al 1992). Review of available data on attributable risk indicates that in so-called Western countries, the risk attributable to previous diet in colorectal cancer is likely to be in the vicinity of 50%. The likely effects of large-scale dietary modifications in developed Western countries is discussed in more detail in Chapter 18 dealing with the primary prevention of colorectal cancer.

COLORECTAL CANCER IN SPOUSES

If the dietary cause of colorectal cancer is as important as the evidence indicates, and if it is assumed that married couples eat a similar diet, and if adult life diet determines colorectal cancer risk, then the spouses of patients with colorectal cancer are also likely to be a high-risk group. In none of the 3 studies which have examined this effect—one being the case-control arm of the Melbourne Colorectal Cancer Study, the second a follow-up study of large bowel cancer in married couples in Sweden, and the third, a study in Denmark—was the risk of colorectal cancer increased among spouses of patients with this cancer (Jensen et al 1980; Kune et al 1987c; Mellemgaard et al 1989).

The assumption that couples have a similar diet is largely intuitive. The evidence for this assumption is a non-quantitative frequency questionnaire for only 11 food items, which showed reasonably good correspondence for most foods eaten by couples who in fact were not cancer sufferers, and for foods eaten away from home (Kolonel and Lee 1981). Neither the Melbourne study nor the

Swedish or Danish studies have data on the dietary habits of couples, of whom one has colorectal cancer.

It is unimaginable that diet is not an etiologic factor in colorectal neoplasia. There may be several explanations why spouses of those with colorectal cancer have not been found to be at an increased risk. It is possible that in couples in which one person develops colorectal cancer, that person's partner has a different dietary habit, illustrating the nursery rhyme "*Jack Sprat could eat no fat, his wife could eat no lean ...*". Another explanation may be that dietary factors are important early in the process of colorectal neoplasia, that is, at a time when colorectal adenomas begin to form, or early in adult life at a time when dietary habits were different from those in married life, and so far a careful study of this factor has not been made. Finally, indirect studies such as the 3 spouse studies described above, are unlikely to be sensitive enough to detect differences due to diet.

FUTURE RESEARCH

There is an important need for several dietary studies to be performed in relation to colorectal cancer etiology. The endless number of largely repetitive case-control studies should cease now, as these are unlikely to produce any further useful data. It is also necessary to focus on cohort studies with an emphasis on quantitative dietary estimates, although the problem here is the enormous cost involved. Several studies could clarify the understanding of the dietary causes of colorectal cancer. At what stage in colorectal neoplasia are dietary factors important? Are they important early during the period of adenoma formation, or later when an adenoma becomes a carcinoma, or throughout the period of colorectal neoplasia? For example, Kinlen in 1982 found no decrease in colorectal cancer mortality among nuns who reduced their meat eating totally or significantly in adult life only. How much is too much or too little as a dietary risk or protective factor in order to make a difference in colorectal cancer etiology? Not only at what stage, but for how long does a particular dietary factor need to be in operation before it becomes a risk? If dietary fat is a causal factor, is it its energy content which matters? What type of fat is important? Is it saturated animal fat? Is fat of vegetable origin protective or does it have a null effect? Is fat of fish origin a protection? The important question with respect to dietary fiber is whether it is the fiber itself which is important, or fiber-rich foods which contain substances which are protective over and above their fiber content, or as seems most likely, is it both the fiber itself and the compounds in vegetables, fruits and cereals which are protective? Are there site-specific and gender-specific effects in the dietary etiology of colorectal cancer? Finally, interrelationship studies of various foods in modifying dietary risk are necessary. This should include research on how food is cooked, such as the effect of boiling, grilling, broiling or frying.

CONCLUSIONS

The principal conclusion of the dietary data is that the previous diet of those who develop colorectal cancer is very different from that of the general population in which these cancers occur. Emerging data indicate that adenomas, the major precursor of colorectal cancer, have almost identical dietary risk and protective associations to colorectal cancer. Most dietary factors are therefore likely to be important early in the process of colorectal neoplasia. The principal components of the dietary etiology of colorectal cancer have been reasonably firmly established, although the emphasis and the relative importance of the various diet factors is being constantly revised and modified as new data emerge.

There are three major dietary hypotheses, put in a simplified "package" form as the "meat/fat/energy/fried/grilled food hypothesis", the "fiber/starch" hypothesis, and the "vegetable/fruit/cereal/phytochemical" hypothesis. These major hypotheses are not mutually exclusive, and can live together and are consistent with current physiologic explanations of mechanisms of action.

Broadly speaking, foods of plant origin are the most important protective factors in the dietary etiology of colorectal cancer. A high vegetable consumption is probably the main protective factor for colorectal cancer. All vegetables are important, particularly but not exclusively cruciferous vegetables. The only vegetables for which an effect has not been consistently found are potatoes and beans. Carotene-containing foods appear to have a protective effect early in the process of colorectal neoplasia. Fruits of all types are next in importance and these probably operate, at least in part, through their vitamin C content, whilst cereals at present appear of least importance as protective foods of plant origin. The evidence that dietary fiber is an important protective factor is strong, although up to the present time it is not known to what extent it is the dietary fiber itself, and to what extent it is due to compounds present in fiber-rich foods which are the sources of this protection against colorectal cancer. The emerging view is that fiber is protective in part because of its fermentation in the colon, and in part because of changes in the physical aspects of feces, while vegetables and to a lesser extent, fruits and cereals are protective because they contain various "anti-carcinogenic" compounds, so that these foods are independently protective, and for different reasons than fiber. A low intake of calcium-containing foods and a low intake or exposure to vitamin D also appear to be risk factors for colorectal cancer, and a modest protective effect of a high calcium and vitamin D intake or vitamin D exposure has been consistently demonstrated.

As a broad generalization, foods of animal origin are risk factors. Meat, particularly red meat, has been consistently found to be a risk for colorectal cancer. The regular consumption of heavily fried and grilled meat and fat appears to be an added risk, especially for those who are fast acetylators, a situation which is under genetic control, adding a hereditary link to the dietary

etiology. There is some evidence that fish consumption is protective. The fat hypothesis is losing some ground in its importance as an etiologic factor for colorectal cancer, and an emerging view is that it is the energy content of fat (and possibly also of protein and carbohydrates) rather than the nutrients themselves which pose the main risk with fat. However, fats of animal origin probably are an independent risk over and above their energy content, while fats of vegetable origin, especially if unsaturated, may have a protective effect, as does fat of fish origin. The animal fat hypothesis should not be abandoned, as there is sound laboratory and experimental evidence which supports it. A high energy consumption, from whatever source, is emerging as an important independent risk for both colorectal adenomas and colorectal cancer. Other dietary risk factors appear to be a high salt intake, natural or cooked sugar, and a high meal frequency.

Further research into the dietary etiology of colorectal cancer should include studies which examine the time frame of exposure for dietary risk factors. The duration of the exposures and the minimum and maximum levels of exposure which would result in a measurable increase or decrease in risk are also important future research projects, as are more detailed studies of dietary interrelationships. The current evidence is that most, if not all, dietary factors operate in the early part of the process of colorectal neoplasia, at the time of preneoplastic changes, and also through to adenoma development, and also later, as the cells change to a carcinoma cell type.

Diet appears to be the most important single etiologic factor for colorectal cancer, and a conservative estimate is that the risk attributable to diet in Western societies is about 50%.

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Data Sources for Table 6.2

This table was compiled from the following studies:

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7

ALCOHOL CONSUMPTION

Stocks in 1957 suggested in the Annual Report of the British Empire Cancer Campaign that alcohol consumption may be a causative factor for colorectal cancer (Stocks 1957). Numerous studies followed, and at the time of writing, 93 studies in humans have examined the relationship between previous alcohol consumption, colorectal adenomas and colorectal cancer. During the last decade a few modest experimental studies have also examined the effect of alcohol on chemically induced colorectal carcinogenesis in rat models. Several hypotheses have been proposed as to how alcohol might operate to cause colorectal tumors, at both a cellular and a pathophysiologic level.

EPIDEMIOLOGIC STUDIES

COLORECTAL ADENOMAS

Although Diamond in 1952 reported on rectosigmoid adenomas in relation to alcohol consumption in almost 6000 patients examined by rigid sigmoidoscopy in a mental hospital, studies performed specifically to test this association were first reported in 1988 by Stemmerman and co-workers from Hawaii. In the 8 years since that report a further 24 studies (3 cohort and 21 case-control) have been published, and the findings of these 25 studies are summarized in Tables 7.1 and 7.2.

In 16 (64%) of the 25 studies, the risk of colorectal adenomas in association with alcohol consumption was raised by 50% or more. However, this included studies in which the elevation was confined to certain subgroups such as men or to particular types of alcohol, such as beer. A statistically significant risk elevation with a p value of 0.05 or less was present in 14 of the positive studies

(88%). The risk elevations were mostly not high, usually between 2 and 3, with a range from a low of 1.7 to the highest of 7.1, and this last was an outlying figure compared to the others. A positive dose-response effect was reported in 9 of 12 studies which examined the quantitative effect of alcohol on adenoma risk. Relative risks among women were generally lower than among men. There were insufficient data to assess site specific risk differences. Only some studies were able to correct for confounding factors; however, risk elevations were still present in all studies which corrected for family history of colorectal tumors, smoking, physical activity and the previous use of aspirin and non-steroidal anti-inflammatories (Table 7.1). A joint effect between alcohol consumption and smoking was reported in two studies (Cope et al 1991; Martinez et al 1995), and this is of interest because synergy has been described between smoking and alcohol consumption in other cancers, notably in cancers of the esophagus, larynx and oral cavity. In an interesting study from Burgundy, France, using population-based controls, alcohol consumption was associated with risk in large adenomas only, and not with either small adenomas (less than 1 cm) or with colorectal cancer, suggesting the stage of the adenoma–carcinoma sequence when alcohol consumption may be of particular importance (Boutron et al 1995a).

Table 7.1 Alcohol consumption and colorectal adenomas. Summary data of 25 studies (3 cohort and 22 case-control studies)

Number of studies	Risk elevation 50% or higher (%)	Result statistically significant $p \leq 0.05$ (%)	Positive dose-response effect (%)	Risk elevation after correction for confounding factors
25	16/25 (64%)	14/16 (88%)	9/12 (75%)	Family history of colorectal tumors 3/3 Diet factors 5/5 Smoking 2/2 Physical activity 1/1 NSAID and aspirin use 1/1

Data sources

This table was compiled from the following studies:
Diamond 1952; Stemmerman et al 1988; Kikendall et al 1989; Kato et al 1990; Kono et al 1990; Cope et al 1991; Kune et al 1991; Logan et al 1991; Riboli et al 1991; Honjo et al 1992; Benito et al 1993; Boutron and Faivre 1993; Giovannucci et al 1993; Lee et al 1993; Nelson et al 1993; Olsen and Kronborg 1993; Sandler et al 1993; Ikuma et al 1994; Jacobson et al 1994; Nelson et al 1994; Stockbrügger et al 1994; Rozen et al 1994; Boutron et al 1995a, 1995b; Martinez et al 1995.

Cohort Studies

All 3 cohort studies have shown a statistically significant positive association between previous alcohol consumption and colorectal adenomas. In the cohort study from Hawaii and in the combined US Nurses' Health Study and Health Professionals' Follow-up Study cohorts, there was a statistically significant increased risk in relation to previous alcohol consumption, and these 3 cohorts also reported a positive dose-response relationship (Stemmermann et al 1988; Giovannucci et al 1993). The Nurses' and the Health Professionals' cohorts were adjusted for dietary factors of fat, red meat, fiber and body mass index. The cohort studies did not report separately on different types of alcoholic beverage.

Case Control Studies

Of the 22 case-control studies, 13 showed a positive association between previous alcohol consumption and colorectal adenomas, statistically significant in 11, with a dose-response effect in 6 of 9 studies which examined this. In 4 of the 9 case-control studies in which an alcohol effect was not shown, hospital-based controls were used and these have been shown to be inappropriate for the examination of alcohol-related cancers, because of the high rate of alcohol consumption among hospitalized patients (Kune and Vitetta 1992).

Table 7.2 Risk of colorectal adenomas by alcohol type. Summary data of 22 case-control studies

Number of studies	Type of control used	Risk elevation 50% or higher (No. stat sig $p \leq 0.05$) Number examined effect			
		Alcohol type not specified	Beer	Wine	Spirits
22	Population or neighborhood 10 Hospital 12	8(5) 17	4(3) 4	0 3	2 5

Data sources

This table was compiled from the following studies:
Diamond 1952; Kikendall et al 1989; Kato et al 1990; Kono et al 1990; Cope et al 1991; Kune et al 1991; Logan et al 1991; Riboli et al 1991; Honjo et al 1992; Benito et al 1993; Boutron and Faivre 1993; Lee et al 1993; Nelson et al 1993; Olsen and Kronborg 1993; Sandler et al 1993; Ikuma et al 1994; Jacobson et al 1994; Nelson et al 1994; Stockbrügger et al 1994; Rozen et al 1994; Boutron et al 1995a, 199b; Martinez et al 1995.

Most of the case-control studies grouped all alcohol together without distinguishing between different alcoholic beverages (Table 7.2). However, all 4 studies which examined beer consumption separately found elevated risks and

these were statistically significant in 3 studies (Kikendall et al 1989; Kune et al 1991; Sandler et al 1993; Kono et al 1990). None of the 3 studies which examined wine consumption separately found elevated risks. However, 2 of 5 studies examining spirit consumption found risk elevations, in one for whisky, and in another for sake (Kono et al 1990; Honjo et al 1992).

Adenomas and Alcohol Consumption Summary

On present evidence, it appears very likely that alcohol consumption and particularly, but probably not exclusively, beer consumption is a contributory cause in the development of colorectal adenomas. Elevated risks, usually statistically significant, were reported in both cohort and case-control studies. The risk elevations were generally not high, most commonly between a twofold and threefold risk. Positive dose-response effects were noted in most studies which attempted a quantitative assessment of the effect of alcohol in adenoma development. Risk elevations persisted after correction for confounding factors in all studies which were able to correct for these. Thus, risk elevations persisted after correction for the important confounding factors of family history of colorectal tumors, diet factors, body mass index, smoking, and physical activity. On present evidence, it appears very likely that alcohol consumption and particularly beer consumption, is a contributory cause of colorectal adenomas.

COLORECTAL CANCER

Numerous major studies have examined the relationship between colorectal cancer and previous alcohol consumption using different methodologies, consisting of 7 correlational, 43 case-control and 18 cohort studies. These 68 studies are analyzed in detail below.

Correlational Studies

A significant association was found between alcohol consumption in the population studied and colorectal cancer incidence or mortality in 5 of the 7 correlational studies (Breslow and Enstrom 1974; Enstrom 1977; Knox 1977; Kono and Ikeda 1979; Potter et al 1982). Beer was significantly associated with the risk in all 5 positive studies, in 4 of which it held for rectal cancer only, and in one it held for colon cancer only. Wine or spirit consumption showed a positive association in only one of 5 studies in which these alcohol variables were measured. No association was found in 2 studies and in both there was probably insufficient diversity to find an effect (Bingham et al 1979; Hinds et al 1980). Correlational studies yield indirect evidence of association, since correlations that exist at the population level may not apply to individuals; nevertheless, the 5 positive studies provide a basis and a consistency for the more precise case-control and cohort studies.

Table 7.3 Alcohol consumption and colorectal cancer risk. Summary data of 61 studies

Type of study	No. of studies	Risk elevation 50% or higher (No. stat sig $p \leq 0.05$) Number examined effect				
		Risk elevation in whole study or in some major subgroup	No association in any part of study	Beer	Wine	Spirits
Cohort	18	14(9) 18	4 18	9(6) 13	1 10	1 9
Case-control	43	21(12) 43	22 43	12(9) 25	3(2) 20	3(1) 17
Total	61	35(21) 61	26 61	21(15) 38	4(2) 30	4(1) 26

Data sources

This table was compiled from the following studies:
Stocks et al 1957; Pernu et al 1960; Higginson 1966; Wynder and Shigematsu 1967; Wynder et al 1967; Bjelke 1974; Modan et al 1975; Williams and Horm 1977; Dales et al 1978; Graham et al 1978; Dean et al 1979; Jensen 1979; Tuyns et al 1982; Manoussos et al 1983; Miller et al 1983; Vobecky et al 1983; Ward et al 1983; Gordon and Kannel 1984; Pickle et al 1984; Pollack et al 1984; Berta et al 1985; Bristol et al 1985; Garland et al 1985; Kono et al 1985; Tajima and Tominaga 1985; Kabat et al 1986; Macquart-Moulin et al 1986; Potter and McMichael 1986; Kune et al 1987; Wu et al 1987; Klatsksy et al 1988; La Vecchia et al 1988; Tuyns et al 1988; Ferraroni et al 1989; Hirayama et al 1989; Jarebinsksi et al 1989; Peters et al 1989; Benito et al 1990; Carstensen et al 1990; De Verdier et al 1991; Choi and Kahyo 1991; Hu et al 1991; Riboli et al 1991; Barra et al 1992; Bidoli et al 1992; Iscovich et al 1992; Peters et al 1992; Hoshiyama et al 1993; Meyer and White 1993; Newcomb et al 1993; Centonze et al 1994; Gapstur et al 1994; Goldbohm et al 1994; Boutron et al 1995a, 1995b; Giovannucci et al 1995a, 1995b.

Case Control Studies

Of the 43 case-control studies only about half found a 50% or higher risk elevation in either the entire study or in some subgroups only of the particular study (Table 7.3). The risk elevations were usually of the order of twofold with a range of 1.5–3.5. Statistically significant effects were present in only 12 of 21 (57%) of the positive studies. A positive dose-response effect was reported in 7 of the 9 studies which examined risk levels in relation to degree of exposure to alcohol.

A null result was recorded in most hospital-based case-control studies in an extensive review (Kune and Vitetta 1992). Although this depends to some extent on the diagnostic categories used, hospital-based controls are in general

inappropriate for these studies because hospitalized patients are likely to have a high rate of alcohol consumption/alcohol-related illness, hence they are "overexposed" to alcohol, and this tends to produce a null effect (Holden 1987; Bell et al 1988; Wynder and Stellman 1992). When population-based or community-based controls are used, these controls better mirror population alcohol consumption practices, and when analyzed further, a positive association was present in 75% of these studies (Table 7.4).

Table 7.4 Alcohol consumption and colorectal cancer risk. Summary data from 16 case-control studies using population controls, with alcohol type and colorectal cancer site identified

Colorectal cancer site	No. of studies	Risk elevation 50% or higher (No. stat sig $p \leq 0.05$) No. of studies examined effect				
		Risk elevation in whole study or in subgroup	No association in any part of study	Beer	Wine	Spirits
Colon	14	10(7)/14	4/14	4(2)/11	2(2)/9	3(2)/9
Rectum	13	9(6)/13	4/13	6(5)/12	1(1)/10	1/10
Total	16	12(8)/16	4/16	7(5)/13	2(2)/10	3(2)/10

Data sources

This table was compiled from the following studies:
Vobecky et al 1983; Ward et al 1983; Kabat et al 1986; Potter et al 1986; Kune et al 1987; Tuyns et al 1988; Peters et al 1989; De Verdier et al 1990; Freudenheim et al 1990; Longnecker et al 1990; Iscovich et al 1992; Peters et al 1992; Hoshiyama et al 1993; Meyer and White 1993; Newcomb et al 1993; Centonze et al 1994.

The 16 studies which used population or community-based controls were analyzed further in relation to risk associated with cancer site and with the type of alcohol consumed (Table 7.4). Gender-specific effects were also analyzed in these 16 studies, but they are not tabulated. Overall, the proportion of studies which showed an elevated risk was similar for colon cancer when compared to rectal cancer, and similar for males and females. However, in general higher risk levels were present for rectal than for colon cancer and these risks were more often statistically significant for rectal cancer than for colon cancer. Also, in general, the risk levels were higher and more often statistically significant for men than for women. With respect to differences in risk according to cancer site,

in a large population-based site-specific case-control study conducted in Japan, an increasing gradient of statistically significant risk elevation was reported from the proximal colon to the rectum for beer drinkers, with a relative risk of 1.5 for proximal colon, 1.7 for distal colon and 1.9 for rectal cancer (Kato et al 1990).

Beer was the most common at-risk alcoholic beverage, and particularly for rectal cancer (Table 7.4). Risk was elevated for wine consumption in 2 and for spirits in 3 studies. Interestingly, in 4 studies spirit consumption was less common among colorectal cancer cases than among controls, and the reason for this is unclear (Modan et al 1985; Tajima and Tominaga 1985; Kune et al 1987; Goldbohm et al 1984).

Cohort Studies

An analysis of the 18 cohort studies that examined the association between previous alcohol consumption and colorectal cancer showed effects very similar to those just described for case-control studies. Overall, a larger proportion of cohort studies showed a positive association, with risk elevations of 50% or more, than did case-control studies (Table 7.3). Thus, a positive association was reported in 14 of 18 (78%) of the cohort studies and statistically significant effects were present in 9 in some aspect or in the whole of the study (Table 7.3). A positive dose-response effect was found in 4 of the 5 studies which made a quantitative assessment of risk in relation to alcohol exposure. In 4 of the 17 cohort studies, alcohol consumption was not associated with the risk of colorectal cancer and it needs to be noted that in 3 of these, a limited assessment of alcohol was made, in one only beer consumption was measured and only on the brewery premises (Jensen 1979), in one only sake consumption was recorded (Kono et al 1985), and in one only the total number of alcohol drinks was investigated (Gordon and Kannell 1984). Risk levels for males were somewhat higher than for females and were more often statistically significant for males than for females. In all of the gender-specific studies, whether they be case-control or cohort studies, exposure rates to alcohol for females was much lower than for males, so that the statistical power for analysis was much weaker for women.

Those cohort studies which examined the colon and rectum separately in relation to the alcoholic beverages of beer, wine and spirits, showed results which were very similar to the population-based case-control studies in the summary data (Table 7.5). Thus, positive effects were reported more often for rectal cancer than for colon cancer. The most important at-risk alcoholic beverage was again beer, and all of the statistically significant positive effects were noted for beer consumption only (Table 7.5). An elevated risk for wine consumption was present in 2, and for spirits in 2 studies also, and none of these elevations were statistically significant (Table 7.5).

Table 7.5 Alcohol consumption and colorectal cancer risk. Summary data from 15 cohort studies, with alcohol type and colorectal cancer site identified

Colorectal cancer site	No. of studies	Risk elevation 50% or higher (No. stat sig $p \leq 0.05$) No. of studies examined effect				
		Risk elevation in whole study or in subgroup	No association in any part of study	Beer	Wine	Spirits
Colon	15	7(5)/15	2/15	3(2)/13	1/9	1/9
Rectum	14	10(9)/14	1/14	8(6)/13	2/9	2/9
Total	15	13(9)/15	2/15	9(6)/13	2/10	2/10

Data sources

This table compiled from the following studies:
Bjelke et al 1974; Williams and Horm 1977; Dean et al 1979; Jensen et al 79; Pollack et al 1984; Wu et al 1987; Klatsky et al 1988; Hirayama et al 1989; Carstensen et al 1990; Stemmerman et al 1990; Gapstur et al 1994; Goldbohm et al 1994; Giovannucci et al 1995a, 1995b.

Beer, Wine, Spirits

It has already been noted that beer is the main at-risk alcoholic beverage in colorectal cancer (Tables 7.3, 7.4, 7.5) and also in colorectal adenomas (Table 7.2). Wine was uncommonly a risk for colorectal cancer while the data are inconsistent on spirit consumption with 4 of 26 studies finding an elevated risk and 4 finding a lowered risk.

In a large case-control study of women, a statistically significant elevation of risk was noted for alcohol consumption, especially for beer and particularly for rectal cancer; however, an inverse association was noted for wine consumption (Newcomb et al 1993). In a study of post-menopausal women, a statistically significant inverse association was found for distal colon cancer and an inverse non-significant association for rectal cancer for wine consumption only (Gapstur et al 1994). Although this study identified only a small number of consumers, a protective effect was found for left colon and rectal cancer at quite low levels of alcohol consumption (median 4.0 g of ethanol per day), and for wine only. An inverse association for rectal cancer in women wine drinkers consuming 2 or more glasses of wine per day was also present in the Melbourne Colorectal

Cancer Study (Kune et al 1987a). Although these 3 studies might at first suggest there is a gender difference, particularly as women are known to metabolize alcohol in a quantitatively different manner to men, it is speculated by the author that at least part of the protective effect of wine consumption in these 3 studies was derived from the vitamin C often used as an antioxidant, especially in white wine, and that women wine drinkers are possibly more likely to drink white than red wine, although data on this were not available in any of the studies.

Extent and Duration of Alcohol Consumption

Drink not the third glasse
Which thou canst tame
When once it is within thee.

George Herbert, 1593–1633

Some case-control and cohort studies attempted to quantify the level of regular alcohol consumption which is associated with statistically significant elevations of risk for colorectal cancer.

Level of Daily Alcohol Consumption

Precise comparative quantification is difficult, because the alcoholic content of beverages is variable in different populations and different countries, and because there is no easy way to define a "standard" drink. For the purposes of this description, a "standard" drink will be assumed to contain 10 g of ethanol and will be equivalent to a glass of beer, glass of wine or a nip of spirits.

Among the prospective studies 3 or more alcohol drinks were associated with risk elevations for both rectal and colon cancer in both men and women in an American study (Klatsky et al 1988). Similar alcohol consumption caused an elevated risk for rectal cancer, when all alcoholic consumption was considered together, for both males and females, in a study from the Netherlands (Goldbohm et al 1994). In the US Health Professionals' Follow-up Study, as well as in the Nurses' Health Study, more than 2 alcoholic drinks per day were responsible for a statistically significant risk elevation for colon cancer for men when all alcoholic drinks were considered together (Giovannucci et al 1995a, 1995b).

Among population-based case-control studies in women, a statistically significant risk elevation was noted for all types of alcohol combined at relatively low levels of consumption for both rectal and colon cancer, of the order of 1–2 or more alcoholic drinks per day (Newcomb et al 1993). In other case-control studies that examined men and women together, 3 or more alcoholic drinks per day showed statistically significant elevations of risk for colon cancer in 2 studies (Peters et al 1992; Meyer and White 1993). In a case-control study involving men only, 4 glasses of beer were responsible for a statistically significant risk elevation for rectal cancer (Kabat et al 1986). In an Australian

population-based case-control study, 2 or more glasses of beer per day were associated with a statistically significant risk elevation for rectal cancer (Kune et al 1987a). Thus, the regular consumption of about 3 alcoholic drinks per day appears to be the level that can be responsible for an elevated risk for colorectal cancer. This level of alcohol consumption may be 2 drinks per day for women.

Duration of Alcohol Consumption

Precise data on the duration of regular alcohol consumption which would be associated with an elevated risk for colorectal cancer is not available. However, in the extensive review of Kune and Vitetta in 1992 in which, among other statistics, data were obtained on the length of alcohol intake measured in 31 case-control studies, it was found that risk elevations were present only in the studies which measured alcohol consumption for 20 years or longer. Moreover, in the Melbourne Colorectal Cancer Study the highest risks for rectal cancer were noted among adult lifelong beer drinkers (Kune et al 1987a). When these data are added to the evidence described previously regarding the relationship between the major precursor lesion of colorectal cancer, namely colorectal adenomas, and alcohol consumption, one cannot escape the conclusion that regular alcohol consumption has its effect in relation to colorectal cancer risk when it is pursued for many years, and probably for two or more decades of adult life.

Alcohol and Diet Interrelationships

As dietary factors are causally important for colorectal tumors, statistical adjustment for diet factors in any study of this association is important. Statistical correction for dietary confounding was made to varying degrees in 3 case-control studies, and in all, an elevated alcohol risk was present after adjustment, suggesting that alcohol has an independent effect (Kune et al 1987a; Freudenheim et al 1990; Riboli et al 1991). In the Melbourne study, which had an accurate quantitative estimate of all foods consumed, a correction was made for all diet risks using a risk model which included vegetables, fiber, milk, fish, vitamin C, meat and fat (Kune et al 1987a, 1987b). Corrections for energy were not made in any of these studies; however, in the one study in which alcohol risk was expressed as a percentage of total energy intake, no association was noted (Olsen and Kronborg 1993).

In the US Health Professionals' Follow-up Study, statistically significant elevations of risk were found for colon cancer in men for a consumption of 2 or more alcoholic drinks per day after adjustment was made for fat, red meat, fiber intake, body mass index, multivitamin use, physical activity and smoking (Giovannucci et al 1995a). In the US Health Professionals' Follow-up Study, particularly high risks were present among alcohol consumers with a low folate diet (found mainly in vegetables and fruits), and in that cohort, as well as in the Nurses' Health Study cohort, alcohol and particularly beer consumers with a low methionine diet (found mainly in red meat, poultry, dairy foods and fish) also

had high risk levels, but in the presence of a high folate-methionine diet, alcohol consumers did not have elevated risks (Giovannucci et al 1995a, 1995b). Similar results were noted by this group previously for colorectal adenomas (Giovannucci et al 1993). In the Melbourne Colorectal Cancer Study a model of dietary risk was developed, which included a low fiber/vegetable, low dietary vitamin C, low fish, low milk and high beef and fat consumption, and this model was significantly associated with colorectal cancer risk (Kune et al 1987b). Alcohol risks (essentially for beer and rectal cancer) remained elevated when adjusted for this dietary risk model (Kune et al 1987a). However, when individual diet risk factors were divided into "low" and "high" consumption levels, and their risk assessed in relation to beer intake, the beer-associated risks were unchanged except in relation to dietary vitamin C consumption. In those who had a high consumption of vitamin C-containing foods, beer drinking was not associated with an elevated risk for rectal cancer (Kune et al 1987a). Since many antineoplastic compounds have now been found in vegetables and fruits (Chapter 6), it is not known whether it is folate, methionine or vitamin C, or all of these compounds, and perhaps others as yet unidentified, that are specifically protective for alcohol consumers. However, it seems clear that a diet high in vegetables and fruit will have a protective effect for colorectal adenomas and colorectal cancer, even among regular alcohol and beer consumers.

Colorectal Cancer and Alcohol Consumption Summary

The epidemiologic data taken together suggest that alcohol consumption and in particular beer, is a two-to-threefold risk for colorectal cancer. Risk levels in general are somewhat higher for rectal cancer than colon cancer, and higher for men than for women. Some inconsistent results in a few studies, namely a protective effects of spirits, and of wine for women, need to be explained. For men, 3 alcoholic drinks per day and perhaps 2 drinks for women, pursued over 2 or more decades in adult life, is responsible for a risk elevation. Among regular alcohol consumers, a diet high in vegetables and fruit (possibly because of their folate and vitamin C content) and high in methionine-containing foods, appears to reverse the alcohol risk.

COLORECTAL CARCINOGENESIS IN RAT MODELS

In 1928 Krebs found that repeated instillation of ethanol in the rectum of the mouse induced rectal adenocarcinoma. In the last decade, 8 rat animal studies examined the relationship between alcohol administration on established models of chemically induced colorectal tumor formation using dimethylhydrazine, azoxymethane or acetoxymethyl nitrosamine. The results show an augmentation of tumor incidence in 5 of the 8 studies, with a positive association in 4 studies, and a distal shift of tumor distribution along the large bowel in one study (Seitz et al 1984; Howarth and Pihl 1985; Garzon et al 1986; Hamilton et al 1987;

Niwa et al 1991). No augmentation was noted in 2 studies (Nelson and Samelson 1985; McGarrity et al 1986) and inhibition by alcohol was present in one study (Hamilton et al 1988). Of interest is that when the alcohol was administered locally or intraperitoneally, a positive effect was also reported (Garzon et al 1986; Niwa et al 1991).

These animal studies were all acute studies with short study periods ranging from 20–38 weeks, and with small study numbers in 6 of the 8 studies. This is in marked contrast to the human studies in which numbers are large and alcohol consumption extends over many years, usually the entire adult life of the respondent. Also, in only 3 studies was beer employed as the agent (Howarth and Pihl 1985; Nelson and Samelson 1985; Hamilton et al 1987). It was noted earlier that beer was found to be the most important at-risk alcohol beverage in the human studies. Moreover, there are also difficulties biologically equating chemically induced large bowel cancer in rats with the known biology of colorectal cancer in humans, because of species differences in anatomy and histopathology of the large bowel, and because of differences in the nature of the tumors produced experimentally as well as in their biologic behavior, when compared with colorectal cancer in humans (Hamilton 1984; Ahnen 1985). These experimental studies add some support to the human studies; however, they do not greatly enhance the understanding of the etiology of colorectal neoplasia in relation to alcohol consumption.

MECHANISMS OF ALCOHOL EFFECT IN COLORECTAL NEOPLASIA

With the exception of the direct stimulation of the colorectal mucosa by alcohol, causing observable morphologic change, the possible mechanisms of the alcohol effect in colorectal neoplasia are poorly understood.

CAUSAL EFFECTS

Several mechanisms of action have been suggested, and these can be non-specific effects which may apply to malignant tumors in general, and effects which are specific to colorectal cancer, that is, a direct carcinogenic effect.

Changes in Bile Composition

Alcohol use is associated with changes in the metabolism of bile acid. There is an increased liver bile acid excretion, an increased enterohepatic recirculation of bile, and an increased production of secondary bile acids in the large bowel (Nestel et al 1976; Thornton et al 1983). As secondary bile acids in the large bowel appear to be involved in the mechanism of colorectal neoplasia, changes in bile composition in response to alcohol consumption may be one of the important indirect ways in which alcohol promotes colorectal tumors.

Hypomethylation of DNA

Hypomethylation of DNA has a role in abnormal gene expression and appears to be an early event in neoplastic change, including colorectal neoplasia (Feinberg and Vogelstein 1983; Geolz et al 1985). Low dietary folate and methionine consumption are important causes of hypomethylation, and alcohol is a methyl group antagonist, interfering with folate/methionine metabolism, and this appears to be the mechanism whereby it contributes to hypomethylation (Finkelstein et al 1974; Barak et al 1987; Garro et al 1991).

The dietary and alcohol effects of hypomethylation of DNA have been most studied in the rodent model of hepatocellular carcinoma. It appears that the hypomethylation effects are probably reversible in the short term. However in the longer term, such as with chronic alcohol consumption, irreversible morphologic changes occur, including the development of benign and malignant tumors (Porta et al 1985; Pascale et al 1991; Naveau et al 1995). These experimental studies further underline the epidemiologic data that the alcohol effect in colorectal neoplasia commences early, and also that long-term exposure to alcohol is necessary.

Nitrosamine Metabolism

In the late 1970s, nitrosamines, including N-nitrosodimethylamine (NDMA), were found to be carcinogenic for experimental animals (Walker et al 1979; Scanlan 1983). Since nitrosamines in beer and in malted spirits were related to part of the malting process, changes in the process itself after the disclosure of the carcinogenic action of nitrosamines, have resulted in reducing the content of volatile nitrosamines in beer and malted liquor to very low levels (Scanlan and Barbour 1991). It is of relevance that most of the studies referred to in this chapter relate to long-term consumption of alcoholic beverages, mostly to periods before changes were made in the malting processes. Apart from the nitrosamine content of beer and malted spirits, which is now minimal, animal experiments indicate that ethanol administration prevents the clearance of nitrosamines by the liver and this would expose various organs and tissues of the body to the carcinogenic effects of nitrosamines (Swann et al 1984).

Important indirect data on the nitrosamine effect in relation to beer consumption were obtained in the Melbourne Colorectal Cancer Study (Kune et al 1987a, 1987b). Data derived from that study show that a high consumption of vitamin C-containing foods is a protective factor and that beer consumption is a risk factor, particularly for rectal cancer (Kune et al 1987a, 1987b). In that study however, the beer-associated risk for rectal cancer was not elevated when dietary vitamin C was also high. Since vitamin C blocks the endogenous synthesis of N-nitrosocarcinogens, this finding may corroborate the postulated role of nitrosamines in beer as a risk factor for colorectal tumor formation.

Direct Carcinogenic Effects of Alcoholic Beverages

Substances which are poorly absorbed in various alcoholic beverages, particularly in beer and malted liquor, may act as a direct carcinogen on the bowel mucosa, and numerous chemical additives and contaminants have been identified in beverages such as beer and malted liquor. The possible carcinogenic action of beer and malted liquor may depend on the method of production such as roasting, nitrosamine content and asbestos filtration; however, specific studies on these aspects are so far not available. It has been suggested in the past that asbestos used in beer filtration results in the ingestion of asbestos fibers, and this may be carcinogenic to the gastrointestinal mucosa, including the mucosa of the large bowel (Biles and Emerson 1968). However, asbestos is no longer used for beer filtration. Moreover, the evidence that asbestos from other exposure sources is a causative factor for colorectal cancer is weak (Chapter 13). The chronic administration of alcohol in rat models of chemically induced colon cancer has been shown to enhance the intestinal activation of procarcinogens and mutagens; however, it is not known whether this is due to a direct effect on the mucosa or due to changes in liver enzymes (Swann et al 1984; Soon et al 1986).

Depression of Immunity

A general immunodepressive effect of alcohol has been described (Dunne 1989). Immune depression may be a factor in the enhancement of tumor growth; however, no data are available on immune depression, alcohol consumption and colorectal cancer.

PROLIFERATION OF COLORECTAL MUCOSA

MORPHOLOGIC EFFECTS OF ALCOHOL

In chronic alcoholics, with or without cirrhosis, as well as in rat models, alcohol increases rectal and colonic mucosal cell proliferation and regeneration (Simanowski et al 1986; Naveau et al 1992, 1995). A high consumption of alcohol in humans who had rectal biopsies showed several histologic and ultrastructural changes in the rectal mucosa, suggestive of a stimulatory action (Brozinsky 1978; Seitz et al 1990; Simanowski et al 1991). Moreover, hyperplastic polyps of the large bowel, regarded as non-neoplastic proliferative lesions and which are markers for colorectal tumors, have been shown to be significantly related to alcohol consumption of over 30 g of alcohol per day (Kearney et al 1995). An increase in the number and rate of cell division has been postulated to be an important mechanism for carcinogenesis in general (Preston-Martin et al 1990). It seems that this stimulatory action of alcohol commences early in the process of colorectal neoplasia and remains in operation while the alcohol habit continues.

PROTECTIVE EFFECTS

Alcohol consumption in moderation (2–3 drinks per day), has been linked with prolongation of life and a degree of protection from various illnesses, in particular cardiovascular disease, for both men and women (Fuchs et al 1995; Duffy 1995). In relation to colorectal cancer, alcohol consumption has been shown to decrease intestinal transit time, especially in men (Probert et al 1995). As intestinal transit time is positively associated with colon cancer risk, a decrease in transit time may have a protective effect (Cummings 1992). This finding is in keeping with the clinical observation that beer drinkers often have a few loose bowel motions the day after drinking.

The addition of vitamin C or its derivatives as an antioxidant in white wine may be another protective factor in colorectal neoplasia, and may explain the protective effect for female wine drinkers in 3 studies described earlier in this chapter. Also, the moderate consumption of spirits had a protective effect in 4 studies, and the explanation for this is not known. Beneficial effects for beer drinking have not been recorded in relation to colorectal tumors.

ALCOHOL AS A CAUSE OF COLORECTAL TUMORS

The evidence from over 90 epidemiologic studies indicates with moderate to high consistency that alcohol is a risk for both colorectal adenomas and colorectal cancer. The epidemiologic data satisfy to varying degrees the criteria of causality (Chapter 1), that is, there is both internal consistency in the studies as well as external consistency in numerous studies from various parts of the world, of differing design, including correlational studies, case-control studies and cohort studies. Moreover, the risk levels are statistically significant in many of these studies and in a number of these studies important confounding factors have been corrected for. Furthermore, there is a body of experimental data in chemically induced large bowel cancer showing augmentation of colonic neoplasia with alcohol consumption. Finally, there are several biologically plausible hypotheses for mechanisms of alcohol action in colorectal neoplasia, and the morphologic changes with exposure to alcohol also point to a cause-and-effect relationship for alcohol in the development of colorectal tumors.

The risk levels are not high, of the order of two to threefold. The risk is higher for men than for women and higher and more consistently found for rectal cancer than for colon cancer. Beer is the alcohol beverage which poses the most important risk. Spirits appear to be a much less important risk, whilst wine seems to pose the least risk in the development of colorectal tumors. The minimum dose appears to be 2–3 alcoholic drinks per day and this may be less for women. The duration of the alcohol exposure needs to occur over several years, and probably for two decades or longer.

In spite of reasonable consistency in the epidemiologic and carcinogenic studies showing a positive relationship between alcohol consumption and colorectal tumors, some caution needs to be exercised in the interpretation of these data as the alcohol effect is generally not strong, some anomalous results such as the protective effect of wine for women, and possibly of spirits for men and women, need explanation. A reasonable overview may be that as alcohol exerts a largely indirect effect on colorectal neoplasia, the effect is caused by widely different factors, so that it may be different in different populations due to dietary interrelationships, such as a varying dietary vitamin C, folate and methionine intake. Also, the mechanism for the alcohol effect may be different during the long period of alcohol action which seems to be necessary (such as hypomethylation early, bile acid and nitrosamine damage throughout, and immune depression late in the process), and may well explain the weak effects and the inconsistencies. However, further research on these areas of doubt is required. Future research also needs to better define both the time-frame and the extent of exposure to alcohol which leads to a risk. Research is also necessary to establish the specific compounds in beer, as currently manufactured, which pose the risk.

The overall conclusion on current evidence is that regular adult life-time alcohol consumption is a component cause of colorectal tumors, both adenomas and cancer, in men and women, for rectal cancer and probably also for colon cancer. Beer is the alcoholic beverage which poses the most important risk in colorectal neoplasia.

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8

SMOKING

Smoke, smoke, smoke that cigarette
Puff, puff, puff and if you puff yourself to death
Tell St Peter at the Golden Gate
That you just hate to make him wait
But you just gotta have another cigarette.

Smoke Smoke Smoke That Cigarette
by Merle Davis and Tex Williams
MCA Records, with permission

The evidence for a link between smoking and colorectal tumors is recent. The development of this hypothesis is historically interesting, as it illustrates the importance of several apparently unconnected scientific observations which can now be unified and suggest that smoking is an important component cause of colorectal tumors, and that it operates early in the process of neoplasia. Although for some time smoking and tobacco use has been known to be an important cause of cancers of the lung, oral cavity, pharynx, larynx, esophagus, pancreas, bladder and others, the concept that smoking may also be a component cause of colorectal tumors has emerged only in the past few years. Smoking is a multi-site carcinogen in humans, and has a unique role in cancer etiology. The most damning evidence of the smoking hazard is that 50% of all cancer deaths are attributable to smoking (McLaughlin et al 1995), and that half of all regular cigarette smokers will eventually die as a result of a smoking-related illness (Doll et al 1994).

EPIDEMIOLOGIC EVIDENCE

There has been great interest in the possible relationship between smoking and colorectal tumors, and altogether 78 studies have investigated this association.

COLORECTAL ADENOMAS

The first clue that there may be a link between colorectal adenomas and smoking was provided by a study from Norway reported in 1987 by Hoff and co-workers. Since then there has been an explosion of publications, and 8 years later up to the end of 1995 there have been 27 studies reported, 22 (81%) of which show a risk elevation which is 50% or higher (Table 8.1). Most were case-control studies; however, there were 4 cohort studies which included the 2 large, US cohorts, the Nurses' Health Study and the Health Professionals' Follow-up Study (Giovannuci et al 1994a, 1994b). The risk elevations were not gender specific in most studies; there were however gender differences in 8, usually with higher risk levels in men, and in one the risk was stronger for women (Hoff et al 1987; Kune et al 1992b; Boutron and Faivre 1993; Nelson et al 1993; Lee et al 1993; Ikuma et al 1994; Jacobson et al 1994; Boutron et al 1995). Most of the studies examined current cigarette smoking. Elevated risks were found among ex-smokers also (Martinez et al 1995).

Table 8.1 Smoking and colorectal adenomas. Summary data of 27 studies (23 case-control and 4 cohort).

Number of studies	Risk elevation 50% or higher (%)	Risk statistically significant $p \leq 0.05$ (%)	Positive dose-response effect (%)	Risk elevated after correction for confounding factors
27	22/27 (81%)	19/22 (86%)	9/10 (90%)	Family history of colorectal tumors 3/3 Diet factors 4/4 Body mass index 3/3 Alcohol 7/7 Physical activity 1/1

Data Sources

This table was compiled from the following studies:
Hoff et al 1987; Demers et al 1988; Stemmermann et al 1988; Kikendall et al 1989; Kato et al 1990; Kono et al 1990; Cope et al 1991; Logan et al 1991; Monnet et al 1991; Zahm et al 1991; Kune et al 1992b; Honjo et al 1992; Nelson et al 1993; Olsen and Kronborg 1993; Boutron and Faivre 1993, 1995; Lee et al 1993; Sandler et al 1993; Giovannucci et al 1994a, 1994b; Ikuma et al 1994; Jacobson et al 1994; Rozen et al 1994; Stockbrügger et al 1994; Nelson et al 1994; Martinez et al 1995; Lin et al 1995.

The one cohort study which did not find an association between previous smoking and colorectal adenomas had a very limited assessment of smoking in which only "ever" versus "never" smoking of cigarettes was examined, and this may have been the reason why an association was not found (Stemmerman et al 1988). Of the 4 case-control studies in which an association between smoking and colorectal adenomas was not found, 3 used hospital controls which, unless carefully selected, are inappropriate for the examination of smoking-related illness, because of the high rate of smoking and of smoking-related illness in hospitalized patients. Thus a 50% or higher risk elevation was present in 10 of 11 (91%) studies using population controls, and in 9 of 12 studies (75%) using hospital-based controls. The fourth study which did not find an association used a very narrow examination of cigarette smoking, obtaining data only on "ever" versus "never" smoking (Logan et al 1991).

The risk elevation was statistically significant ($p \leq 0.05$) in 19 of the 22 studies (86%) which have found a risk elevation of 1.5 or higher (Table 8.1). In most, the risk elevation was about twofold. A positive dose-response effect for tobacco consumption was noted in 9 of the 10 studies which examined this effect quantitatively (Table 8.1).

Statistical correction for several important confounding factors was made in numerous studies, and this is summarized in Table 8.1. Although "correction" for confounding factors is usually not complete, risk elevations remained after statistical correction was made for positive family history of colorectal tumors in all 3 of the studies which examined this confounding effect (Giovannucci et al 1994a, 1994b; Martinez et al 1995). Correction for dietary factors was made in 4 studies, and in all, the risk for smoking remained elevated after adjustment for these diet factors. In one study dietary correction was made for dietary fiber (Olsen and Kronborg 1993), in another corrections were made for dietary fiber and vitamin C (Martinez et al 1995), and in the 2 US cohorts corrections were made for fat, fiber and folate (Giovannucci et al 1994a, 1994b). In 3 studies the risk remained elevated after corrections were made for body mass index (Giovannuci et al 1994a, 1994b; Martinez et al 1995). The risk remained elevated in all 7 of the studies which have made statistical corrections for alcohol consumption (Kikendall et al 1989; Zahm et al 1991; Kune et al 1992b; Giovannucci et al 1994a, 1994b; Martinez et al 1995; Boutron et al 1995). A joint effect between smoking and alcohol was noted in all 3 studies which examined this (Cope et al 1991; Stockbrügger et al 1994; Martinez et al 1995). Finally, in one study, the smoking effect remained elevated after correction was made for both physical activity as well as for previous use of non-steroidal anti-inflammatories, including aspirin (Martinez et al 1995).

Hyperplastic polyps which are regarded as biomarkers of colorectal adenomas, were statistically significantly associated with smoking in both studies which examined this association (Hoff et al 1987; Kearney et al 1995).

The epidemiologic evidence is therefore consistent and convincing, reasonably satisfying several criteria of causality with respect to consistency, statistically significant risk, positive dose-response effect, and correction for various important confounding factors, and suggests that smoking is an important component cause of colorectal adenomas.

COLORECTAL CANCER

There were 51 studies which examined the association between colorectal cancer risk and smoking, consisting of 27 case-control studies and 24 cohort studies, with most case-control studies and several cohort studies finding a null effect (Table 8.2). This finding, which conflicts sharply with the smoking and adenoma studies just described can now be largely explained.

Cigarettes

Case-control Studies

Of the 27 case-control studies which examined this association, only 10 found risk elevations higher than 50% in some major subgroups of the study, and of these, in only 4 was the elevated risk statistically significant (Table 8.2). A positive dose-response effect was present in all 3 studies which examined this effect. A 50% or higher risk rise was present in 7 of the 12 studies (58%) using population-based controls, but only in 7 of 19 (37%) using hospitalized controls. Moreover, none of the case-control studies in which hospitalized controls were used showed statistically significant risk elevation. Hospital controls, unless carefully selected, are not suitable for the study of smoking, because of the high prevalence of smoking and of smoking-related illness in these patients, and this may explain some of the null results. In the population-based Melbourne study, in which a statistically significant elevation of risk for both colon cancer (RR = 1.9) and rectal cancer (RR = 2.1) was found in men smoking hand-rolled plus ready-made cigarettes, the smoking risks remained largely unchanged after correction for diet risks found in the study (Kune et al 1992a). In 3 of the 4 case-control studies in which statistically significant risk elevations were found for smoking, colon and rectal cancer risk was measured separately (Williams and Horm 1977; Kune et al 1992a; Inoue et al 1995). In two, the risk was for rectal cancer only (Williams and Horm 1977; Inoue et al 1995) and in the third (Kune et al 1992a) the risk for rectal cancer was slightly higher than for colon cancer.

An inverse association, with a 50% or greater risk reduction in some major aspect of the investigation, was present in 4 case-control studies (Higginson 1966; Staszevski 1969; Tajima and Tominaga 1985; Peters et al 1989). In 3 of these 4 studies hospitalized controls were used, and in none was the risk reduction statistically significant.

Cohort Studies

In half of the 24 cohort studies (Table 8.2), cigarette smoking was not associated with the risk of colorectal cancer (Hammond and Horn 1958; Hammond 1966; Kahn 1966; Weir and Dunn 1970; Rogot and Murray 1980; Williams et al 1981; Garland et al 1985; Kono et al 1987; Sandler et al 1987; Klatsky et al 1988; Chute et al 1991; Bostick et al 1994). In one cohort, an inverse association was recorded, but the risk could not be calculated from the data provided (Williams et al 1981). In 6 of the 24 cohorts, the elevations of risk were 50% or higher; however, these risks were either internally inconsistent, or statistically non-significant (Hirayama 1975; Doll et al 1980; Wu et al 1987; Carstensen et al 1987; Suadicani et al 1993; Tverdal et al 1993). In these studies, with the exception of Doll et al 1980, the follow-up period was less than 20 years, and in some the number of cases or deaths identified were few.

Table 8.2 Smoking and colorectal cancer. Summary data of 51 studies (27 case-control and 24 cohort)

Type of study	Number	Risk elevation 50% or higher in some major part of study	Risk statistically significant $p \leq 0.05$	Positive dose-response effect
Case-control	27	10/27	4/10	3/3
Cohort	24	12/24	6/12	5/9
Total	51	22/51	10/22	8/12

Data Sources

This table was compiled from the following studies:
Hammond and Horn 1958; Hammond 1966; Higginson 1966; Kahn 1966; Wynder and Shigematsu 1967; Graham et al 1968; Staszewski 1969; Wynder et al 1969; Weir and Dunn 1970; Haenszel et al 1973; Hirayama 1975; Martinez et al 1975; Doll and Peto 1976; Williams and Horm 1977; Graham et al 1978; Dales et al 1979; Doll et al 1980; Garfinkel 1980; Haenszel et al 1980; Jain et al 1980; Rogot and Murray 1980; Williams et al 1981; Tuyns et al 1982; Vobecky et al 1983; Papadimitriou et al 1984; Pickle et al 1984; Garland et al 1985; Tajima and Tominaga 1985; Kabat et al 1986; Carstensen et al 1987; Kono et al 1987; Wu et al 1987; Klatsky et al 1988; Sandler et al 1988; Ferraroni et al 1989; Jarebinski et al 1989; Peters et al 1989; Akiba and Hirayama 1990; Slattery et al 1990; Choi and Kahyo 1991; Kune et al 1992a; Olsen and Kronborg 1993; Suadicani et al 1993; Tverdal et al 1993; Doll et al 1994; Giovanucci et al 1994a, 1994b; Heineman et al 1994; Boutron et al 1995; Inoue et al 1995; Siemiatycki et al 1995.

There are, however, 7 important cohort studies which are described in more detail below, that have several features in common, and all 7 have shown elevated risks, statistically significant in 6, in relation to smoking. In each of these studies there was a long period of follow-up of 16 years or longer (or if the follow-up was shorter then there was information on smoking habit over many years), in each there were large study numbers, each study was carefully performed with respect to smoking habit, and in 2 of the 7 studies, statistical corrections were made for several important confounding factors (Doll et al 1980, 1994; Garfinkel 1980; Akiba and Hirayama 1990; Giovannucci et al 1994a, 1994b; Heineman et al 1994; Doll 1996).

In the British Male Doctors' study conducted by Sir Richard Doll and co-workers, after a follow-up period of 20 years an elevated risk of 2.7 (not statistically significant) was found in cigarette smokers compared to lifelong non-smokers among the 78 rectal cancer deaths identified, with the suggestion of a dose-response effect (Doll and Peto 1976). However, after 40 years follow-up of this cohort, in which several updates were made of smoking habit, there was a statistically significant positive association between smoking and the 168 fatal rectal cancers which were identified, with a significant dose-response effect also (Doll et al 1994). In that study a statistically non-significant risk elevation of 1.3 was found for colon cancer.

In a somewhat smaller study of over 6000 British female doctors followed for 22 years, a statistically non-significant risk elevation was noted for 7 rectal cancer deaths in relation to previous smoking (Doll et al 1980). In that study the results for colon cancer were not given.

In the last analysis of the large Japanese cohort of 265,000 men and women established in 1965 by Dr. Hirayama, with a follow-up period of 16 years to 1981, and in which 204 rectal cancer deaths were identified, there was a 40% statistically significant risk elevation noted in relation to rectal cancer and smoking (Akiba and Hirayama 1990). Risk elevation for colon cancer was not found in that study.

In the large American Cancer Society cohort of non-smokers followed during two periods, altogether for 13 years, the risks for both colon and rectal cancer deaths in men were significantly less than in the general US population, a population which clearly includes both smokers and non-smokers (Garfinkel 1980). The risk lowering was of the order of 10% for colon cancer and 40% for rectal cancer among non-smokers in that study, and the relative risk for smokers was 1.1 for colon cancer and 1.4 for rectal cancer (Doll 1996).

In the 2 large US cohorts—the Nurses' Health Study and the Health Professionals' Follow-up Study—a statistically significant risk elevation was reported for colorectal cancer, after an induction period of 35 years or more was allowed for (Giovannucci et al 1994a, 1994b). Thus, both these studies identified a risk for colorectal cancer only when smoking was started 35 years or more previously. These 2 studies are also important because they were able to adjust

for the confounding factors of family history of colorectal cancer, body mass index, alcohol consumption and for the dietary factors of fat, fiber and folate.

In the large cohort of almost 250,000 American Veterans who have been followed prospectively for 26 years, a statistically significant increased risk was noted for both colon cancer and rectal cancer among both current and former cigarette smokers, after controlling for social class and occupational physical activity (Heineman et al 1994; McLaughlin et al 1995). A statistically significant dose-response effect was present for both colon and rectal cancer (McLaughlin et al 1995). Although the data are not strictly comparable, shorter observations on this cohort of US Veterans did not show elevated risks for colon or rectal cancer (Kahn 1966; Rogot and Murray 1980).

With respect to site, in the 4 cohort studies with a long follow-up which distinguished between colon and rectal cancer (American Cancer Society, US Veterans, British Male Physicians, Japanese Population), the risk levels were higher for rectal cancer than for colon cancer, with an average of about 1.5 for rectal cancer and 1.2 for colon cancer (Doll 1996). The risk levels for "current smokers" were higher in the British Male Physicians cohort in which several updates of smoking habit change were made, when compared with the US Veterans cohort, in which changes in smoking habit over time were not available.

These 7 cohort studies reinforce the very consistent positive relationship found between smoking and colorectal adenomas. However, the global view of the data for smoking and colorectal cancer suggests that if smoking is a causal factor for colorectal neoplasia, the main effect occurs early in the process, that is, during the formation of an adenoma, or, if the cancer did not develop from an adenoma, during the neoplastic transformation of a dysplastic colorectal epithelial cell.

Cigar and Pipe Smoking

Cigar smoking and pipe smoking in association with colorectal cancer risk has not been studied in such detail as has cigarette smoking. However, cigar smoking shows a fairly consistent positive association with the risk of colorectal cancer (Wynder and Shigematsu 1967; Williams and Horm 1977; Dales et al 1979; Slattery et al 1990). In the US Veterans cohort followed for 26 years, a statistically significant elevation of risk was found for cigar smokers, with a dose-response effect (Heineman et al 1994).

Similarly, most studies examining pipe smoking alone, found elevated risks for colorectal cancer, and this includes some in which elevated risks were not found for cigarette smoking (Wynder and Shigematsu 1967; Williams and Horm 1977; Dales et al 1979; Slattery et al 1990). Finally, most studies which have examined colorectal cancer risk in association with cigar and pipe smoking combined, found elevated risks (Doll and Peto 1976; Kabat et al 1986; Kune et al 1992a; Heineman et al 1994). This suggests that the agents which contribute to

the development of colorectal neoplasia are more concentrated in cigars and pipe tobacco than in cigarettes; perhaps with cigar smoking more of the tobacco is swallowed and gets to the large bowel than with cigarettes (Kune et al 1992a). The chewing of tobacco or snuff has been found to be associated with elevated risks in the case-control study of Williams and Horm 1977, and the cohort study of Heineman et al 1994, adding some support to the possible role of ingested tobacco in colorectal neoplasia.

Attributable Risk

The only study which calculated attributable risk of smoking for colorectal cancer was the 26 year follow-up of US Veterans by Heineman et al 1994. In this study, it was estimated that if the association is causal, tobacco use may be responsible for about one-fifth of the attributable risk of colorectal cancer among the Veterans studied.

Limitations of Epidemiologic Studies of Colorectal Cancer and Smoking

Confounding Etiologic Factors

Dietary factors and alcohol consumption are important component causes of colorectal neoplasms (Chapters 6 and 7). Smokers, as a group, have higher consumption of fats and lower intakes of vegetables, fruit and the corresponding nutrients of fiber and vitamin C, and of beta-carotene, than non-smokers, a dietary pattern noted in Chapter 6 to be associated with elevated risks for colorectal tumors (Subar et al 1990; Cade and Margetts 1991; Subar and Harlan 1993).

Most epidemiologic studies were not able to correct statistically for dietary factors as this information was not available in the population being studied. Although correction for confounding factors is never complete, 5 studies were able to adjust in varying degrees to dietary risks, and statistically significant risks in relation to smoking still remained. In the case-control study of Slattery et al 1990, after adjustment for body mass index, fiber, calories and alcohol, statistically significant elevated risks for smoking remained. In the Melbourne Colorectal Cancer Study, a statistically significant risk for hand-rolled cigarettes and cigars remained after adjustment was made for all the dietary risk factors found in the study (Kune et al 1987; Kune et al 1992a). The risk of colorectal cancer in the cohort study of males in a retirement village in California had a statistically significant elevated risk when adjusted for physical activity, body mass index and alcohol consumption (Wu et al 1987). In the Health Professionals' Follow-up Study, and the Nurses' Health Study reported by Giovannucci et al in 1994, statistically significantly elevated risks remained after adjustment was made for family history of colorectal cancer, body mass index, fat, fiber, folate, and alcohol consumption.

Moreover, in the 26 year follow-up of US Veterans reported by Heineman et al 1994, an adjustment was made for social class, which is in part correlated with diet, and for occupational physical activity, and statistically significant elevations of risk still remained.

Type of Control Used in Case-Control Studies

In case-control studies, the use of unselected hospital controls or "cancer" controls has been shown to be inappropriate for the study of putative smoking-related illnesses, because of the high prevalence of smoking in these populations (Linet and Brookmeyer 1987; Heineman et al 1994). The use of hospital or "cancer" controls would negate the smoking effect, that is, the effect of smoking would be smaller or absent in these studies.

Length of Follow-up in Cohort Studies

It seems clear from the preceding review of cohort studies that either a follow-up or a smoking history which is of the order of 20 years or longer is necessary before a positive association between smoking and colorectal cancer is found. The effect of the length of follow-up is well reflected in the successive reports of both the US Veterans cohort and the British Male Physicians cohort, in which increased length of follow-up revealed higher risk levels (Doll et al 1994; Heineman et al 1994). Moreover, in both the Health Professionals' and Nurses' cohort, risks for colorectal cancer emerged only after an induction period of 35 years (Giovannucci et al 1994a, 1994b).

Cessation of Smoking

In a number of cohort studies, tobacco use was ascertained only at the time of enrolment of the cohort, such as in the US Veterans study, and as there is a high rate of quitting smoking, there may be a misclassification error regarding the smoking association and this would tend to make the smoking effect appear weaker than the true association. Interestingly, in the British Physicians cohort, several updates of smoking habit were made, and the risk levels were higher than in the US Veterans cohort (Doll et al 1994; Heineman et al 1994).

Mortality Studies Using Death Certificates

With respect to the accuracy of death certificates, colorectal cancers as a group are usually correctly identified; however, a significant proportion of rectal cancers are classified as colon cancer, hence studies relying on death certificates may be inaccurate with respect to risk levels for colon versus rectal cancer (Percy et al 1981; McMichael and Giles 1994). This would result in a relatively exaggerated increase in colon cancer risk versus rectal cancer risk.

Summary of Critique of Epidemiologic Studies

The positive association between colorectal cancer and smoking is likely to be stronger and more consistent than is indicated by the epidemiologic data, because of the several methodologic shortcomings in several studies, as discussed above.

MECHANISMS OF ACTIONS

TIME FRAME OF SMOKING EFFECT

Most of the epidemiologic data suggest that the effect of smoking occurs early in the process of colorectal neoplasia, namely at a time when a normal colorectal mucosal cell becomes an adenoma, or when such a cell becomes a hyperplastic or an early dysplastic cell.

The early effect of smoking is indicated by the consistent association of smoking and colorectal adenomas, by elevated risk for both adenomas and colorectal cancer being found among ex-smokers, and by the finding of risk elevations with a follow-up of 20 years or longer, as previously described. This long time-frame of the smoking effect fits in well with current estimates for the adenoma–carcinoma sequence (Chapter 4). Furthermore, 2 recent European population-based studies found smoking to be significantly more frequent in patients with adenomas than in those with colorectal cancer (Boutron et al 1995; Ponz de Leon et al 1995). However, in 2 studies, colorectal cancers in smokers were diagnosed more frequently at a more advanced stage than in non-smokers (Daniell 1986; Longnecker et al 1989), data which indirectly suggest that smoking may also act at a later stage of colorectal neoplasia, perhaps by modifying the anti-tumor immune defenses.

MOLECULAR GENETIC CHANGES

Recent data in oral cavity premalignant lesions and oral cancers and other head and neck cancers, which are all smoking-related tumors, suggest that smoking is associated with mutation of the p53 gene, a gene also known to be important in colorectal neoplasia (Kaur et al 1994; Brennan et al 1995). These are important findings, since p53 mutations have been found in relation to many cancers and premalignant lesions, including colorectal tumors (Chapters 3 and 5). However, in a small study of 42 Dukes C stage colorectal cancers reported recently, no association was noted between smoking and p53 overexpression (Zhang et al 1995).

The glutathione transferase (GSTM1) null genotype controls an enzyme which detoxifies polycyclic aromatic hydrocarbons, including those found in tobacco smoke. An examination of colorectal adenoma risk was statistically significantly elevated among smokers, although the risk levels were similar irrespective of GSTM1 null genotype status (Lin et al 1995).

PATHWAY OF SMOKING EFFECT

The pathways whereby tobacco may produce its effects in colorectal neoplasia are either via ingested tobacco and\or via carcinogenic substances derived from tobacco and tobacco smoke reaching the colorectal mucosa through the circulatory system (Kune et al 1992a; Giovannucci et al 1994a). The ingested tobacco hypothesis proposed by Kune et al 1992a, is supported by their findings of highest risk being present for hand-rolled cigarettes, and from other studies in which cigar smoking and the chewing of tobacco were associated with elevated risks, even when other forms of smoking were not, since these modes of smoking are likely to be associated with more tobacco ingestion than smoking ready-made cigarettes, especially if filtered. Also, it was noted that as all gastrointestinal tract cancers may be smoking related, there is a general gradient of decreasing risk from the oral cavity to the large bowel, although risk levels are often higher for esophagus than oral cavity, and in both case-control and cohort studies, higher for rectal cancer than for colon cancer.

CHEMICAL SUBSTANCES RESPONSIBLE

At present it is uncertain which of the almost 4000 substances present in tobacco and tobacco smoke are responsible, although nitrosamines, aromatic amines and aromatic hydrocarbons are high on the list as candidates for these effects (Hoffman and Hecht 1985; IARC 1986; Weisburger and Jones 1990; Kadlubar et al 1992).

CONCLUSIONS

Evidence, which has mainly emerged in the last 8 years, suggests that smoking is an important component cause of colorectal tumors. The smoking effect appears to operate early in the process, at a time when the colorectal mucosal cell is transformed into an adenoma, or possibly when a normal colorectal epithelial cell is transformed into a hyperplastic and then a dysplastic epithelial cell, if an adenoma does not develop. It appears that smoking may not greatly influence the later stages of the neoplastic process. Established smokers have about a twofold risk for colorectal adenomas. The risk after 20 or more years of smoking is elevated by about 50% (RR 1.5) for rectal cancer, and by about 20% (RR 1.2) for colon cancer, in relation to whole-life nonsmokers. The evidence suggests a causal relationship between smoking and the precursor lesion of colorectal adenomas; however, at present it is uncertain whether smoking has a significant additional effect in the adenoma–carcinoma–invasion–metastasis stages of the neoplastic process.

Smoking may influence colorectal neoplasia directly because of ingested tobacco, and more importantly, indirectly from compounds in tobacco smoke reaching the colorectal mucosa through the circulatory system. The actual

compounds concerned in colorectal neoplasia have so far not been accurately identified in view of tobacco containing almost 4000 substances, although nitrosamines, aromatic amines and aromatic hydrocarbons are some of the compounds which may be involved.

Apart from the other well known ill-effects of tobacco use, the recent data on the association between smoking and colorectal tumors adds further weight to total abstention from tobacco use.

* * * * *

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9

PHYSICAL ACTIVITY

Sedentary occupations are highly injurious (for cancer).

The Honourable Rollo Russell
Preventable Cancer
Longmans, Green, London 1912

Since it was first suggested by Huseman and colleagues in 1980 and Garabrant and colleagues in 1984 that a sedentary occupation for males was a risk for colon cancer, 35 studies have examined the association between physical activity and colorectal cancer or colorectal adenoma. Physical inactivity has been consistently associated with increased risk for colon cancer. Interestingly, looked at from the evolutionary perspective, requirements for physical activity were much greater at the end of the Stone Age than they are at present (Eaton and Nelson 1991).

EPIDEMIOLOGIC EVIDENCE

COLORECTAL ADENOMA

Since 1988, 9 studies have investigated the association between physical activity and colorectal adenoma risk in the form of 7 case-control studies and 2 cohort studies (Stemmerman et al 1988; Kato et al 1990b; Kono et al 1991; Little et al 1991; Giovannucci et al 1992, 1995; Benito et al 1993; Rozen et al 1994; Sandler et al 1994). Five of the 7 case-control studies found an inverse relationship between physical activity and colorectal adenoma risk, or putting it another way, physical activity was a protective factor, whereas physical inactivity was a risk (Kato et al 1990b; Kono et al 1991; Little et al 1991; Benito et al 1993; Rozen et al 1994). The sixth case-control study showed a weak protective effect only for

leisure activities and only in women, though the measurement of physical activity was not particularly sensitive in this study (Sandler et al 1994). These associations in the case-control studies were not strong and in only 2 was it statistically significant (Kono et al 1991; Rozen et al 1994). In 3 of the 7 studies, the site of the colorectal adenoma was not specified, whilst the study of Kono et al 1991 examined sigmoid colon adenomas only, whereas the study of Kato et al in 1990 examined left colon, right colon and rectum separately and found an inverse association in each of those subsites. A measurement of exposure gradient to physical activity was made in 3 case-control studies, and in 2 of these, a gradient of protection was shown with increasing levels of physical activity (Kono et al 1991; Benito et al 1993). A correction for the confounding effect of energy consumption in relation to physical activity was made in 3 case-control studies and in all studies the physical activity effect remained (Kono et al 1991; Little et al 1991; Rozen et al 1994). In 2 of the earlier cohort studies an association between physical activity and colorectal adenoma was not found (Stemmerman et al 1988; Giovannucci et al 1992). However, in the recently reported cohort of the US Health Professionals' Follow-up Study, an inverse association was noted for adenomas larger than 1 cm but not for smaller adenomas (Giovannucci et al 1995). The results of the US Health Professionals' Follow-up cohort with respect to physical activity are important because of the comprehensive nature of this study, and because the physical activity effect for large adenomas remained after statistical corrections have been made for several important confounding factors, including parental history of colorectal cancer, previous adenomas, previous endoscopy, smoking, alcohol consumption, dietary factors of red meat, dietary fiber, folate and methionine intake and aspirin use.

The data show a weak association only between colorectal adenomas and physical activity, no effect in 2 cohort studies, and in the third cohort an inverse relationship only for adenomas which are larger than 1 cm; all data suggest that if physical activity is a protective factor for colorectal tumors, then its effect needs to operate over several years, commencing early in the process of neoplasia and possibly continuing for decades.

COLORECTAL CANCER

There were 26 epidemiologic studies (14 case-control studies and 12 cohort studies) which examined the association between physical activity and colorectal cancer risk (Table 9.1). Of the 26 studies, 15 examined occupational physical activity only, in which a particular activity level was assumed for a particular occupation; however, 11 studies also included leisure activity.

Consistency and Strength of Association

Of the 26 studies, 20 (77%) found physical activity to be a protective factor, or put another way 20 studies found physical inactivity to be a risk for colorectal

cancer. The strength of the association was not strong, and if expressed as a risk for physical inactivity, most studies had a risk level of 1.5–2.0, and only 3 of the 20 positive studies had risk levels over 2, and these were risks between 2.5 and 3.6. This association is therefore not strong with a median value of a twofold risk for physical inactivity. Moreover, in only 8 of the 20 positive studies was the association statistically significant at the 95% level. The association holds for both men and women. Of particular interest is that in both cohort and case-control studies, when lifelong levels of physical activity are measured an association is found, whereas in studies which measure relatively recent physical activity only, the relationship is either weak or absent (Lee et al 1991; Kune et al 1990).

Table 9.1 Physical inactivity and colorectal cancer risk. Summary data of 26 studies

Type of study	Number of studies	Risk elev 50% or higher (No Stat Sig $p \leq 0.05$) No. of studies examining effect		
		Large bowel site unspecified	Colon	Rectum
Case-control	14	0	11(5) 14	2(2) 7
Cohort	12	2 3	7(1) 9	0 5
Total	26	2 3	18(6) 23	2(2) 12

Data Sources

This table was compiled from the following studies:
Garabrant et al 1984; Vena et al 1985; Gerhardsson de Verdier et al 1986, 1988, 1990; Paffenbarger et al 1987; Wu et al 1987; Slattery et al 1988; Albanes et al 1989; Fredriksson et al 1989; Peters et al 1989; Severson et al 1989; Ballard-Barbash et al 1990; Benito et al 1990; Kato et al 1990a; Kune et al 1990; Whittamore et al 1990; Brownson et al 1991; Lee et al 1991, 1994; Thun et al 1992; Fraser and Pearce 1993; Vineis et al 1993; Giovannucci et al 1995; Longnecker et al 1995.

Colorectal Cancer Site

Table 9.1 points to a marked difference between colon and rectum and risk for physical inactivity. In 18 of 23 studies (78%) examining colon cancer a risk elevated above 1.5 with physical inactivity was found, whereas only 2 of 12 studies (17%) found a risk elevation of 1.5 or above for rectal cancer. Although there is some inconsistency among various studies which have compared left

colon with right colon, the study of Kato et al 1990 is of particular interest because in that study a decreasing gradient of statistically significant risk was noted for physical inactivity, with a right colon rate of 1.9, left colon 1.5, and rectum 1.4.

Exposure Gradient

What may be termed a "dose-response effect", that is, increasing levels of protection with increasing levels of physical activity or increasing risk with increasing physical inactivity, were observed in 5 studies which have attempted to quantify this aspect of the physical activity-colorectal cancer relationship (Garabrant et al 1984; Slattery et al 1988; Gerhardsson de Verdier et al 1990: Whittemore et al 1990; Giovannucci et al 1995). Strenuous physical activity in adolescence and early adult life, at least in women, does not appear to confer protection from colon cancer (Marcus et al 1994).

Correction for Confounding Factors

In several of the studies, the relationship between physical activity and colorectal cancer risk remained after statistical adjustment was made for body mass index (Wu et al 1987; Slattery et al 1990; Severson et al 1989; Gerhardsson de Verdier et al 1990; Ballard-Barbash et al 1990; Thun et al 1992; Giovannucci et al 1995). A recent analysis of the Harvard Alumni cohort indicates protection from colon cancer with high levels of energy expenditure, and this particularly applies to those who are overweight (Lee and Paffenbarger 1994). The relationship between physical activity, energy intake, energy expenditure and body mass index is intertwined, although physical activity appears to have some independent effect.

A relationship between physical activity and colorectal cancer was also noted in those studies which corrected for a history of previous endoscopy and previous colorectal polyps, smoking, alcohol consumption, family history of colorectal cancer, aspirin use and several dietary factors (Wu et al 1987; Severson et al 1989; Ballard-Barbash et al 1990; Brownson et al 1991; Giovannucci et al 1995). As confounding for dietary factors is likely to be important, the studies making dietary corrections are of note. A complete correction for dietary factors was not possible in any of the studies which showed a relationship between physical activity and colorectal cancer risk because of the unavailability of complete data. However, partial adjustments were made in several studies. Thus, Slattery et al in 1990 adjusted for crude fiber, Gerhardsson de Verdier et al 1990 adjusted for fat, protein, fiber and meat browning in cooking, Thun et al 1992 adjusted for vegetables, citrus fruit, grains and fat and Giovannucci et al 1995 adjusted for red meat, dietary fiber and folate.

Experimental Data

In an experimental study of chemically induced colon cancer in the rat, physical activity was shown to be weakly protective for colon cancer, and this reinforces the epidemiologic data described above (Andreanopoulos et al 1987).

CONCLUSION

When measured against criteria of causality discussed in Chapter 1, the weight of evidence indicates physical inactivity to be a twofold risk for colon cancer, and that this risk probably indicates a causal effect. The evidence for rectal cancer is weak. If physical inactivity is a cause, it needs to operate for several years, and probably for decades, and this is gleaned from the generally weak or absent association for adenomas, an association for larger but not smaller adenomas, an association for cohorts with a long follow-up, and an absence of association in those studies which have measured physical activity levels relatively recently in relation to cancer diagnosis, and over relatively brief periods.

MECHANISMS OF ACTION

It is a very popularly held belief, particularly in Western countries, that physical activity influences bowel habit. Those who are largely sedentary in their life habits are regarded as being prone to constipation, whereas those who are physically active, are not. The hypothesis for which there is most data is that physical activity alters the mechanical function of the large bowel in such a way that there is a reduction in colorectal cancer risk. Other hypotheses relate to hormonal and immunologic changes which occur during physical activity and which may also influence colorectal cancer risk.

CHANGES IN BOWEL MOTILITY AND TRANSIT TIME

Early studies of gastrointestinal tract motility indicated that in some subjects, assuming the direct posture from the supine and the performance of gentle physical activity is associated with a stimulation of peristalsis in the colon, and perhaps also a decrease in segmentation type non-propulsive colonic activity (Connell et al 1964; Holdstock et al 1970). However, in a careful study of 14 healthy but usually sedentary people who were on a constant diet, no change was observed in fecal weight nor in bowel frequency (Bingham and Cummings 1989). In this group of 14 healthy volunteers, significant changes occurred in 5 (with decrease of transit time in 2 and an increase in transit time in 3), and overall transit time increased in 9 subjects and decreased in 5 of the 14 (Bingham and Cummings 1989). In 2 other studies which examined the effect of running or jogging on bowel transit time, one found a fall in transit time in 3 of 11 subjects, and the second found a significant fall in transit time in all 9 subjects following an aerobic running program; however, in neither study were dietary factors

controlled for (Harrison et al 1980; Cordain et al 1986). There is also more recent evidence that moderate physical activity reduces intestinal transit time (Dapoigny and Sarna 1990; Oettle 1991; Koffler et al 1992). Symptomatic diverticular disease of the colon has been hypothesized to be positively associated with bowel transit time, and in a large prospective US cohort it has been shown to be inversely related to physical activity (Aldoori et al 1995).

As described in Chapter 11 dealing with bowel habit, intestinal transit time and dietary fiber intake are closely correlated and both are inversely associated with colon cancer risk. This means that dietary factors need to be corrected for when studying large bowel function. Up to the present time, a large study of intestinal transit time and various levels of physical activity observed over some weeks and in which diet is kept constant, has not been conducted.

This somewhat fragmentary physiologic evidence indicates that in some, though not all subjects, physical activity stimulates large bowel peristalsis, decreases transit time, and is thereby protective for colon cancer (not rectal cancer), and this is consistent with the extensive epidemiologic data reviewed earlier in this chapter.

HORMONAL CHANGES

Physical activity decreases insulin levels and increases the production of pancreatic polypeptide, and these hormones inhibit colonic motility, resulting in a lengthening rather than a shortening of transit time (Krotkiewski et al 1984; Tache 1984). Physical activity increased circulating prostaglandin F levels, but whether this has any relationship to protection against colorectal neoplasia is unknown (Demers et al 1981; Bartram and Wynder 1989).

In women, exercise increases the levels of estrogens, progesterone, prolactin as well as of follicle-stimulating hormone and luteinizing hormone, whilst the resting levels of all of these hormones tends to decrease (Potter et al 1993). This dual action is difficult to equate to colonic function, particularly when an increase in estrogen and progesterone has a tendency to inhibit large bowel peristalsis and propulsion. In one study in which the effect of physical activity was recorded separately in men and women, the level of protection for sustained high levels of physical activity were more pronounced in women than in men (Slattery et al 1988). The difficulty with this is that high levels of physical activity would be associated with an increase in hormone levels of estrogen and progesterone with the effect of increasing intestinal transit time, a situation associated with an increased risk for colon cancer (Chapter 11). Thus at present, hormonal factors, at least in women, seem to be an unlikely explanation of the inverse relationship between physical activity and colon cancer risk.

CHANGES IN IMMUNE FUNCTION

It was proposed by Potter et al in 1993 that moderate forms of physical activity have a favourable effect on T-cells, B-cells and natural killer cells, and that this may be the reason for the inverse relationship noted between physical activity and colorectal cancer (Simon 1984; Mackinnon 1989; Shephard 1990; Shephard et al 1991; Eichner and Calabrese 1994). Although the role of the immune system in colorectal neoplasia is unclear, based on data in relation to "stress" it has been speculated (Chapter 15) that a depressed immune function is likely to have an effect late in the stage of neoplasia, after colorectal cancer cells have formed, and at a time when the tumor becomes invasive and metastatic. Moreover, epidemiologic data suggest that the physical activity effect needs to operate for many years for it to have an effect, which makes immune depression an unlikely mechanism since almost all those who eventually develop colorectal cancer do not have an immune deficiency in the many years prior to the diagnosis of their cancer.

CONCLUSION

Both retrospective case-control studies and prospective cohort studies consistently indicate a protective effect for physical activity, or a risk for physical inactivity, in relation to colon cancer, in both men and women. The effect is relatively weak, most studies finding about a twofold risk for physical inactivity or a protective effect of physical activity of the order of 0.5. An exposure–gradient effect has also been noted in all studies which examined this. The association has been seen infrequently for rectal cancer. This effect appears to be independent of alcohol consumption and smoking, body mass index, and several diet factors. A weak association has been found also between physical activity and the major known precursor lesion, colorectal adenoma. One study of chemically induced colon cancer in the rat and physical activity supports the epidemiologic data. These data are consistent with the hypothesis that physical activity is an independent etiologic factor for colon cancer. The evidence for this association in rectal cancer is weak. If physical activity is independently protective, or physical inactivity is a risk, the current evidence suggests that this effect needs to operate over many years, and possibly over decades.

The effect of exercise on large bowel function has not been consistent although, in some subjects, an increase in physical activity is associated with a stimulation of large bowel peristalsis and a decrease in transit time. This remains the most likely mechanism of a protective effect for colon cancer. Endocrine and immune mechanisms have also been proposed, but the evidence to support these is rather fragmentary. The overall conclusion is that long-standing regular physical activity has a twofold independently protective effect for colon cancer, and that motility changes in the colon are largely responsible for this effect.

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10

CHOLECYSTECTOMY AND CHOLELITHIASIS

It was first suggested by Capron and co-workers in France and alluded to by Castleden and co-workers in Australia and New Zealand, both in 1978, and by Peters and Keimes 1979 in Germany, that cholecystectomy is a risk for colorectal cancer. These early reports were followed by numerous epidemiologic studies, as well as post-mortem investigations, in which this association was examined. At the end of 1995, 72 studies have reported on the cholecystectomy risk in colorectal cancer, 7 on colorectal adenomas and 15 studies which examined the association between gallstones and colorectal cancer risk, a total of 93 epidemiologic investigations.

The hypothesis that cholecystectomy is a risk for colorectal cancer fits well with physiologic and pathologic changes which are known to follow cholecystectomy, and with current theories of colorectal carcinogenesis. Following cholecystectomy, there is an increased formation and therefore exposure of the large bowel mucosa to secondary bile acids, particularly in the proximal colon, which is thought to damage the lining cells, resulting in dysplasia and neoplasia.

CHOLECYSTECTOMY

EPIDEMIOLOGIC EVIDENCE

In the 17 years since the association between colorectal cancer and cholecystectomy was first researched, 78 studies have examined this association for colorectal cancer and colorectal adenomas. The association for colorectal cancer has been assessed by several methods, namely one correlational study, numerous case-control studies, several cohort studies, studies which compared

cholecystectomy rates in right and left colon cancer, as well as autopsy studies. Several case-control studies also examined this association in colorectal adenomas.

COLORECTAL ADENOMAS

Since 1987, 7 case-control studies examined this association (Mannes et al 1984; Llamas et al 1986; Sandler et al 1988; Neugut et al 1988, 1991; Giorgio et al 1989; Moorehead et al 1989). Elevated risks were consistently noted in women, and in the study of Mannes and co-workers, in men also. Two of the 4 studies which examined the association by subsite found risk elevations mainly for the right colon (Llamas et al 1986; Neugut et al 1991). Elevated risk was predominantly seen in those who had their cholecystectomy more than 10 years before the adenoma was diagnosed (Mannes et al 1984; Moorehead et al 1989; Neugut et al 1991). Thus, elevated risks for adenomas are present mainly among those who had a cholecystectomy over 10 years previously, and they apply mainly for right colon cancer. The one study which attempted to distinguish the effects of cholelithiasis from those of cholecystectomy concluded that the elevated risk is due to the cholecystectomy and not to the gallstones (Mannes et al 1984).

COLORECTAL CANCER

Of the 54 epidemiologic studies which examined the association between previous cholecystectomy and colorectal cancer, there are 39 case-control studies, most using hospital-based controls and 15 cohort studies (Table 10.1). One case-control study was excluded because it used gastric cancer patients as controls (Grobost et al 1991), and cancer patients are regarded as an inappropriate control group.

In the 29 studies which were able to separate the colorectal cancer site as right and left colon (or proximal and distal large bowel), elevated risks over 1.5 were noted for right colon cancer in 16, and this elevation was statistically significant in 11 (Table 10.1). In contrast, elevated risks over 1.5 were noted for left-sided tumors in only one of 25 studies and in this study only 7 post-cholecystectomy patients were identified with distal large bowel cancer, so that this finding is likely to be due to chance (Papadamitriou et al 1984). Moreover, in only one of 35 studies which considered rectal cancer separately was there an elevation of risk (Turnbull et al 1981), and the reason why the results of this study are different from the other 34 studies is not clear (Table 10.1). Of the 9 studies which considered the entire colorectum grouped together, all 9 found risk elevations over 1.5, statistically significant in only 3 (Table 10.1). Finally, of the 18 studies which considered the colon separately, 8 found elevations of risk over 1.5, statistically significant in 4 (Table 10.1). These risk elevations in the studies considering the entire large bowel and those considering the entire colon are

likely to be explained by the cases of proximal colon cancer within each study in view of the subsite specific findings for proximal colon cancer just described.

Table 10.1 Previous cholecystectomy and colorectal cancer risk. Summary data of 54 epidemiologic studies

Type of study	No. of studies	Risk elevation 50% or higher (No. stat sig $p \leq 0.05$) Number of studies examining site				
		Large bowel site unspecified	Colon	Rectum	Right colon	Left colon
CASE-CONTROL	39					
Hospital controls 30		9(3)	8(4)	1(1)	16(11)	1
Population controls 9		9	18	35	29	25
COHORT	15					

Date Sources

This table was compiled from the following studies:
Wynder and Shigematsu 1967; Hoare 1974; Capron et al 1978; Castleden et al 1978; Peters and Keimes 1979; Caprilli et al 1981; Linos et al 1981; Manoussos et al 1981; Markman 1982; Weiss 1982; Abrams et al 1983; Adami et al 1983; Alley and Lee 1983; Giordano et al 1983; Kwai 1983; Rundgren and Mellstrom 1983; Vobecky et al 1983; Blanco et al 1984; Eriksson and Lindstrom 1984; Fixa et al 1984; Papadimitrou et al 1984; Fixa et al 1985; Preitner et al 1985; Regula et al 1985; Simi et al 1985; Spitz et al 1985; Terranova et al 1985; Kaibara et al 1986; Moorehead et al 1986; Papa et al 1986; Adami et al 1987; Friedman et al 1987; Gafa et al 1987; Maringhini et al 1987; Vlajinac et al 1987; Wu et al 1987; Kune et al 1988; Mamianetti et al 1988; Caprilli et al 1989; Furner et al 1989; Gudmundsson et al 1989; Lee et al 1989; Li Destri et al 1989; Moorehead et al 1989; La Vecchia et al 1991; Neugut et al 1991; Neilsen et al 1991; Jorgensen and Rafaelsen 1992; Paul et al 1992; Goldbohm et al 1993; Ekbom et al 1993; Zeng and Zhang 1993.

The risk elevation in 5 of the positive studies was confined to women only, and in 3 to men only. As the rate of cholecystectomy in women is 3 times that in men, this quantitative gender difference for colorectal cancer risk in relation to previous cholecystectomy may in part be explained by the relatively low cholecystectomy rates in men who subsequently develop colorectal cancer, resulting in a low statistical power in individual studies.

This overview of 54 epidemiologic studies indicates a risk elevation of about 1.5 to 2.0 for right colon cancer in about half of the studies, with a null result in the rest. The effect was more often noted in women than in men.

Proximal Versus Distal Colorectal Cancer

There were 5 studies which reviewed hospital medical records and only compared the frequency of previous cholecystectomy according to the presence of proximal versus distal colorectal cancer. All 5 studies found an elevated ratio (statistically significant in one) between proximal and distal colorectal cancers (Vernick et al 1980; Vernick and Kuller 1981; Brancato et al 1983; Sonoda et al 1983; Spitz et al 1985). These data are therefore consistent with the elevated risk being confined to right colon cancer in the case-control and cohort studies just described.

Autopsy Studies

There were 12 autopsy studies which examined the relationship between previous cholecystectomy and colorectal cancer. In 3 of the 4 studies which were site-specific, previous cholecystectomy was associated with right colon tumors but not with left colon or rectal cancers, confirming the findings of the epidemiologic studies (Table 10.2). In the 7 studies in which subsite was not recorded, the elevated risks found in 6 are likely to have been due to right colon tumors.

Table 10.2 Previous cholecystectomy and colorectal cancer risk. Summary data of 11 autopsy studies

Type of study	No. of studies	Risk elevation 50% or higher (No. stat sig $p \leq 0.05$) Number of studies examining site			
		Large bowel site unspecified	Right colon	Left colon	Rectum
AUTOPSY	11	6(2)/7	3(2)/4	0/4	0/3

Data sources

This table was compiled from the following studies:
Capron et al 1978; Turunen and Kivilaakso 1981; Lowenfels et al 1982; Pinter et al 1983; Schmauss and Ehrhardt 1983; Weitz et al 1983; Allende et al 1984; Eriksson et and Lindstrom 1984; Machnik 1986; Hladik et al 1987; Breuer et al 1988.

Critique of Epidemiologic Data

It is important to examine several methodologic issues and confounding factors which may have been responsible for the positive effects as well as for the null effects found in the epidemiologic studies.

Methodologic Issues

In hospital-based case-control studies, there may have been observer bias present, the colorectal cancer cases may have been better documented with respect to previous cholecystectomy than in population-based studies, and there may have also been a publication bias for null results. These methodologic issues cannot be quantitatively assessed; however, these biases probably did artificially increase the strength of the association.

The null results in the cohort studies may in part be due to the very small number of cases identified in each cohort, and in part because few of the studies were followed for longer than 15 years. As discussed later, the risk for right colon cancer tends to increase only 15 years or longer after cholecystectomy. The largest study reported up to the present time, by Ekbom et al 1993, shows a statistically significant elevation of risk for right colon cancer among women, but only 15 years or longer after cholecystectomy.

Confounding Factors

Time Since Cholecystectomy

The interval between cholecystectomy and the diagnosis of colorectal cancer is of importance for a number of reasons. Gallstones are particularly common in adult Western populations, especially in women, and the symptoms of colorectal cancer may be confounded with those of gallstones. Gallstones in most are asymptomatic, and in those in whom cholecystectomy and colorectal cancer diagnosis is separated by a short time interval, say 2–5 years, it is possible that in a number, the symptoms of the colorectal cancer were attributed to gallstones (Friedman et al 1987; Kune et al 1988). Against this effect, recent cholecystectomy could attenuate the risk because insufficient time would have elapsed for it to have an effect. Cholecystectomy performed say 5 years or less before the diagnosis of colorectal cancer, is best omitted from calculations of risk. A further aspect of the time interval between cholecystectomy and colorectal cancer is that risk increases over time and particularly so 15 years or more after cholecystectomy (Giovannucci et al 1993; Ekbom et al 1993).

Dietary Factors and Alcohol

A high energy intake, a high fat intake and obesity are risks for both colorectal cancer and gallstones. Statistical correction for these diet factors should result in a decrease in risk for cholecystectomy. However, the 2 studies which have corrected for some dietary factors, one in Puerto Rico and the other in Singapore Chinese, found that elevated risks for colorectal cancer still remain after statistical corrections were made (Lee et al 1989; Soltero et al 1990). The alcohol risk operates in opposite directions, being a risk for colorectal tumors (Chapter 7) and protective for gallstones.

Reproductive and Hormonal Factors

An increasing number of children increases the risk of gallstones in women, but in general, decreases the risk of colorectal cancer in both men and women (Chapter 12). The use of oral contraceptives in women has been shown to increase the risk of gallstone formation in numerous studies (Kune and Sali 1980). However, oral contraceptive use has not shown a consistent effect for colorectal cancer, and not for right colon cancer in particular (Chapter 12). Estrogen replacement therapy probably lowers the risk of colorectal cancer (Chapter 12), although it probably increases the risk of gallstone formation (Petitti et al 1988).

Summary of Epidemiologic Evidence

The above data suggests that previous cholecystectomy poses a modest elevation of risk, which is one and a half to twofold, for proximal colon cancer 15 years or longer after cholecystectomy, even after the various methodologic issues and confounding factors have been taken into consideration.

Table 10.3 Gallstones and colorectal cancer risk. Summary data of 15 studies.

Type of study	No. of studies	Risk elevation 50% or higher (no stat sig $p \leq 0.05$) Number of studies examining site				
		Large bowel site unspecified	Colon	Rectum	Right colon	Left colon
EPIDEMIOLOGIC Case-control 5 Cohort 2	7	3(2) 4	1(1) 1	1(1) 1	1(1) 2	0 2
AUTOPSY	8	4(1) 5	0	0 1	3 3	0 1
TOTAL	15	7(3) 9	1(1) 1	1(1) 2	4(1) 5	0 3

Data sources

This table was compiled from the following studies:
Doouss and Castleden 1973; Castleden et al 1978; Lowenfels et al 1982; Schmauss and Ehrhardt 1983; Weitz et al 1983; Allende et al 1984; Machnik 1986; Gafa et al 1987; Maranghini et al 1987; Breuer et al 1988; La Vecchia et al 1991; Jorgensen et al 1992; Paul et al 1992; McFarlane and Welch 1993; Zeng et al 1993.

CHOLELITHIASIS AND COLORECTAL CANCER

The effect of gallbladder gallstones on colorectal cancer risk was the subject of 16 investigations and these comprised 2 cohort, 5 case-control and 9 autopsy studies (Table 10.3). Two case-control studies were excluded, one because it used gastric cancer and other gastrointestinal tract diseases as controls, and another because the colorectal cancer cases had laparotomy confirmation of gallstones whilst the controls did not (Narisawa et al 1983; Bundred et al 1985). The remaining 15 studies show a trend but less strong than that for cholecystectomy, namely, null results for left colon and rectum and elevated risk for right colon cancer (Table 10.3). Elevated risks were present for women only, in 3 of the autopsy studies (Allende et al 1984; Gafa et al 1987; McFarlane and Welch 1993). There was one Italian study in which statistically significant elevations of risk were noted for both colon and rectal cancer (La Vecchia et al 1991). The elevated risks in 7 of the 9 studies of colorectal cancer grouped together, without subsite separation, are probably explained by the cases of right colon cancer in these series (Table 10.3).

SEPARATING THE GALLSTONE EFFECT FROM THE POST-CHOLECYSTECTOMY EFFECT

Among the 11 studies which attempted to distinguish between the effects of cholecystectomy and the effects of cholelithiasis with respect to colorectal cancer risk, there is an amazing spectrum of conclusions. The risk was limited to previous cholecystectomy in 2 (Turunen and Kivilaakso 1981; Ceraudo et al 1984), 2 found elevated risks for both but higher for cholecystectomy than for gallstones (Schmauss and Ehrhardt 1983; Machnik et al 1986), 2 suggested that the risk was equally elevated (Allende et al 1984; Breuer et al 1988), 3 found elevated risks to be mainly due to gallstones (Gafa et al 1989; Jorgensen and Rafaelsen 1992; McFarlane and Welch 1993), whilst 2 studies did not find elevated risks for either (Doouss and Castleden 1973; Maringhini et al 1987).

A difficulty in distinguishing between the gallstone effect and the post-cholecystectomy effect is that in the natural history of cholelithiasis, a significant proportion develop what may be termed a "functional cholecystectomy" in which the gallbladder does not function, either because it is blocked at its outlet at the cystic duct by a gallstone, or that the gallbladder comes to be packed solidly with gallstones and does not function as a concentrating reservoir (Kune and Sali 1980). This "functional cholecystectomy" would probably have similar physiologic effects to a surgical removal of the gallbladder in relation to bile output into the gut.

Colorectal tumors and gallstones have some overlapping diet related risks such as obesity, a high fat and a high energy intake (Kune and Sali 1980; Friedman et al 1986; Maclure et al 1989). Whilst alcohol consumption increases

the risk of colorectal tumor (Chapter 7), there is evidence that it reduces the risk of gallstone formation (Maclure et al 1989). An increasing number of children increases the risk of developing gallstones in women, but decreases the risk of colorectal cancer in both men and women (Chapter 12). Exogenous female sex hormone use, namely the oral contraceptive and estrogen replacement therapy, increases the risk of gallstone formation (Kune and Sali 1980; Petitti et al 1988); however, as noted in Chapter 12, the use of hormone replacement therapy is protective for colorectal cancer.

Clearly, a quantitative distinction between the post-cholecystectomy effect and the gallstone effect cannot be made at present. Both gallstones and cholecystectomy probably contribute independently to the risk elevations for right colon cancer, with the weight of current evidence pointing to previous cholecystectomy being more important than cholelithiasis.

EXPERIMENTAL EVIDENCE

In several experimental animal models of colorectal carcinogenesis, the performance of cholecystectomy has been shown to enhance the induction of colonic tumors in mice and hamsters (Werner et al 1977; Weitz et al 1984; Kuniyasu et al 1986; Rodriquez et al 1988). However, 2 studies in mice have not shown an enhancing effect of cholecystectomy on chemically induced colon cancer (Schattenkerk et al 1980; Narisawa et al 1985). Because of species differences, and because of non-comparability of the biologic behavior of the tumors in experimental animals compared to humans, the results of experimental studies need to be viewed with caution. Nevertheless, these investigations add limited support to the concept that cholecystectomy does raise the risk of large bowel cancer in humans.

MECHANISMS OF ACTION

It is known that following cholecystectomy, the wave-like and largely intermittent delivery of bile into the duodenum, together with an intermittent delivery of concentrated bile from the gallbladder after meals, changes to a more constant flow, particularly during the day (Malagelada et al 1973; Kune and Sali 1980). Following cholecystectomy there is also an increased degradation of primary bile acids into secondary bile acids in the gut (Hepner et al 1974; Roda et al 1978). Following cholecystectomy, an increased amount of undigested and unabsorbed fat can appear in the large bowel, particularly in the presence of a high fat intake (Brydon et al 1982). A correlational study has shown an increasing risk of large bowel cancer with increasing amounts of fecal fat in various populations, and following cholecystectomy there is an increased amount of fecal fat present (Sperry et al 1976; Brydon et al 1982).

It is hypothesized that this increased exposure of the large bowel to secondary bile acids and to fat, results in damage to the colorectal mucosal cell, and this results in an increased rate of cell multiplication and proliferation, which enhances the process of colorectal neoplasia. It was noted in the chapters dealing with dietary factors and alcohol consumption that in both human and animal studies an increase in fecal bile acids increases the risk of colorectal cancer. Both the effects of increased secondary bile acids and of fat in the large bowel are likely to have their maximum effect in the proximal colon where these compounds are maximally exposed to the mucosa, and this is consistent with the epidemiologic data showing an elevation of risk for cancer in the proximal colon of those who had a previous cholecystectomy.

CONCLUSIONS

A global view of the current evidence is that cholecystectomy causes a modest elevation of risk for proximal colon cancer (and adenomas) in both men and women. The level of risk elevation is of the order of 1.5–2, and this risk becomes important 15 years or more after cholecystectomy. The risk may be higher for women than for men.

Gallbladder gallstones may contribute independently to this elevated risk to a small extent; however, the cholecystectomy effect appears to be the major one. The confounding effect of shared diet related risks between gallstones and colorectal cancer, particularly obesity, a high fat and a high energy diet, have not been entirely eliminated, although cholecystectomy does appear to have an independent effect on proximal colon cancer risk.

The effect of cholecystectomy on proximal colon cancer risk is indirect and the likely mechanism of this action is an increased exposure of the proximal colonic mucosa to secondary bile acids and probably also an increased exposure to undigested fat. There is plausible and reasonably consistent evidence for this mode of action from both human and experimental studies.

* * * * *

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11

BOWEL HABIT – CONSTIPATION, DIARRHEA AND LAXATIVE USE

I have finally come to the conclusion, that a good reliable set of bowels is worth more to a man, than any quantity of brains.

Henry Wheeler Shaw (1818-1885)
Sayings of Josh Billings

It has been suggested that slow intestinal transit of feces through the large bowel is a risk for colorectal cancer. Slow intestinal transit may lead to constipation, however defined, so that constipation may be a marker for elevated colorectal cancer risk. At the other end of the bowel habit spectrum, it has been suggested that intestinal hurry, whatever the cause, and this may include laxative use, may have an irritant action on the mucosa of the large bowel, resulting in hyperplasia, dysplasia and neoplasia. It is known that in chronic ulcerative colitis and in chronic Crohn's colitis, the risk of colorectal cancer is increased, but whether this is in part due to the associated chronic diarrhea, or mainly to other factors, is not known.

This chapter will discuss current data on the role of bowel habit in the etiology of colorectal cancer in relation to the frequency, consistency and shape of bowel motions, intestinal transit time, fecal weight, chronic constipation, chronic diarrhea and chronic laxative use.

DIETARY FIBER AND BOWEL HABIT

Bowel habit in an individual is determined by several factors, of which dietary factors, the influence of the autonomic nervous system, and possibly hormonal factors play an important part. Among the dietary factors, fiber intake appears to have a central role in large bowel function. When dietary fiber intake is increased, there is an increase in stool weight, an increase in the frequency of bowel motions, a change in the consistency of bowel motions towards increasing softness of the motions, a change in the shape of the bowel motion towards being less well formed, and finally, there is a decrease in intestinal transit time (Davies et al 1986; Cummings et al 1992).

Although at present it is unknown to what extent it is the dietary fiber itself, and to what extent other components of fiber-rich foods are responsible for the highly protective effects of a high fiber diet, at least in part, changes in large bowel function due to a high intake of dietary fiber appear to be responsible.

INTESTINAL TRANSIT TIME

In 1971 Denis Burkitt proposed that the volume of feces is inversely related to the risk of colorectal cancer. A recent correlational study by Cummings and co-workers in 1992, in which the daily average stool weight expressed on a logarithmic scale, was correlated with standardized incidence rates of colon cancer from 23 population groups in 12 countries, showed an excellent and statistically significant inverse relationship. Stool weight is statistically significantly positively correlated with the intake of dietary fiber and inversely with intestinal transit time (Davies et al 1986; Cummings et al 1992). This means that dietary fiber intake and stool weight are inversely related to colon cancer incidence, whilst intestinal transit time is positively associated with colon cancer rates. The transit time in men as a group may be shorter than in women (Probert et al 1993). The transit time in the second half of the menstrual cycle and in those taking oral contraceptives is increased, probably because of the inhibition of the gut stimulating hormone motilin, by progesterone (Christofides et al 1982; Davies et al 1986; Probert et al 1994). Physiologic evidence is somewhat fragmentary; however, in some subjects gentle or moderate physical activity does shorten intestinal transit time, and seems to be the main mechanism whereby moderate physical activity is protective for colon cancer (Chapter 9).

NORMAL FREQUENCY, SHAPE AND CONSISTENCY OF BOWEL MOTIONS

In apparently healthy people, there is a wide range in the frequency, shape and consistency of bowel motions.

NORMAL FREQUENCY

Data on what may be regarded as a "normal" range of frequency of bowel evacuation has not been extensively studied. Surveys of reported bowel frequency in Western societies have shown that almost all members of the adult population have a frequency of bowel habit which falls between 3 bowel motions per day and 3 bowel motions per week. Thus in a study by Connell and colleagues in 1965, 99% of 1500 people had this frequency of bowel habit, in a study by Dent and co-workers in 1986, 95% fell into this category, whilst in the population-based Melbourne Colorectal Cancer Study, 99% of the population-based controls were in this category (Connell et al 1965; Dent et al 1986; Kune et al 1988). The frequency of bowel evacuation in populations which are not so-called Western societies, has not been well studied. Stool frequency in general increases with an increase in the dietary fiber intake (Davies et al 1986). However, self-reported stool frequency does not appear to be well correlated with intestinal transit time (Probert et al 1993; Heaton and O'Donnell 1994).

Based on the available data, it is reasonable to assume, at least in Western societies, that a normal frequency of bowel motions has a range between 3 per day and 3 per week. This range is likely to be too wide to be useful in clinical or epidemiologic studies of bowel function and colorectal cancer.

NORMAL SHAPE AND CONSISTENCY

A three-point scale of bowel motion shape and consistency, namely when the motion is liquid/does not hold its shape, when the bowel motion holds its shape and is in general sausage-shaped, and when it is in small, hard pellets, as devised for the Melbourne Colorectal Cancer Study, was not sufficiently sensitive, as almost 80% of the respondents were in the middle group (Kune et al 1988). Thus, the consistency and shape of the bowel motion which retains its shape to varying degrees needs to be subdivided in such a way that it can be useful for clinical and epidemiologic study.

A scale which may be useful for future epidemiologic research in colorectal cancer has been devised by Heaton and colleagues in Bristol, and is known as "The Bristol Stool Form Scale" (O'Donnell et al 1990). This is a seven-point scale which divides bowel motions into the following categories: 1) Separate hard lumps like nuts; 2) Sausage-shaped, but lumpy; 3) Like a sausage, but with cracks on its surface; 4) Like a sausage, smooth and soft; 5) Soft blobs, with clear cut edges; 6) A mushy stool; and 7) Watery.

Studies using the Bristol Scale or other similar scales, have shown that intestinal transit time correlates reasonably well with the shape and consistency of bowel motions irrespective of whether the shape and consistency is self-reported or investigator-assessed (Davies et al 1986; Probert et al 1993; Heaton and O'Donnell 1994). These studies have shown that as the shape and consistency of the bowel motion changes from watery/unformed to various grades of a form which holds it shape, and with increasing grades of firmness to small hard lumps or pellets, the intestinal transit time increases. This therefore may be of some value in clinical practice and epidemiologic research, to identify in a relatively simple way those with a slow intestinal transit time and therefore at an increased risk for colon cancer.

BOWEL HABIT AND COLORECTAL CANCER RISK

In this section, the association between colorectal cancer risk and self-reported bowel habit in terms of bowel frequency, consistency and shape of bowel motion, as well as self-reported chronic constipation and chronic diarrhea, will be discussed.

FREQUENCY OF BOWEL MOTIONS

There is little epidemiologic data on the association between the frequency of bowel motions and colorectal cancer risk, with only one study having examined this relationship. In the Melbourne Colorectal Cancer Study self-reported frequency of the usual number of bowel actions was examined for the previous 10 and 20 years (Kune et al 1988). Based on the assumption that in Western societies a normal frequency of bowel motions has a range between 3 per day and 3 per week, a three-point scale of bowel frequency was established, namely less than 3 per week, between 3 per week and 3 per day, and more than 3 bowel motions per day. This scale was not sensitive enough to measure differences between cases and controls because 99% of the population-based controls and 97% of the population-based colorectal cancer cases belonged to the normal range. Of 1100 respondents, less than 3 bowel motions per week were reported by 7 cases and 3 controls (RR 2.6), and more than 3 bowel motions per day were reported by 10 cases and 2 controls (RR 5.4), but clearly these numbers were far too small for any meaningful conclusions to be drawn. Future studies clearly need a more sensitive scale for self-reported bowel frequency, for this measurement to be useful in clinical and epidemiologic research in relation to colorectal cancer.

SHAPE AND CONSISTENCY OF BOWEL MOTIONS

The Melbourne Colorectal Cancer Study was the only epidemiologic investigation which examined the association between self-reported shape and consistency of bowel motions and colorectal cancer risk (Kune et al 1988). As described previously, a three-point scale was devised for shape and consistency of bowel motions, namely when the bowel motion is liquid/does not hold its shape, when it holds its shape and when it is present as small hard pellets. This three-point scale was too insensitive to discriminate between cases and controls, as 77% of both cases and controls in over 1100 respondents were in the middle category, that is, the bowel motion holding its shape. Liquid motions which do not hold their shape were equally distributed between cases and controls occurring in 22% of instances in each group. Small hard pellets were reported in 9 cases and 5 controls (RR 2.4), but clearly these numbers were too small for any significant conclusions to be drawn. In a recently reported Japanese study "soft or loose" versus "moderate or hard" motions was a statistically significant risk for both genders and for both colon and rectal cancer, and particularly for the distal large bowel (Inoue et al 1995). Interestingly, a detailed study of the association between the "irritable bowel" syndrome and colorectal cancer risk has not been made so far. Future studies would need to use a more sensitive scale, such as the Bristol Stool Form Scale to examine the association between bowel consistency and shape in relation to colorectal cancer risk.

CHRONIC CONSTIPATION

Methodologic Considerations

In studies of bowel habit, there are a number of important methodologic difficulties in the interpretation of self-reported constipation. The word "constipation" is interpreted in different ways by respondents in different cultures and by different individuals in the same culture and population. Thus in the Melbourne Colorectal Cancer Study, about 2.5% of the respondents (equally distributed between cases and controls) reported no constipation, yet took laxatives in order to make their bowels move (Kune et al 1988). In that study also, a further 3.6% of respondents (equally distributed between cases and controls) reported no constipation, took no laxatives but reported the presence of "hard motions". Similar difficulties and ambiguities were encountered in other studies also (Connell et al 1965; Probert et al 1994). Passing fewer than 3 bowel motions per week that are hard in consistency, would reasonably define constipation in a Western society. A more precise definition has been created by the so-called "Rome" criteria for constipation, which requires a history of two or more of the following: straining with more than one-quarter of bowel motions, passing hard or pellet-like stools in more than one-quarter of bowel motions,

feeling of incomplete evacuation in more than one-quarter of bowel movements, and passing fewer than 3 stools per week (Drossman et al 1990).

Although there appear to be gender differences with women, especially younger premenopausal women, having a slower transit time and a smaller fecal output than men, this is not reflected in epidemiologic studies (Gapstur et al 1994). A further difficulty is the possible confounding of constipation as a presenting symptom of colorectal cancer itself. In the Melbourne Colorectal Cancer Study in order to overcome this problem, the question was phrased in such a way as to determine how far back symptoms went in time, that is, did the constipation appear before the development of colorectal cancer, and this difficulty could be resolved in most, though not all cases (Kune et al 1988).

A detailed, large-scale study correlating bowel transit time, fecal weight, self-reported frequency, shape and consistency of bowel motions and self-reported constipation has not been made so far. Such an investigation would be most relevant in clarifying the role of bowel habit in colorectal neoplasia.

Epidemiologic Findings

Of 7 case-control studies, 5 found no association between the risk of colorectal cancer and self-reported constipation (Pernu 1960; Wynder and Shigematsu 1967; Wynder et al 1969; Dales et al 1979; Jain et al 1980). The case-control study reported by Vobecky and co-workers in 1983 found that severe longstanding constipation was present statistically significantly more often in colorectal cancer patients than in controls and that this difference applied to both colon cancer and rectal cancer. Unfortunately the above 6 studies were not able to correct statistically for factors in the diet which may influence bowel habit.

In the population-based Melbourne study, self-reported chronic constipation was statistically significantly more common in colorectal cancer cases than in the controls and restricted to males under 65 years of age with colon cancer (Kune et al 1988). In a meta-analysis, a statistically significant elevated risk of 1.5 was reported; however, this risk was regarded as reflecting dietary confounding factors (Sonnenberg and Muller 1993).

Chronic Constipation and Diet

An examination of the association between various dietary factors and self-reported constipation was only possible in the Melbourne study, as this was the only study which had information in one data set on all putative risk and etiologic factors (Kune and Kune 1986, 1987). In that study, the dietary factors that were statistically significantly associated with the risk of colorectal cancer included among others, dietary fiber, vegetable consumption, beef intake and fat intake. In that study also, a model of dietary risk factors that included fiber, vegetables, dietary vitamin C, beef, fish, milk and fat was created (Kune et al 1987). In the Melbourne study, when the relative risks for those reporting

constipation were estimated by simultaneous adjustment for the dietary risk factors grouped together as a "diet model", it was shown that the risk of self-reported constipation was confounded by the diet model, and that the risk of colorectal cancer was predominantly described by the diet rather than by self-reported constipation (Kune et al 1988).

In the Melbourne study, the risk of colorectal cancer was found to be predominantly explained by the fiber and vegeterable intake and not by self-reported constipation, and this finding is consistent with the previously discussed positive association between colorectal cancer risk and a low fiber intake, resulting in a slow transit time and leading to the clinical symptom of constipation. A statistically significant association was also found with the risk of colorectal cancer in those who reported constipation and also had a high fat intake, defined as more than 100 g of fat per day (Kune et al 1988). This finding is consistent with the "fat hypothesis", in that with a high fat intake there is more fat in the large bowel and a slow transit through the large bowel results in damage to the colonic mucosa.

CHRONIC DIARRHEA

There are again methodologic difficulties similar to those described for constipation in the interpretation of self-reported diarrhea. The word "diarrhea" is defined in various ways; however, generally the combination of frequent bowel motions (more than 3 per day) of loose or watery consistency can be regarded as diarrhea. Also, in all studies of so-called "ordinary" colorectal cancer, it is important to exclude any cases of chronic ulcerative colitis as a pre-existing condition, as in that condition chronic diarrhea is an important clinical feature. This was largely possible in the Melbourne Colorectal Cancer Study as detailed pathology reports were available in those colorectal cancer cases which had a resection, and the resection rate in that series was 90% (Kune et al 1990).

In the 7 case-control studies which investigated bowel habit and which are described above in relation to chronic constipation, one noted chronic diarrhea to be present more often in cases than in controls, and as the relevant study numbers were small, no firm conclusions could be drawn (Dales et al 1979).

LAXATIVE USE AND COLORECTAL CANCER

FREQUENCY OF LAXATIVE USE IN WESTERN POPULATIONS

The definition of what may be considered to be a laxative poses some problems, but in general, most studies include only commercially produced laxatives and do not include nutritional or home remedy types such as bran, warm water or orange juice. Also, what is regarded as regular use can vary from one study to another, but in general, if commercially produced laxatives are used more often

than once per month during a large part of adult life, then this can be reasonably regarded as regular and chronic laxative use. In fact, most "regular" laxative users use a commercially produced laxative once per week, or more often.

Keeping in mind the above methodologic difficulties, the frequency of regular laxative use during a large part of adult life in otherwise apparently well Western populations is about 20%. Thus, Connell and co-workers found laxative use in 20%, Dent and co-workers in 17%, Wu and co-workers in their California cohort study found it in 19%, and in the Melbourne study, Kune and co-workers found chronic laxative use in 22% of the population-based controls. The frequency of laxative use increases with age, increases in those with clinical features of constipation, and in those who consider themselves constipated (Heaton and Cripps 1993).

COLORECTAL CANCER RISK AND LAXATIVES

No statistically significant differences were found in all 5 previous epidemiologic studies which examined laxative use and colorectal cancer risk (Boyd and Doll 1954; Wynder and Shigematsu 1967; Dales et al 1979; Wu et al 1987; Kune et al 1988). In the Melbourne study in which laxative use was known in over 1400 respondents, the relative risk was 1.1 with 24% of the cases and 22% of the controls using commercial laxatives regularly (Kune et al 1988).

It has been found that certain anthraquinones are mutagenic in bacterial models (Brown and Brown 1976; Tikkanen 1983). These mutagenicity studies were more recently confirmed by Westendorf and co-workers in 1990, and as anthraquinones are not uncommonly a part of commercially produced laxatives, it was hypothesized by Westendorf and co-workers that chronic use of anthraquinone laxatives, known to be mutagenic, may also induce tumors in humans. This hypothesis was also supported in relation to colorectal cancer by the previous findings of Mori and co-workers in 1985, who found that in rats fed large doses of danthron, which is an anthraquinone derivative, 4 out of 12 rats developed adenocarcinoma of the large bowel, versus none in 14 control rats when all animals were observed for one year. However, a cohort of almost 2000 dye workers exposed to various anthraquinones did not show an increased mortality from cancer of any type (Gardiner et al 1982).

In a recently reported carefully conducted German study, melanosis coli, which is a good marker of chronic anthraquinone use, was statistically significantly associated with colorectal cancer risk (Siegers et al 1993a). Unfortunately, this study had no data on bowel habit or diet, important confounding factors for colorectal cancer risk, and it needs to be assumed that the elevated risk is more likely to be related to the reason for chronic laxative use, than to the laxatives themselves. An experimental study from the same group in Germany showed that anthranoid fed mice, using sennosides and aloin,

did not promote dimethylhydrazine-induced colorectal tumors in mice (Siegers et al 1993b).

In the Melbourne study, as the hypothesis regarding commercial laxative use being a risk was not strongly held by the investigators, and as at that time there was no hypothesis that any particular type of commercial laxative use may be a risk, all previously used commercial laxatives were grouped together and examined in relation to those who did not report regular laxative use (Kune et al 1988). Because of the suggestion that anthraquinone-containing laxatives may be related to colorectal cancer risk, the original data in the Melbourne Colorectal Cancer Study were re-analyzed according to the class of laxative used (Kune 1993). In this re-analysis, when laxatives were divided into various groups, namely those containing anthraquinones, phenolphthalein, mineral salts and "others", previous laxative intake was similar between cases and controls. In particular, the previous use of anthraquinone-containing laxatives was not associated with the risk of colorectal cancer, the relative risk being 1.0 (Kune 1993).

On present evidence, chronic laxative use including the chronic use of anthraquinone-containing laxatives, is probably not etiologically associated with colorectal cancer.

CONCLUSIONS

The central most important finding related to bowel function and colorectal cancer is that intestinal transit time is inversely related to large bowel cancer risk, that is, the longer the transit time the higher the risk. Thus, factors which influence intestinal transit time are likely to indirectly influence large bowel cancer risk. Studies have not been sufficiently detailed to assess risk for colon cancer and rectal cancer independently, and most work relates to the colon.

Dietary fiber intake has an important influence on large bowel function and bowel habit. An increase in dietary fiber intake is associated with increases in stool weight and the frequency of bowel motions, a change in the consistency of bowel motions towards softness with the bowel motions becoming less formed, and most importantly, a decrease in transit time. These aspects of bowel function in relation to a high fiber intake appear to be, at least in part, responsible for the protective effect of a high fiber diet for colorectal cancer.

Normal bowel habit in so-called Western communities can be reasonably defined as having between 3 bowel motions per day and 3 bowel motions per week, consisting of formed stools retaining their shape. This so-called "normal" range of bowel habit is too broad to be useful in the clinical or epidemiologic assessment or prediction of colorectal cancer risk.

The present major difficulty is the lack of a simple method for assessing intestinal transit time that would be useful to predict colorectal cancer risk in the clinical or epidemiologic setting. Self-reported frequency of bowel motions alone

has not been found to be useful. A method of self-reported consistency and shape such as the seven-point Bristol Stool Form Scale, may be useful; however, this has not been given either a clinical or an epidemiologic trial in relation to colorectal cancer risk. Very likely, a measure which combines stool frequency, consistency and shape may become the most useful in the clinical and epidemiologic setting.

Self-reported chronic constipation is not a reliable predictor of colorectal cancer risk, probably because of difficulties in the interpretation and definition of the word "constipation". In the one study which was able to examine self-reported constipation in detail, it was a risk for colon cancer in males, and this risk was largely explained by the high fiber/vegetable intake, probably reflecting the role of dietary fiber in relation to transit time.

In the absence of pre-existing chronic ulcerative colitis or Crohn's colitis, self-reported chronic diarrhea in most studies, with one exception, was not associated with colorectal cancer risk. Chronic laxative use is prevalent in Western communities and about one in five adults use commercial laxatives regularly. No association was found between commercial laxative use and colorectal cancer risk, including the absence of a relationship with previous use of anthraquinone laxatives, phenolphthalein-containing laxatives, mineral salt-containing laxatives, and also when all laxatives were grouped together.

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12

NUMBER OF CHILDREN, AGE AT FIRST BIRTH, HORMONES

Two Jews are talking about their family:
"And how many children do you have?"
"None".
"No children?! So what do you do for aggravation?"

The Joys of Yiddish by Leo Rosten
Penguin Books 1971, with permission

NUMBER OF CHILDREN AND AGE AT FIRST BIRTH

Early clues that colorectal cancer is in some way related to parity were that higher than expected rates of colorectal cancer were noted in nuns as well as in single women compared to married women (Fraumeni et al 1969; Ernster et al 1979).

There were 3 studies which used census-type data to relate parity with colorectal cancer risk, and of these, 2 found no association while the third study found a statistically significant protective effect with parity when compared to women who had no children (Miller et al 1980; McMichael and Potter 1984; Plesko et al 1985).

There were 21 studies which directly examined the relationship between the number of children and colorectal cancer risk (16 case-control, 5 cohort), of which 18 also examined the association between age at first birth and risk of colorectal cancer (Table 12.1). Of particular interest is that only 3 studies

examined the effect of the number of children and age at first birth in males, as well as in females (Wu et al 1987; Kune et al 1989; Kampman et al 1994). The census-type study by McMichael and Potter in 1984 compared males with females, but not in the same population in which a protective effect was found for parity and colorectal cancer.

NUMBER OF CHILDREN

Of the 16 case-control studies which examined the association between increasing parity and colorectal cancer risk, a protective effect was found in 11 (Table 12.1), statistically significant in 7. In 2 of 7 studies which were site-specific for colon and rectum, the protective effect was noted for colon cancer only (Weiss et al 1981; Potter and McMichael 1983). In one study the protective effect was present with only 4 or more children (Gerhardsson de Verdier and London 1992). Of the 10 studies which used population or neighborhood controls, 9 found a protective effect, while only 2 of 6 studies using hospital-based controls found protection with an increasing number of children (Table 12.1). Hospital-based controls are less suitable than population-based or neighborhood controls for the study of a cancer which is likely to have several lifestyle-related causes, since hospitalized controls are likely to be "over-exposed" to some of the likely etiologic agents such as alcohol consumption and smoking, and this will tend to a null result (Wynder and Stellman 1992). Although Peters et al 1990 found a U-shaped relationship between the number of pregnancies and colorectal cancer risk, with a decreasing risk up to 4 successive pregnancies, and then an increasing risk with additional pregnancies, the study from Northern Italy by Franceschi et al 1991 showed increasing levels of protection with successive pregnancies up to 5 or more compared to nulliparous women. Colorectal cancer diagnosed at older ages seems to show a more consistent parity effect (Potter et al 1993). In the 3 studies which were able to correct for other important risk factors of colorectal cancer, namely age, occupation, previous diet, weight, physical activity, oral contraceptive use in females, and a family history of colorectal cancer, the protective effects remained unchanged, indicating that the number of children effect is likely to be an independent risk factor (Kune et al 1989; Peters et al 1990; Kampman et al 1994). In one study the protective effect of children was only present in women who did not use exogenous hormones (Davis et al 1989). In that study also, after controlling for smoking, the parity protection became less evident, consistent with the likely anti-estrogen effect of smoking.

Of the 5 cohort studies, only the study of Wu and colleagues 1987 found a statistically non-significant protection with an increase in the number of children (Table 12.1). In the Iowa Women's Study, Bostick and co-workers 1994 found a risk and a statistically significant trend with an increasing number of live births. A meta-analysis of 8 studies by Peters et al 1990 showed a statistically significant protective effect for colorectal cancer with increasing parity.

Table 12.1 Summary data of 21 studies (16 case-control, 5 cohort), showing association between number of children, age at first birth and colorectal cancer

Study method	Number of studies	Studies with 50% or more protection Number examined effect	
		Protection with increasing number of children	Protection with early age of first birth
CASE-CONTROL Population or neighborhood controls	10	9/10	4/9
CASE-CONTROL Hospital-based controls	6	2/6	1/4
ALL CASE-CONTROL	16	11/16	5/13
COHORT	5	1/5	0/5

Data Sources

This table was compiled from the following studies:
Dales et al 1979; Weiss et al 1981; Byers et al 1982; Potter and McMichael 1983; Papadimitriou et al 1984; Howe et al 1985; Wu et al 1987; Davis et al 1989; Kune et al 1989; Negri et al 1989; Peters et al 1990; Chute et al 1991; Franceschi et al 1991; Kvale and Heuch 1991; Wu-Williams et al 1991; Gerhardsson de Verdier and London 1992; Bostick et al 1994; Jacobs et al 1994; Kampman et al 1994; Olsen et al 1994: Troisi et al 1995.

Two of the 3 studies which examined males as well as females found a protective effect of an increasing number of children for men also (although less pronounced than in women), findings likely to be of etiologic significance (Wu et al 1987; Kune et al 1989). The study which did not find an effect in men had relatively few study numbers (232), and even in women the effects noted were not statistically significant (Kampman et al 1994). The one study which examined the effect of having children in men only, very interestingly found a statistically highly significant protective effect of fatherhood for distal colorectal adenomas, after statistical corrections were made for diet factors, smoking, alcohol, body mass index and physical activity (Jacobson et al 1994). The

number of children effect is a reasonably consistent finding in case-control studies and it may be an etiologic candidate for colorectal cancer, although the absence of an effect in 3 of the 4 cohort studies is concerning. Moreover, the mechanism involved is unclear, particularly as the "female sex hormone hypothesis" would be unable to explain an effect which in men is similar, though less pronounced than in women, unless it is postulated that the protection afforded by an increasing number of children has more than one mechanism, of which one is the female sex hormone effect, and that there are also other factors involved which are as yet unidentified (Kune et al 1989; Kravdal 1994).

AGE AT FIRST BIRTH

Of the 13 case-control studies which examined the association between age at first birth and colorectal cancer risk, only 5 found a protective effect of early age of first birth (Table 12.1), and this was statistically significant in 3. None of the 5 cohort studies that examined this association found a protective effect of early age at first birth (Table 12.1). The one study that was able to make statistical corrections for other risk factors in colorectal cancer, namely the Melbourne Colorectal Cancer Study, in which the confounding factors of age, occupation, previous diet, oral contraceptive use in females and a family history of colorectal cancer were corrected for, the age at first birth effect remained a statistically significant stable trend after these corrections (Kune et al 1989). The early age of first birth protection is much less strong and less consistent than the number of children effect, and the null results in all 5 cohort studies is concerning.

THE EFFECT OF FEMALE SEX HORMONES

In this section, the effects of endogenous female sex hormones, as reflected by the age of menarche and menopause, of hysterectomy with oophorectomy, as well as the effects of exogenous female sex hormone administration, will be discussed in relation to colorectal cancer risk.

ENDOGENOUS FEMALE SEX HORMONE EFFECTS

Age of Menarche and Menopause

No association has been found between colorectal cancer and age at menarche in any of the studies which investigated this effect (Wu et al 1987; Peters et al 1990; Franceschi et al 1991; Bostick et al 1994; Troisi et al 1995). A weak protective effect for a late age of menopause has been noted in several studies (Papadimitriou et al 1984; Wu et al 1987; Peters et al 1990; Franceschi et al 1991; Kampman et al 1994). This last finding adds some support to the female sex hormone hypothesis of colorectal cancer, suggesting that a longer exposure to these hormones with a late menopause has a protective effect.

Effects of Hysterectomy and Oophorectomy

Hysterectomy performed for a uterine cancer is more common among colorectal cancer patients than the population in which they live, and this would be expected since cancer of the body of the uterus appears to have similar etiological factors to colorectal cancer (Kune et al 1988). However, for benign lesions of the uterus, with the exception of the study of Wu and colleagues 1987, in which an excess risk was associated with hysterectomy, other studies found no association between previous hysterectomy and colorectal cancer (Weiss et al 1981; Potter and McMichael 1983; Kune et al 1988; Furner et al 1989; Peters et al 1990; Jacobs et al 1994). Documented ovary removal in association with hysterectomy was, however, only known in 2 studies (Furner et al 1989; Jacobs et al 1994). Thus the effects of bilateral oophorectomy on colorectal cancer risk have not been extensively studied.

EXOGENOUS FEMALE SEX HORMONE ADMINISTRATION

Oral Contraceptive Use

Of the 5 studies which examined oral contraceptive (OC) use and colorectal cancer risk, site unspecified, 4 found a protective effect, statistically significant in one (Furner et al 1989; Chute et al 1991; Franceschi et al 1991; Fernandez et al 1996), and one showed a non-significant risk (Weiss et al 1981). A recently reported case-control study from Northern Italy shows significant protection with OC use and colorectal cancer risk after adjustment for social class, family history of colorectal cancer, age at menarche and parity, with a significant inverse trend for exposure to OC for longer than 2 years (Fernandez et al 1996).

Case-control studies which examined OC use and colon cancer separately showed inconsistent results, Potter and McMichael 1983 finding statistically non-significant protection whilst Kune et al 1990, Peters et al 1990, Jacobs et al 1994 and Troisi et al 1995 found no association. Two of the studies with a null result controlled for several confounding variables, suggesting that OC use is unlikely to be associated with the risk of colon cancer (Kune et al 1990; Peters et al 1990). The 3 studies which examined OC use and rectal cancer separately showed a statistically non-significant level of protection by Potter and McMichael 1983, and a statistically significant risk with OC use by Kune et al 1990 and by Troisi et al 1995. The study by Kune et al 1990 was adjusted for several confounding factors including all dietary risk factors found in the study, alcohol consumption, family history of colorectal cancer, age at first birth and number of children, and OC use risks remained largely unchanged for both colon and rectal cancer. In that study, previous OC use and beer drinking showed a statistically significant joint effect (Kune et al 1990), and the explanation for this may lie in changes of DNA methylation which are known to occur among

alcohol consumers (Chapter 7) and possibly at estrogen receptor gene sites also, as noted by Issa et al in 1994.

The cohort studies reported in their survey by Milne and Vessey 1991, the cohort of the Nurses' Health Study reported by Chute et al 1991, and the Iowa women's cohort reported by Bostick et al 1994, do not show any associations between previous OC use and colorectal cancer, colon cancer or rectal cancer risk. The problem with all the above studies is that user numbers are small and also that oral contraceptives have undergone major formula changes which have not been considered in any of the epidemiologic studies. A pooled analysis has so far not been made. On present evidence, neither colon nor rectal cancer appears to be related to previous OC use.

Hormone Replacement Therapy

Hormone replacement therapy (HRT), usually in the form of estrogen, has not been associated with statistically significant changes in the risk of colorectal cancer in several studies (Weiss et al 1981; Potter and McMichael 1983; Wu et al 1987; Davis et al 1989; Peters et al 1990; Wu-Williams et al 1991; Bostick et al 1994; Risch and Howe 1995). A meta-analysis of HRT and colorectal cancer risk showed a null effect, although it did not include several important recent studies (MacLennan et al 1995). Moreover, a recent review argues that there are cogent reasons why HRT should be seriously considered as a candidate in the chemoprevention of colorectal cancer (Potter 1995).

In one study of long-term HRT use following hysterectomy for benign conditions, fewer than the expected number of colon cancers developed (Burch et al 1975). In the Nurses' Health Study, past users of HRT were statistically significantly protected (Chute et al 1991). In 2 population-based case-control studies, previous HRT was statistically significantly protective for colon cancer (Gerhardsson de Verdier and London 1992; Newcomb et al 1992). In 2 other studies HRT was significantly protective for colorectal cancer, and this effect remained after controlling for parity, age at first birth and hysterectomy, as well as some other factors (Furner et al 1989; Jacobs et al 1994). An important recent report of the American Cancer Society cohort begun in 1982, revealed a statistically significant protective effect of estrogen replacement therapy for fatal colon cancer, with a significant dose-response effect, and this protective effect remained after confounding factors were controlled (Calle et al 1995). A recent large case-control study reported from the USA revealed that colon cancer risk, but not rectal cancer risk, was reduced by about half in women who have used HRT, after adjustment for family history of colorectal cancer and alcohol consumption (Newcomb and Storer 1995). A recent case-control study from

Northern Italy has shown a statistically significant protective effect of HRT for colorectal cancer after correction for social class, family history of colorectal cancer, age at menarche and parity, and in this study there was also a significantly increased protection with more than 2 years use of HRT (Fernandez et al 1996). Finally, in a large US cohort of over 50,000 women observed up to 10 years, a statistically non-significant 40% protection was present for both colon and rectal cancer among current HRT users of over 5 years duration (Troisi et al 1995). There are therefore 9 important, well-conducted recent studies which have consistently found a protective effect for previous HRT.

As the more recent studies generally found a protective effect, this result may in part reflect larger user numbers in the later studies due to greater acceptance of HRT, and therefore a stronger statistical power to show an effect, and in part a longer period of use of HRT in the community, the latter indicating that a dose effect is involved. Current evidence suggests that HRT, especially if used for several years, is protective for colorectal cancer. This conclusion has several important corollaries. First, as OC use has shown inconsistent and largely a null effect and as the parity effect is not strong (and also found in men), it may be that exposure to female sex hormones is a more important protective factor in the peri and postmenopausal period, rather than when that exposure occurs during the reproductive years. Secondly, the protective effect of HRT may be a pharmacologic rather than physiologic effect, and HRT among its other benefits, may be added to the candidate list for chemoprevention of colorectal cancer (Chapter 18). It has even been speculated that one of the reasons for the drop in US female colorectal cancer mortality during the 30 years 1960–1990 is related to an increasing use of HRT (current prevalence of 20%) among menopausal women (Potter 1995). Although colon and rectal cancer has not been clearly separated in most positive studies, and as it is known that rectal cancer can be missclassified for colon cancer, at present there is no strong evidence for a qualitative site-specific difference in the HRT protection of large bowel cancer, though on current evidence the protection seems more important for colon cancer than for rectal cancer.

In all HRT considerations, it needs to be noted that HRT formulations initially included estrogens only, however more recently progestogens have been added to a number, and the effects of these changes in relation to colorectal cancer risk have so far not been addressed.

The understanding of the etiologic role of administered female sex hormones, be they oral contraceptives or hormones used around and after the menopause, needs to be regarded as fragmentary at present, and a large well-designed study that delineates hormone type as well as dose, would be useful.

POSSIBLE MECHANISMS INVOLVED

The mediation of the number of children and age at first birth effect is uncertain. It is also unclear how endogenous or exogenous female sex hormones influence colorectal cancer risk. There are several hypotheses, of which the female sex hormone hypothesis has been the most explored.

FEMALE SEX HORMONE HYPOTHESIS

What may be referred to as the "female sex hormone hypothesis" was first proposed by McMichael and Potter in 1980. In several large population-based studies, incidence rates were higher in males than in females for both colon and rectal cancer with the exception of colon cancer between the ages of 35 and 60 years in which there was a female excess, and particularly so for right colon cancer (Correa and Haenszel 1978; McMichael and Potter 1980; Kune et al 1986; Giles et al 1987). This may be interpreted as indirect evidence that a decrease in the level of female sex hormones in some way contributes to the female excess found for colon cancer at those ages. However, in more recent US data, incidence rates are higher for men than for women for both colon and rectal cancer at all ages (Chow et al 1991). In the study of Potter and McMichael 1983, the protection afforded by the increasing number of children was evidenced more for right colon cancer, and in the study of Howe et al 1985, the early age at birth of the first child protection was noted particularly for right colon cancer. Positive associations were noted in a number of studies for right colon cancer in females following cholecystectomy, and this may be interpreted as indirect evidence of the female sex hormone hypothesis (Chapter 10). The cholecystectomy effect appears to be only quantitatively different in men, and this difference may in part be due to a low statistical power of studies in men, who have a lower cholecystectomy rate than women (Chapter 10).

It was proposed that female sex hormones influence bile acid metabolism, as progestogens during pregnancy reduce bile acid production and thereby decrease the risk of large bowel cancer (McMichael and Potter 1980). However, data on bile acid metabolism and particularly on human bile composition in the duodenum, are inconsistent, and the amount and composition of bile acids in the large bowel during pregnancy has not been studied in detail (Bennion and Grundy 1978; Nakagaki and Nakayama 1982).

It has also been proposed that women have slower bowel transit times, smaller fecal bulk, and produce a smaller volume of bile acids than men, suggesting that these effects may be female sex hormone related (Lampe et al 1993). Intestinal transit time is positively associated with colon cancer risk (Cummings et al 1992). Men as a group probably have shorter transit times than women (Probert et al 1993). Furthermore, the transit time in menstruating women is slower than in older women, it is slower in the second half of the menstrual cycle and slower in those taking oral contraceptives, and these effects

probably occur because of the inhibition of the gut stimulating hormone motilin by progesterone (Christofides et al 1982; Davies et al 1986; Lampe et al 1993; Probert et al 1995). These effects appear to be female sex hormone related, but they act as a risk, and not as a protective factor, as proposed by the female sex hormone hypothesis.

Although both male and female sex hormone receptors have been identified in human colorectal cancers as well as in normal colorectal mucosal cells, their actual role and how they relate to sex hormones in the development of colorectal cancer is unknown (D'Istria et al 1986; Stebbings et al 1986; Hendrickse et al 1993; Singh et al 1993). Hypomethylation of DNA has been associated with genetic change in relation to alcohol consumption and low folate and methionine diets in the development of colorectal tumors (Chapters 6 and 7), and recently changes in DNA methylation at the estrogen receptor gene in colon tumors were also found; however, this finding does not bring one closer to an understanding of the role of hormone receptors in colorectal neoplasia (Issa et al 1994). Female sex hormones may have a direct effect on the mucosa of the large bowel, since experiments on mice indicate that progesterone, present in high levels during pregnancy, promotes the differentiation and inhibits the proliferation of colonic epithelial cells, thereby making these cells less susceptible to neoplastic change, and this effect is in keeping with current general concepts of carcinogenesis (Hoff and Chang 1979; Albanes and Winick 1988; Preston-Martin et al 1990).

An experimental study which examined pregnancy and parity in rats in relation to dimethylhydrazine-induced large bowel cancer found that multiparous female rats showed reduced rates of colon cancer relative to nulliparous rats (Sjogren 1977). This study supports the number of children effect, but provides no clues to the mechanism of its mediation.

The protective effects found in men as well as in women for the number of children effect, the weak or null results in relation to the ages of menarche and menopause and to the previous use of OC has weakened the female sex hormone hypothesis of colorectal cancer etiology. The excess female incidence rates for right colon cancer between the ages of 35 and 60 in studies conducted during the 1970s, 1980s, the parity protection being stronger for women than for men and becoming important in women who have colorectal cancer diagnosed at older ages, the weak protective effect of a late menopause, and the protective effect of prolonged HRT, remain the cornerstones for the female sex hormone hypothesis. The data suggest that female sex hormones have a protective effect, which is not strong, and which may be important for women at the menopause, and later.

OTHER HYPOTHESES

It was suggested that increased physical activity associated with having a large family may be the reason for the protective effect seen in both women and men (Wu et al 1987). As the effect appeared to be independent of the major putative

etiologic factors of hereditary predisposition, diet and alcohol consumption, it was suggested by Kune et al 1989, that some other so far unidentified lifestyle factors associated with having children is responsible for these effects. More recently, Kravdal also suggested that when a relationship between motherhood and cancer incidence is being examined, the effect on fatherhood should also be studied (Kravdal 1994). It is speculated that not only the physical activity, but also the social support, as well as the emotional involvement with the joys and problems of a large family, is in some way protective against malignant tumors in general, including colorectal cancer, and this is worthy of further study.

CONCLUSION

Having no children appears to be a risk for colorectal cancer, while having children is protective, with the level of protection increasing with the number of children. The effect appears to be qualitatively similar for males and females, though it is stronger in women, and this suggests that there is more than one mechanism involved. An early age at first birth may be protective for colorectal cancer, although this effect has been found much less consistently than the number of children effect.

A weak protective effect of late menopause has been found in some studies, and this is opposite to the effect in breast cancer, a cancer which has epidemiologic similarities to colorectal cancer. No effect has been found with an early menarche. Previous hysterectomy, irrespective of whether the ovaries were or were not removed at the time of surgery has shown null results in relation to colorectal cancer risk, although this effect has not been extensively studied.

The use of female sex hormones in the form of OC use has so far shown no consistent relationship with colon cancer nor with rectal cancer risk; however, individual studies have had small study numbers and a pooled analysis has not been done so far. Statistically significant risk elevation with OC use and rectal cancer in 2 studies, with a joint effect in relation to beer consumption in one, requires further examination. The present evidence suggests that OC use is not associated with the risk of colorectal cancer. However, a protective effect for menopausal HRT has emerged in most recent studies, and especially so with prolonged use. These findings have important implications in relation to HRT as a potential chemopreventive agent for colorectal cancer in menopausal women.

The mediation of the number of children, age at first birth, endogenous female sex hormone changes, and of administered female sex hormones in the form of OC and HRT, is unclear. The "female sex hormone hypothesis" has been weakened by the finding that the number of children effect applies to males as well as to females, by the absence of any effects in relation to an early menarche, and in relation to previous oophorectomy, and also by inconsistent, weak and mainly null findings in relation to previous OC use. However, the female sex hormone hypothesis should not be abandoned because it is supported by the

number of children effect being stronger in women than in men, by the protective effect noted with a late menopause, and by the important protective effect of menopausal HRT found in most recent studies. The protective effect of female sex hormones appears to be important for women around the menopause and later. The physical activity associated with having a large family has been another mechanism suggested, since physical activity has been consistently found to be a protective factor for colorectal cancer. The idea that there may be some other, so far unidentified, lifestyle factors which are associated with having a large family, though worthy of study, has so far not been explored.

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13

ASBESTOS AND OTHER OCCUPATIONAL EXPOSURES

Occupational factors are probably not an important contributory cause of colorectal tumors. Sedentary occupations have been consistently noted to be a risk for both colorectal cancer and colorectal adenomas (Chapter 9). Occupational exposure to asbestos fiber is discussed separately because of the unique place of asbestos in cancer epidemiology.

ASBESTOS FIBER EXPOSURE

HISTORICAL ASPECTS

Although the association between exposure to asbestos fiber and chronic lung disease was noted in the 1930s, its possible relationship with lung cancer was first hinted at in 1935, and then first systematically studied in 1955 (Lynch and Smith 1935; Doll 1955; Breslow 1955). By 1960, cases of pleural mesothelioma were described and related to asbestos mining in South Africa, and from about this time, the study of malignant tumors related to occupational exposure to asbestos fiber had expanded (Wagner et al 1960).

The first major study on asbestos exposure and gastrointestinal tract malignancy was published by Selikoff and co-workers in 1964. In that study, cancers of the esophagus, stomach, colon and rectum were grouped together, probably because of small numbers identified, and it was found that there was a threefold increase in the number of deaths compared to that expected, and it was suggested that significant exposure to asbestos was at least in part responsible for this excess mortality (Selikoff et al 1964). The association between occupational

exposure to asbestos and colorectal cancer risk was first reported in 1979 (Puntoni et al 1979; Selikoff et al 1979).

EPIDEMIOLOGIC EVIDENCE

Of the 21 cohorts of workers who were heavily exposed to asbestos fiber by inhalation, standardized mortality ratios from colon cancer were elevated above 1.5 in 7 (Selikoff et al 1979; Puntoni et al 1979; Zoloth and Michaels 1985; Ohlson and Hogstedt 1985; Peto et al 1985; Seidman et al 1986; Woitowitz et al 1986), whilst in 14 other cohort studies this ratio was below 1.5 (McDonald et al 1980; Peto et al 1985; Ohlson et al 1984; Woitowitz et al 1986; Gardner et al 1986;Hodgson and Jones 1986; Hughes et al 1987; Enterline et al 1987; Armstrong et al 1988; Raffn et al 1989; Piolatto et al 1990; Albin et al 1990). In a recently reported cohort study from Sweden, mortality was not increased, but the incidence rate was statistically significantly elevated for right colon cancer (Jacobsson et al 1994). The risk levels associated with the positive cohort studies were modest elevations only, ranging from 1.5 to 2.2.

A meta-analysis of 5 cohorts reported by Morgan and associates in 1985 showed a statistically non-significant elevation of standardized mortality ratio and concluded that there was no association between asbestos exposure and the risk of colorectal cancer. Similarly, a meta-analysis of Frumkin and Berlin in 1988 reported 15 cohorts of asbestos-exposed workers with an overall pooled standardized mortality ratio of colorectal cancer of 1.11, and this elevation was not statistically significant. However, in those studies in which the standardized mortality ratio for lung cancer was more than 2.0, there was a statistically significant elevation of the mortality ratio of 1.61 for colorectal cancer, in comparison with no elevation for colorectal cancer in those studies which reported a ratio for lung cancer less than 2.0 (Frumkin and Berlin 1988). Based on this dichotomy with respect to lung cancer risk, the authors concluded that this indicates asbestos exposure to be a risk for colorectal cancer because a high risk of lung cancer would indicate a high degree of exposure to asbestos fiber. Doll and Peto in 1987 reported on 18 cohorts, correlating the standardized mortality ratios for lung cancer and gastrointestinal cancers, with a highly statistically significant correlation coefficient. These data are consistent with the meta-analysis of Frumkin and Berlin for colorectal cancer. Doll and Peto concluded that the correlation was not due to an increased risk of gastrointestinal cancer in relation to increased exposure to asbestos fiber, but rather that it was due to miscertification of the cause of death of gastrointestinal cancer, which was over-reported. Selikoff examined the question of miscertification in detail and concluded that there were true excesses of risk for colorectal cancer in relation to previous occupational exposure to asbestos (Selikoff 1982).

A further meta-analysis of 20 asbestos-exposed cohorts examined the relationship of colorectal cancer to asbestos type, and found that exposure to amphibole asbestos, but not to serpentine asbestos, is associated with colorectal

cancer risk. However, the problem of miscertification bias could not be excluded with any confidence in this meta-analysis (Homa et al 1994). The problem with cohort studies is that they are generally unable to make statistical corrections for important confounding etiologies, such as diet, alcohol consumption and smoking. A clear exposure dose-response gradient for colorectal cancer risk has not been shown in any of the studies (Gamble 1994).

Of 6 case-control studies, the study of Fredriksson et al 1989 found an elevated risk of 2.1 which was statistically not significant in relation to exposure to high grade asbestos fiber, and the study of Vineis et al 1993 found a statistically significant risk elevation. A statistically non-significant elevation of risk for adenomas was present in one study (Neugut et al 1991). Three other studies found either no association with the risk, or only very slight risk elevations, and one found a decreased risk (Spiegelman and Wegman 1985; Peters et al 1990; Garabrant et al 1992; Demers et al 1994). The study by Garabrant et al 1992 is of special importance because they were able to statistically correct for confounding factors such as family history of colorectal cancer, some aspects of diet, weight and physical activity, and when these corrections were made, the slight and statistically non-significant elevation of risk was reduced from 1.16 to below 1.0. It was concluded that before causality can be attributed to asbestos exposure and colorectal cancer, confounding by other known risks for colorectal cancer need to be controlled for (Garabrant et al 1992).

Regarding the degree of previous exposure to asbestos, there are 2 studies which have recorded an excess mortality for colorectal cancer in the presence of relatively short exposures or only intermittent exposures to asbestos; however, precise data on the degree of exposure is not available (Zoloth and Michaels 1985; Seidman et al 1986).

If gastrointestinal cancer, including colorectal cancer, is related to previous asbestos exposure, then this may become evident by drinking water which is contaminated with asbestos. Numerous studies examining drinking water showed null effects, including a study by Siemiatycki from an area in which chrysotile asbestos contamination of the drinking water was extremely heavy. However, in the study by Conforti et al 1981, a weak association was found with drinking water for gastrointestinal cancer, taken together, but not for colorectal cancer.

Thus the epidemiologic evidence of an association between previous exposure to asbestos fiber and colorectal cancer risk is weak, and particularly so when it is considered that most studies were unable to control for important confounding factors, and that a dose-response effect was not found in the positive studies.

EXPERIMENTAL EVIDENCE

Numerous studies of lifetime ingestion of various forms of asbestos by rats and hamsters, studied in the National Toxicology Program of the National Institutes of Health in the USA, have uniformly failed to show evidence of an increase in the number of colon cancer tumors, and other studies also failed to show any effects of prolonged ingestion of asbestos in experimental animals (Bolton et al 1982; Condie 1983; National Toxicology Program publications 1985, 1990; McConnell 1988, 1990). An earlier report by Donham and colleagues in 1980 showed a statistically non-significant increase in both benign and malignant tumors of the colon after long-term feeding of rats with asbestos compared to controls, although this was not confirmed by later studies. Donham and colleagues noted chrysotile fibers in the colons of 6 of 10 asbestos-fed rats on electron microscopy, suggesting that ingested asbestos is not inert in the colon. In a recent study crocidolite and chrysotile asbestos induced aberrant crypt foci were present in the colon of rats, but this exposure was 10 times less effective than the known carcinogen azoxymethane (Corpet et al 1993).

The experimental evidence that the ingestion of asbestos fiber is carcinogenic to the gastrointestinal tract and to the large bowel in particular, has not been firmly established in experimental studies, and most studies showed no association.

MECHANISMS

At present there is no scientific evidence for any mechanism whereby asbestos fiber ingestion may cause colorectal cancer. The most important hypothesis is that asbestos is a chronic irritant of the tissue in which it is found, resulting in an increase in cell multiplication. The problem is that there is no evidence that such is the case in experimental animals which have been fed asbestos. When asbestos fibers were fed directly into the stomach of a baboon, this fiber was not shown to be present subsequently in any of the baboon's organs (Hallenbeck et al 1981). However, minuscule amounts of the fiber ingested by rats have been found in their lymph streams, indicating that at least some fibers do traverse some part or parts of the gastrointestinal tract epithelium of the rat (Sebastien et al 1980). The Donham study also indicates that in asbestos-fed rats, chrysotile fiber may traverse the colonic mucosa. This has also been examined in humans, and the migration of asbestos fiber into the colon has been noted in those occupationally exposed to asbestos fiber (Ehrlich et al 1991). Furthermore, exposure of chrysotile and crocidolite asbestos produced aberrant crypt foci in the rat colon (Corpet et al 1993).

Ingestion of asbestos fibers which find their way to the large bowel is the most likely route of action. If ingested asbestos fiber is the manner in which asbestos is responsible for gastrointestinal cancers at several sites, then there should be a decreasing gradient of risk from the oropharynx to the rectum, and

this appears to be the case (Doll and Peto 1987). The recently reported Swedish cohort showing a statistically significant elevation of risk for right colon cancer only, also points to this effect (Jacobsson et al 1994).

CONCLUSIONS

In only one-third of 21 asbestos-exposed cohorts have standardized mortality ratios exceeded 50% of the expected rate. Elevated risks were noted in only 2 of 5 case-control studies. The studies that have found elevated risks were not able to control for important confounding factors, in particular for family history of colorectal cancer, diet, alcohol consumption and smoking. The one study that was able to control for some confounding factors found no elevation of risk. A clear dose-response effect was not found in any of the studies. Among the positive cohort studies there is also the possibility that the elevated risks are largely explained by miscertification of the cause of death. A lifetime of drinking water that is contaminated with asbestos, sometimes heavily, has not been shown to be associated with elevated risks of colorectal cancer in the populations being studied. However, a recent meta-analysis has shown an association between colorectal cancer exposure to amphibole asbestos but not serpentine asbestos.

With two exceptions, there is no evidence which indicates that the chronic ingestion of asbestos by experimental animals results in an increased rate of colonic tumor development. There are no mechanisms specifically postulated as to how ingested asbestos fiber may produce colorectal cancer. A small proportion of ingested asbestos fiber can traverse the gastrointestinal tract of experimental animals, including the colon, and this was also shown in one study of the human colon. The presence of asbestos fiber has been shown to result in aberrant crypt foci in the rat colon.

At present, it appears unlikely that occupational exposure to asbestos fiber is an important risk for colorectal cancer, and it may not be a risk at all. However, the epidemiologic studies are not precise enough to exclude the possibility that a few instances of colorectal cancer are contributed to by a heavy ingestion of asbestos fiber, a substance known to be carcinogenic in several other organs.

OTHER OCCUPATIONAL EXPOSURES

Excess colorectal cancer risk has been reported in the chemical, textile, rubber, petroleum, automotive, woodworking, shoe and leather, and metal industries (Neugut and Wylie 1987; Brownson et al 1989; Gerhardsson et al 1992; Chow et al 1993, 1994).

Exposures which have been suggested as occupational factors in colorectal neoplasia, apart from asbestos, include aromatic hydrocarbons, polypropylene, fuel and other heavy oils and solvents, dyes, wood and metal dust, abrasives and synthetic fiber (Spiegelman and Wegman 1985; Siemiatycki et al 1986; Neugut

and Wylie 1987; Acquavella et al 1988, 1991; Chow et al 1994). None of these exposures have been conclusively associated with colorectal tumors; however, the aromatic hydrocarbon exposure appears to be the most consistent.

The most consistent occupational risk for colorectal cancer has been that of sedentary occupations; physical inactivity appears to be the basis of this increased risk (Chapter 9), rather than any exposures which may be associated with the occupations themselves.

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14

RADIATION

Ionizing radiation is neither an important nor a common contributory cause of colorectal cancer. However, there is evidence from a large cohort of Japanese atomic bomb survivors, evidence from experimental studies, and clinical evidence from patients receiving pelvic irradiation, which shows that ionizing radiation can be an occasional component cause of colorectal cancer.

JAPANESE ATOM BOMB SURVIVORS

The 25 and 30 year follow-up data of the survivors of Hiroshima and Nagasaki atomic bombs published in the 1970s showed an increased mortality for a number of malignancies such as leukemia, thyroid cancer and breast cancer, but did not show elevated mortality rates for colorectal cancer (Okada et al 1975; Beebe and Hamilton 1975; Beebe et al 1978). When the follow-up was extended for a longer period, elevated mortality rates for colorectal cancer were also noted, and particularly for colon cancer (Kato and Schull 1982; Thompson et al 1984; Shimizu et al 1990). A radiation effect was not present among the survivors for either colon or rectal adenomas (Ron et al 1995).

EXPERIMENTAL EVIDENCE

Colonic cancers were induced using irradiation of rats by Denman et al 1978. Previously irradiated rectal mucosa has also been shown to undergo DNA abnormalities in the upper parts of the crypts, and this change may or may not be accompanied by the morphologic features of proctitis (Risio et al 1990).

HUMAN STUDIES

Apart from the Japanese atomic bomb survivor cohort, there have been no prospective or retrospective controlled studies of the relationship between irradiation and the subsequent development of colorectal cancer. All the human information relates to series of cases in which pelvic irradiation, usually for gynecologic cancer or occasionally for benign gynecologic conditions, was subsequently followed by the development of colorectal cancer (Castro et al 1973; Jao et al 1987; Levitt et al 1990; Kimura et al 1995).

The excess risk of colorectal cancer caused by pelvic irradiation is difficult to measure, partly because of the absence of controlled studies, and partly because gynecologic malignancies are known to be associated with excess colorectal cancer risk also (Chapter 20). Patients who have had radiation for the treatment of ovarian cancer have an increased risk of colorectal cancer subsequently, in comparison to patients with ovarian cancer who do not receive radiation, and this excess risk becomes apparent 5 or more years after irradiation, and can be as long as 20 years (Curtis et al 1985; Teppo et al 1985; Kimura et al 1995). There are also case reports of colorectal cancer developing following irradiation for benign conditions (Palmer and Spratt 1956; Jao et al 1987).

Both early radiation proctitis and late proctitis with scarring are present in many, though not all, subsequent cases of colorectal cancer, so that a history of proctitis, or the endoscopic appearance of proctitis, cannot be used as a definite indication that distal large bowel cancer will or will not develop (MacMahon and Rowe 1971; Castro et al 1973; Jao et al 1987).

CONCLUSION

Data are limited; however, both descriptive human studies and experimental studies in rats indicate that pelvic irradiation in therapeutic doses may be a contributory cause of distal colonic and rectal cancer in a small proportion of patients receiving pelvic irradiation, and that such a cancer may develop 5 or more years after therapy. Clearly, this group is best screened and followed by subsequent surveillance with the use of flexible fiberoptic sigmoidoscopy alone (Chapter 20), since elevated risk occurs at sites within the reach of the flexible sigmoidoscope.

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15

PERSONALITY FACTORS AND LIFE STRESSES

Cases are so frequent in which deep anxiety, deferred hope and disappointment are quickly followed by the growth and increase of cancer.

Sir James Paget, 1870

Causal research in the past has mainly focussed on physical factors such as an inherited tendency, alcohol consumption, diet, or various cancer producing substances such as tobacco and exposure to asbestos or to ionizing radiation. The role of psychosocial factors, such as personality characteristics and stressful life changes, have been researched much less frequently. There are several cogent reasons for this lack of research regarding the psychosocial etiology of cancer. There were major problems of measurement of psychosocial factors in cancer etiology, there were no plausible biologic mechanisms hypothesized connecting psychologic factors with the development of a malignant tumor, and most importantly, the overriding medical ethos for a long time dictated a rigid division between mind and body, thereby focussing on physical factors only in cancer etiology.

In spite of these difficulties, alongside the research on the physical causes of malignant disease, another body of research has developed hypothesizing initially that certain personality factors, and more recently, that stressful life changes and their perception, also have a role in the development of malignant disease.

There appear to be three phases in the development of this psychosocial research. The first relates to observations going back to Galen and subsequently

to several eminent surgeons and physicians who described the personality type of the cancer patient as being different to individuals who do not develop cancer. The second phase belongs to the 20th century, in which uncontrolled and usually small studies were performed examining the personality and psychologic or psychiatric profile of the cancer patient. The third phase is the advent of the controlled scientific study, in which specifically designed controlled clinical observations are made to test specific hypotheses. During this third and current phase, the biologic link is also being made between these hypothesized psychosocial factors in cancer etiology, and various hormonal, neurologic, and immune changes, thereby pointing to mechanisms of how these factors may operate in the development of malignant disease in humans. This link, which is being developed between the psychosocial etiology of cancer and its mechanism, is making biologic scientists feel increasingly comfortable that this type of research is more in line with the mainstream mechanistic ethos of cancer etiology than had been previously believed.

There have been three streams of research examining psychosocial factors in the development of malignant disease, namely the concept that depression and a feeling of "hopelessness" is related to the development of cancer, secondly that there is a certain "cancer-prone personality" characterized by an absence of emotional reaction or its suppression, and more recently, the concept that when humans are challenged by stressful life changes, their responses to these changes can lower their resistance to disease, including cancer.

In contrast to physical factors such as asbestos exposure, smoking or alcohol consumption in which certain particular sites such as the lung or large bowel are at risk, with psychosocial factors the overall hypothesis has remained general, and the assumption is made that psychosocial factors may be a component cause in the development of malignant tumors anywhere in the body. A description will be given of the current data on etiologic cancer research in relation to psychosocial factors for malignant tumors in general, as well as for colorectal cancer in particular.

THE CANCER PRONE PERSONALITY

Galen, in the 2nd century AD, was the first to observe that cancer in women was more commonly noted in those with a "melancholic" personality than those with a "sanguine" personality. Subsequently, several other notable physicians and surgeons reported that a particular temperament, depression and low affect are related to the development of various cancers, and later this anecdotal information was reviewed by several researchers (Paget 1870; LeShan 1959; Bahnson 1980, 1981; Eysenck 1985).

Early reports of the personality characteristics of cancer patients have also been reviewed extensively (Brown 1966; Abse et al 1974; Bahnson 1980, 1981). Although these early descriptions show some consistency in indicating denial,

repression, conformity and an inability to express negative emotions, the criticisms are that no control groups are used, that usually cancers from several sites were grouped together and that there was the possibility for major biases, such as recall bias and sample bias, to distort the data. Although these early studies contributed important observations, because of serious methodologic shortcomings they were not acceptable as evidence for a causal relationship.

Early research on the relationship between what is now called "stressful life events" or life changes, and the development of cancer, were again first observed by astute physicians such as Snow, who in 1893, reported that cancers of the breast and uterus following a major loss of a depressing nature is seen too frequently to be attributed to chance. Major loss, particularly of an important relationship such as death of a spouse, was frequently reported in early studies on life change and cancer and reviewed by a number of authors, however, major methodologic problems similar to those just described beset the acceptance of these uncontrolled reports (LeShan and Worthington 1955; Reznikoff 1955; LeShan 1959; Greene 1966; Bahnson 1980, 1981).

With the enormous advances in cancer epidemiology methodology, with the adoption of controlled studies by scientists working in the psychological arena, and with important advances in the understanding and measurement of the relationship between stress and illness in the 1960s, one sees the emergence of important studies shedding light on the possible relationship between psychological factors and the cause of cancer (Kissen 1960; Kissen and Eysenck 1962; Holmes and Rahe 1967; Rahe and Arthur 1978). Nevertheless, serious criticisms of the methodology used in studies attempting to relate psychosocial factors to cancer etiology up to the late 1970s, such as by Fox in 1978, still remained and dominated scientific thinking. Since the 1980s, criticism has been less visible with the accumulation of evidence from more rigorously conducted controlled studies (Kune and Bannerman 1992).

Against this background, the body of this chapter examines current evidence of the possible relationship between psychosocial factors and cancer etiology in general, and of colorectal cancer etiology in particular, drawn from well-conducted controlled studies. Both the validity and the shortcomings of these data, as well as avenues of future research are discussed.

DEPRESSION

All Cancer Sites

An early cohort study of 2500 persons in Sweden reported by Hagnell in 1966, using Sjöbring's test, indicated that women with cancer were more likely to have a depressive personality type than did controls. In the Western Electric Health Study, a cohort of over 2000 men employed at the Western Electric Company in 1957 and 1958, had the Minnesota Multiphasic Personality Inventory (MMPI) administered and the cohort followed in the first report for 17 years, and in the

second report for 20 years, in relation to incidence and mortality from cancer (Shekelle et al 1981; Persky et al 1987). This well-conducted study was positively associated at both 17 years and 20 years with both incidence and mortality from cancer and this positive association with psychologic depression, as measured by MMPI, remained after adjustment was made for age, smoking, alcohol intake, occupational status, family history of cancer, body mass index and serum cholesterol.

An interesting observation made in the Western Electric Study was that depression was associated more strongly with cancer mortality than with cancer incidence, suggesting that if depression is in some way causally linked with the appearance of cancer, it may operate at a later rather than earlier stage of neoplasia.

Colorectal Cancer

In the Western Electric Study the association did not appear to be stronger for one type of cancer than for another, although the number of cancers at each site were not large enough to have the statistical power to detect differences among different cancer sites. However, the association held for the 52 colorectal cancers detected in that study (Persky et al 1987).

In the case-control part of the population-based Melbourne Colorectal Cancer Study, depression was not measured by any known scale. However, self-reported childhood or adult life "unhappiness" was statistically significantly more common among colorectal cancer cases than among controls (Kune et al 1991a). In this study, the possibility of recall bias to explain case-control differences was examined and though this possibility may not have been completely controlled for, it was unlikely to be an important factor in explaining these results. These findings can be interpreted as indicating an etiologic aspect for depression, or that cancer-prone patients are more likely to perceive their past life experiences in a more negative way than those who do not develop cancer (Greer 1979; Bahnson 1980, 1981).

These studies, both prospective and controlled retrospective studies, indicate that depression (however measured), a low affect level during childhood and adult life, or a negative perception of life experiences, may be related to subsequent cancer risk and that this risk occurs at all cancer sites, including colorectal cancer.

A number of controlled studies have shown a relationship between a long-standing feeling of "hopelessness", often evoked by major losses in life, and malignant tumors (Schmale and Iker 1971; Grossarth-Maticek et al 1984). However, as this concept of hopelessness is usually enmeshed with serious life changes of loss, it will be considered in more detail when dealing with stressful life events and their perception.

ABSENCE OR REPRESSION OF EMOTIONAL EXPRESSION

Absence or suppression of emotional expression, particularly for negative emotions such as anger, has long been held to be an important part of the so-called "cancer-prone personality". Controlled studies in general lend support to this concept for all cancer sites, including colorectal cancer.

All Cancer Sites

Apart from the early anecdotal and descriptive observations of the personality of the cancer patient, which is deemed to be different from the population at large, a number of controlled studies have now shown that marked differences exist in the personality characteristics of cancer patients and controls either when all cancer cases are taken as one group and also when specific sites of cancer such as lung, breast, malignant melanoma and large bowel, are examined (Kissen and Eysenck 1963; Kissen 1967; Greer and Morris 1975; Grossarth-Maticek et al 1983, 1988; Kneier and Temoshok 1984; Eysenck 1985; Bremond et al 1986; Cooper et al 1986; Kune et al 1991a). Furthermore, some of these studies were prospective cohort studies, whilst others were prospective in the sense that the psychosocial and personality data were obtained before a diagnosis had been made (Greer and Morris 1975; Grossarth-Maticek et al 1985; Cooper et al 1986). In one other study several measures were taken to exclude selection and exclusion bias and recall bias, and also statistical corrections were made for the other known risk factors for the cancer under study (Kune et al 1991a). The internal and external consistencies of these studies, the prospective nature of some of the studies, and the statistical corrections which were made for confounding variables in some studies, make one conclude that there is a particular type of personality which is independently associated with the development of cancer at various sites.

The composite profile drawn from these various studies is that those prone to cancer have a personality which includes the elements of denial and repression of anger and of other negative emotions, a commitment to the prevailing social norms resulting in the outward appearance of a "nice" or "good" person, a suppression of reactions which may offend others, that is, self-abnegation in order to achieve harmonious social relationships and in order to avoid conflict. These characteristics appear to be present throughout adult life. It needs to be noted that this personality profile is not uncommon in Western society in general; however, it appears to be more prevalent among cancer patients than in the general population.

Colorectal Cancer

A study of the role of occupational factors in colorectal cancer identified "high demand–low control" jobs as being at-risk occupations (Spiegelman and Wegman 1985). These jobs can be interpreted as giving rise to difficulties of

self-expression at work, with the possibilities for repeated repression and denial of negative emotions.

The Melbourne Colorectal Cancer Study has carefully examined personality profile as a risk factor in large bowel cancer (Kune et al 1991a). This study found that the personality profile of the colorectal cancer patient was statistically significantly different from the controls, even after corrections have been made for other risk factors previously determined in the study, such as all the dietary risk factors identified, beer intake, and family history of colorectal cancer. This was a large population-based study in which a rigorous attempt was made to deal with selection and exclusion bias, as well as with recall bias. As with other cancers, the personality profile of the cancer patient showed the presence of repression and denial of anger and other negative emotions, a commitment to the prevailing social norms, suppression of reactions and emotions which may offend others, as well as the avoidance of conflict, statistically significantly more often than in the controls (Kune et al 1991a).

Although criticisms can be levelled at some methodologic problems with both the retrospective and prospective studies described above, it is difficult to escape the conclusion that the data taken together are consistent with the hypothesis that a personality profile which shows an absence or repression of certain emotional reactions, and also shows certain behavior described above, may play a causal role in the clinical expression of cancer, including colorectal cancer.

STRESSFUL LIFE CHANGES

Stressful life changes preceding the onset of all types of illness has been extensively examined using controlled studies. However, in relation to cancer development, apart from numerous anecdotal and uncontrolled observational studies, only a dozen controlled studies have been noted in which the association between recent stressful life changes and cancer was investigated.

Various Cancer Sites

Two early controlled studies, one examining breast cancer, the other cervical cancer, failed to find an association between previous stressful life changes and the particular cancer under study (Snell and Graham 1971; Graham et al 1971). Both of these studies used hospitalized controls, which included many patients with other types of cancer also, and given the known association of recent life changes with the later onset of almost all types of illness, this null result was predictable. The general effect of stress on the expression of almost all types of disease demands the use of non-hospitalized and preferably population or community-based controls. The controls used in these studies would be regarded as being over-exposed to previous life changes, predictably yielding a null result (Wynder and Stellman 1992). Two other controlled studies, one in relation to

lung cancer and another in relation to gastric cancer, also used cancer patients as controls and although some differences were found in relation to younger age groups, precise inferences cannot be made because of inappropriate choice of controls (Lehrer 1980, 1981).

In 1977 LeShan reported on over 400 cancer patients and controls; over 70% of the cancer patients had a major relationship loss in the 8 years prior to the onset of their cancer, compared to only 10% among the controls. In a well-conducted controlled study by Horne and Picard reported in 1979, in which 110 men with undiagnosed chest x-ray lesions were interviewed, with the interviewer being unaware of the diagnosis also, a statistically significant difference was reported of a "recent significant loss" during the previous 5 years in those who eventually were found to have lung cancer compared to controls.

In a prospective cohort in Yugoslavia, Grossarth-Maticek et al 1984, found a statistically significant number of traumatic life events that evoked chronic hopelessness in people who subsequently developed lung cancer as well as other cancers.

In a study conducted in the United Kingdom, reported by Priestman and colleagues in 1985, no differences were observed in the number of stressful life events experienced by patients with breast cancer, benign breast lumps and 100 healthy controls, after a life events inventory was completed. Unfortunately, the life events were only assessed for the previous 3 years, no record was made of the actual date of the event in relation to diagnosis or interview, and no record was made of the degree of upset experienced by the events. An Eysenck Personality Inventory was also conducted in that study, and the personality indices were similar for all groups.

In a large prospective multicenter study, over 2000 women completed a psychosocial questionnaire prior to breast examination and prior to diagnosis (Cooper et al 1986). These women were subsequently diagnosed as having either a breast cancer, breast cyst, benign breast disease or normal breasts. It was found that the group with breast cancer had experienced statistically significantly more loss and illness-related events, and they perceived life events to be statistically significantly more stressful than did the controls. In a case-control study of breast cancer patients and controls in France, Bremond, Kune and Bahnson in 1986 found that breast cancer patients had a depleting life change in the previous 5 years more often than did the controls, and particularly so for those breast cancer patients who were under 45 years of age at the time of diagnosis (Bremond et al 1986).

Colorectal Cancer

In the large population-based Melbourne Colorectal Cancer Study several etiological factors were investigated in one data set, including recent life changes, as well as the degree of upset experienced as a result of these changes (Kune et al 1991b). In the case-control arm of the Melbourne study, major illness

or death of a family member, major family problems and major work problems were found to be statistically significantly more common in cases over the 5 years preceding diagnosis, compared to population-based controls. Cancer cases also reported being significantly more upset by their recent life changes than did the controls. There were no major differences in the results between males and females or between colon and rectal cancer patients. The elevated risk levels when adjusted for other previously found statistically significant risks, namely all the diet risks found in the study, alcohol consumption, family history of colorectal cancer, number of children and age at birth of first child, remained unchanged, indicating that recent life change is an independent risk factor for colorectal cancer. A number of steps were taken to examine the possibility of recall bias in the Melbourne study and these steps included a comparison of responses from cases who did and did not know they had cancer. Although the possibility of recall bias was not completely controlled for in this study, it was probably not an important factor in explaining the statistically significant case-control differences (Kune et al 1991b).

In a large population-based case-control study conducted in Sweden and reported by Courtney and co-workers in 1993, a history of serious work problems, change of residence, or death of a spouse in the previous 10 years, were all statistically significantly associated with the risk of colorectal cancer. In that study, a number of important known risk factors for colorectal cancer were controlled for including some dietary variables, body mass index and physical activity. The elevated risks were not altered. Steps taken in the Swedish study to examine recall bias led the authors to conclude that this bias was not important.

The data presented above consistently indicate that it is the relatively recent life events of 5 to 10 years before diagnosis that are associated with the onset of various cancers, including colorectal cancer. The accumulation of recent life changes, and their perceptions, has been interpreted as lowering resistance to whichever diseases a person is constitutionally susceptible, thus facilitating an illness, including cancer, thereby encouraging the multiplication of cancer cells so that the cancer becomes a clinical entity. If life change (and its perception) is an etiologic factor for cancer, including colorectal cancer, it is likely to act late in the process of carcinogenesis, shortening the latent period of the cancer.

MECHANISMS OF ACTION OF PSYCHOSOCIAL FACTORS

The mechanisms which have been suggested to explain how psychosocial factors influence cancer development are neurologic, endocrine and most importantly, immunologic changes. The evidence is fragmentary, and there have been very few human studies which have directly examined neurologic, endocrine or immunologic changes in well-controlled prospective studies.

The fragmentary evidence of mechanism which is available at present indicates that the personality and stress effects referred to previously are probably not directly causal, but rather that their effects are indirect and influence the neuro-endocrine and immune systems in such a way as to promote an increased rate of multiplication of cancer cells and thereby an early focal cancer becomes a clinical entity, shortening the latent period. Several reviews of this subject, including those of Rogers and co-workers 1979, Bahnson 1980, 1981, Penn 1981, Farrant and Perez 1987 and most recently, O'Leary in 1990, point to both the complexity of the subject and the scarcity and fragmentary nature of the scientific data.

Studies of the primate, the cotton-top tamarin monkey, living in the wilds of Columbia, South America, are of great interest, because this animal develops an illness like ulcerative colitis, as well as colon cancer, under conditions of captivity (Wood and Peck 1991). Recently, a carcino-embryonic antigen (CEA), similar to that in humans, has been isolated from these monkeys, suggesting that this CEA molecule may play a role in the pathogenesis of colitis and cancer in both species (Tobi et al 1994).

Clearly, much more collaborative work is required between behavioral scientists, immunologists, endocrinologists and cancer epidemiologists, so that a better understanding of how psychosocial factors, such as depression, absence and repression of emotional expression, and stressful life changes, influence the development of cancer.

Animal experiments conducted in Russia and reviewed by Bahnson in 1980 and 1981 indicate enhancement of malignant tumor growth with stimulation of the central nervous system, and particularly of the hypothalamus. Similar studies in the USA showed that changes in the cerebral cortex and hypothalamus can directly, or through immunologic changes, reduce the experimental animals' resistance to the development of malignant tumors (Bahnson 1980, 1981).

It has also been noted in chronic depression and in a personality which is non-expressive and has difficulty coping with life's problems, as well as in situations of stress, that steroid levels are increased and the more marked the depressive or stress situation, the higher is the level of cortisol and other similar steroids. A direct relationship between high levels of steroids and a decreased immune function is also known to be present (Bahnson 1980, 1981).

Stressful life events, such as bereavement, have been shown to suppress lymphocyte function (Bartrop et al 1977; O'Leary 1990). Natural killer cell lymphocytes are thought to be important in host defence against cancer, and these have been noted to be decreased in their numbers and function in cancer patients (Greer and Brady 1988).

Thus, there are a number of plausible neuro-endocrine and immune mechanisms which may explain how depression, hopelessness, a personality profile characterized by an absence or repression of emotional reaction, as well

as stressful life changes and their perceptions of being stressful, may influence the development of malignant tumors, including colorectal cancer.

CONCLUSION

There is ample uncontrolled anecdotal and observational evidence, and a small but increasing number of relatively well-controlled, retrospective and prospective studies, which provide a basis for the view that psychosocial factors do have a role to play in the development of malignant tumors in general, including colorectal cancer. On present information, these psychosocial factors do not appear to be either specific or have unique features for any one particular cancer site. The psychosocial factors which seem to be of importance include long-term depression, a long-term feeling of "hopelessness", a personality profile characterized by absence or repression of emotional reactions, and particularly of negative reactions such as anger, and importantly, stressful life changes and a perception that they are stressful.

A depression of cellular immunity, and possibly changes in the neuro-endocrine system, appear to be the mechanisms whereby psychosocial factors operate in the development of malignant tumors. The data on mechanisms is fragmentary, and much collaborative work needs to be done between behavioral scientists, cancer epidemiologists, immunologists and endocrinologists to unravel the mechanisms involved.

At present the most informed view is that psychosocial factors are not a direct cause of malignant tumors, but rather, that they cause a depression of cellular immunity and possibly also cause other neuro-endocrine changes, which usually operate late in the process of carcinogenesis and which allow a focus of already present cancer cells to multiply and become a clinical entity.

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16

RELIGION AND RELIGIOUSNESS

The health of the members of religious orders such as nuns and priests has interested scientists since the 18th century, and several studies examined their illness and mortality rates, including rates for various cancers, and these rates have been compared to those in the general population (Fraumeni et al 1969). Although no startling differences in cancer rates were seen among monks and other male religious orders from those in the general population, nuns in several studies were found to have lower rates for cancer of the cervix, and higher rates for cancers of the breast, body of uterus, ovary and large bowel, than the population in which they live (Fraumeni et al 1969).

Cancer rates at several sites in relation to various religious denominations have been studied since the 1960s, and differences in cancer mortality by religious denomination has been noted, particularly for Seventh Day Adventists, Mormons and Jews. In relation to colorectal cancer, lower than expected rates were present in Seventh Day Adventists and in Mormons, and higher than expected rates were found in Jews, particularly those of European origin. These differences in incidence and mortality for religious groups were largely attributed to differences in life habits, particularly dietary factors, alcohol consumption and smoking.

Perceived or otherwise defined criteria of "religiousness" or "religiosity" have received little attention in relation to cancer risk. In a large cohort, Comstock and Partridge in 1972 found no association between frequency of church attendance and cancer of the colon or rectum, although they quote a study by Monk and others in which those with rectal cancer were less likely to belong to a religious body, or attended services less often than did matched controls.

This chapter focusses attention on colorectal cancer rates among religious groups, various religious denominations and on "religiousness", since these

aspects of religion may shed light on the causes of cancer in general, and of colorectal cancer in particular.

COLORECTAL CANCER IN NUNS

Two studies have reported higher than expected rates of large bowel cancer in nuns (Nix 1964; Fraumeni et al 1969). In the study by Fraumeni and co-workers, higher than expected rates of cancer of the colon, but not of the rectum, was reported, particularly for post-menopausal nuns. This is a somewhat surprising finding, as one assumes that the life habits of nuns in relation to diet, smoking and alcohol are such that they would be at a lower risk level than the general population.

Female sex hormones in relation to having no children were invoked to explain these higher rates of large bowel cancer among nuns (Chapter 12). Perhaps also the sedentary lifestyle of some nuns, or some other factors associated with not having a family, could be additional explanations of why nuns have higher than expected rates of colorectal cancer.

COLORECTAL CANCER IN RELIGIOUS DENOMINATIONS

It was first noted in the 1970s that Seventh-Day Adventists and Mormons have lower than expected rates of colorectal cancer, and Jews of European origin have higher than expected rates. Lifestyle factors, in particular dietary practices, alcohol consumption and smoking, were invoked to explain these differences in these religious denominations.

SEVENTH DAY ADVENTISTS

Seventh-Day Adventists (SDA) living in California, have been extensively studied in relation to cancer incidence and mortality. Among this group, rates for colorectal cancer have been consistently and significantly lower than those for the USA white population (Phillips 1975; Phillips et al 1980; Phillips and Snowdon 1985). When Danish male SDA members were compared with members of other temperance societies, the risk of colon cancer, and to a lesser extent of rectal cancer, was reduced in SDA members (Jensen 1983). In the Adventist Health Study, over half SDA members are lacto-ovovegetarian and most also abstain from alcohol and tobacco (Beeson et al 1989). Although the "spiritual" aspects of belonging to the SDA church in relation to colorectal cancer risk have not been studied, the diet, alcohol and smoking factors would be sufficient to account for the protective effects noted.

MORMONS

The population of Utah in the USA has over 70% of Mormons (members of the Church of Jesus Christ of Latter-day Saints), and Utah has significantly lower levels of cancer in general, and of colorectal cancer in particular than the US population as a whole. Furthermore, a specific study of Mormons in Utah and in California, also shows low rates of colorectal cancer in comparison with the US population (Enstrom 1978, 1980; Lyon et al 1976, 1980).

The Church proscribes smoking and alcohol consumption, and although compliance rates are not certain, these two factors are likely to result in decreased rates of colorectal cancer. The Mormon Church, however, does not advocate a vegetarian diet and does not proscribe the eating of meat. Indeed, data from 1972 show that the per capita beef consumption in Utah is about 15% higher than that for the USA as a whole (Lyon et al 1976). Mormons have larger families than is the case for the USA as a whole, and this could be a further factor leading to lower colorectal cancer rates among Mormons (Chapter 12). The lower rates of colorectal cancer among Mormons has been largely attributed to their abstinence from alcohol, and more recently, smoking, and to this we may also add the protective factor of having a large family (Lyon et al 1976; Enstrom 1978; Lyon and Sorenson 1978; West et al 1980; Slattery et al 1990). Up to the present time the "spiritual" aspects of belonging to the Mormon Church has not been analyzed as an independent factor in relation to cancer risk.

JEWS

Jews of European origin have elevated rates of colorectal cancer and especially colon cancer, in USA, Australia, South Africa and Israel (Seidman 1971; Haenszel 1971; Greenwald et al 1975; Waterhouse et al 1976; Walker and Segal 1979; Kune et al 1986). Of interest is that Asian- and African-born Jews living in Israel have low rates of colorectal cancer (Waterhouse et al 1976).

The reasons for an elevated risk for colorectal cancer among Jews of European origin is not clear. In the Melbourne Colorectal Cancer Study it was found that Jews (almost all first-generation European migrants) had rates double those of the Melbourne population, and as this study examined all major candidate causes of colorectal cancer, it was expected to shed light on the cause of this high rate among Melbourne Jews (Kune et al 1986). The investigations unfortunately failed because, for the dietary assessment, there were too few in the sample (42 cases) for any meaningful conclusion in relation to the very detailed quantitative dietary assessment. With respect to an accurate family history of colorectal cancer, this was incomplete because several close relatives of the Jewish respondents were killed during the Second World War by the Nazis, at an age before they could develop colorectal cancer. However, Rozen and colleagues working in Tel Aviv on a screening program of colorectal cancer, came across a "natural experiment" which shed light on the possible causes of

elevated rates among Jews of European origin (Rozen et al 1981). In that study, when the screening program was extended from Tel Aviv, which has a high incidence of colorectal cancer with a high proportion of inhabitants of European origin, to a nearby communal farm (Kibbutz), also with a high proportion of Jews of European origin, it was noted that for the previous 20 years there were only 2 cases of colorectal cancer instead of the expected 6.5 cases, a difference unlikely to be due to chance (Rozen et al 1981). This population had an economy based on agriculture, light industry and tourism, it had been stable for the previous 20 years, and the members of the Kibbutz had eaten a diet low in animal fat and high in fiber, apparently in an attempt to prevent coronary artery disease. A later study in another Kibbutz largely failed to confirm these data, although in this Kibbutz there was a significantly higher intake of energy than in the first study (Rozen et al 1987). Thus, dietary factors may be a part explanation of the high colorectal cancer rate among Jews of European origin. The physical activity levels in the Kibbutz studies of Rozen and co-workers were not detailed, and it is possible that different levels of physical activity were also contributing to the variation in the risk of colorectal cancer among these Jews of European origin.

RELIGIOUSNESS

With the exception of the Melbourne Colorectal Cancer Study, no other data have been identified in the scientific literature which have investigated the possible role of "religiosity" or "religiousness" on the risk of cancer in general, and of colorectal cancer in particular, as distinct from risk associated with being in a religious order, or being a member of a particular religious denomination (Kune et al 1993). In the Melbourne study, perceived or self-reported degree of religiousness was a highly statistically significant protective factor ($p = 0.002$). Furthermore, this statistically significant level of protection remained after the previously determined major risk factors found in the study, namely a positive family history of colorectal cancer, all dietary risk factors, beer consumption, number of children and age at birth of the first child, were statistically corrected for. There was, however, no association between the staging of the cancer and the perceived degree of religiousness.

What lies behind this finding of perceived religiousness being apparently an independent protective factor for colorectal cancer, is at present uncertain. There are no other studies with which a comparison can be made. However, it opens the door to scientific study of the "spiritual" aspects of cancer in general, including colorectal cancer. For example, one may speculate that having the perception of being religious, irrespective of religious denomination, confers a degree of tranquillity and relief from life's stresses, thus affording a degree of protection against cancer, including colorectal cancer.

CONCLUSIONS

Higher than expected rates of colorectal cancer among nuns may be due to some factors associated with not having a family, and possibly also with low levels of physical activity. Low rates of colorectal cancer among Seventh Day Adventists can be largely explained on the basis of a vegetarian diet and avoidance of alcohol and smoking. Similarly, among Mormons, low rates of colorectal cancer can be largely explained by avoidance of smoking and alcohol, even though Mormons appear to consume high levels of fat and meat. Mormons having large families probably also contributes to these low colorectal cancer rates. Elevated rates of colorectal cancer among Jews of European origin can probably be explained by dietary factors and possibly also by low levels of physical activity. The inherited aspects in Jews of European origin have so far not been determined.

As distinct from being members of religious orders, or members of specific religious denominations, perceived religiousness has been found to be a statistically significant and independent protective factor for colorectal cancer, a finding which opens the door to an examination of the "spiritual" aspects of religion in relation to the risk of developing cancer, including colorectal cancer.

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17

CAUSES OF COLORECTAL NEOPLASIA A MODEL OF CANCER ETIOLOGY

In most cases of intestinal carcinoma, no previous lesions or causative factors are recognizable. In a small proportion of cases, the disease supervenes on polypi or inflammatory lesions.

Rupert Willis MD, 1950
Professor of Pathology
University of Leeds

Enormous progress has been made in the understanding of colorectal cancer etiology since this authoritative pronouncement by Professor Willis 45 years ago, yet large gaps in our understanding still remain. The early lead that there is an inherited susceptibility in colorectal neoplasia came from studies of familial polyposis syndromes and later from studies of family cancer syndromes. In the past decade, knowledge of the inherited susceptibility to colorectal neoplasia has moved forward enormously with research in molecular genetics. The early clues that environmental factors are also important in colorectal neoplasia came from several sources, namely from noting the enormous geographic variation in the incidence of colorectal cancer, from migrant studies showing striking changes in the incidence of colorectal cancer with migration, and from some religious and cultural groups showing differences in colorectal cancer incidence in relation to the population in which they live. The various hypotheses of inherited and environmental exposures were being tested in humans by several groups of cancer epidemiologists around the world using a variety of methodologies, as well as by laboratory scientists using experimental models of colorectal cancer.

At the same time, the mechanisms of colorectal tumor formation were being examined by many groups in carcinogenesis research, and more recently by molecular genetic studies also.

The results of this astounding multidisciplinary focus on colorectal cancer over the past generation allows a reply to the pronouncement of Professor Willis some 50 years later, that close to the year 2000 there is a solid, albeit basic understanding of colorectal tumor etiology and carcinogenesis.

The author's view of the process of colorectal neoplasia is that several environmental exposures are present, as well as an inherited predisposition in some, which initiate a number of physiologic and pathologic changes in the milieu of the colorectal mucosa, and which cause a progression of the neoplastic process through one of several morphologic pathways, from a normal mucosal cell to a carcinoma, through the accumulation of a number of specific inherited and acquired mutations. The etiology of colorectal neoplasia therefore needs to be discussed and interpreted at four levels, namely the level of causes, the level of mechanisms of action, the level of genetic changes, and finally the morphologic level of change from a normal colorectal mucosal cell to a colorectal tumor. The general model of cancer causation developed in Chapter 1 (Figure 1.1), when transposed to colorectal neoplasia, reveals a cascade of causes, mechanisms, mutations, and morphologic changes resulting in the development of colorectal cancer emerges (Figure 17.1). A summary of the etiology and carcinogenesis of colorectal tumors described in detail in Chapters 3–15 is presented as a model in this chapter.

CAUSES OF COLORECTAL TUMORS

The overview of the several proposed causal associations which follows is of necessity an oversimplication, as with new data it is likely to change. The likely causes of the main precursor lesion, colorectal adenoma, are identical to those of colorectal cancer, with the exception of smoking, which appears to operate mainly early in the process, and of so-called stress and the perception of stress, which appears to operate late in the process, probably at a time when colorectal cancer cells are already present.

A multicausal model of cancer etiology has the greatest utility to explain cancer causation in general (Chapter 1), and colorectal tumors provide a classic illustration of this model. Reviewing over 400 epidemiologic studies of colorectal tumor etiology, only 4 (1%) were designed to test multicausal explanations for the etiology of colorectal tumors. These are the Melbourne Colorectal Cancer Study conducted in Melbourne, Australia, a population-based study of colorectal cancer incidence, etiology (with a case-control design), and survival, and 3 prospective USA cohort studies of mailed questionnaires—the Nurses' Health Study, the Health Professionals' Follow-up Study, and the Iowa Women's Health Study (Kune and Kune 1986, 1987; Willett et al 1987; Folsom

et al 1989; Rimm et al 1993). These 4 studies have already contributed enormously to an overall understanding of colorectal tumor etiology.

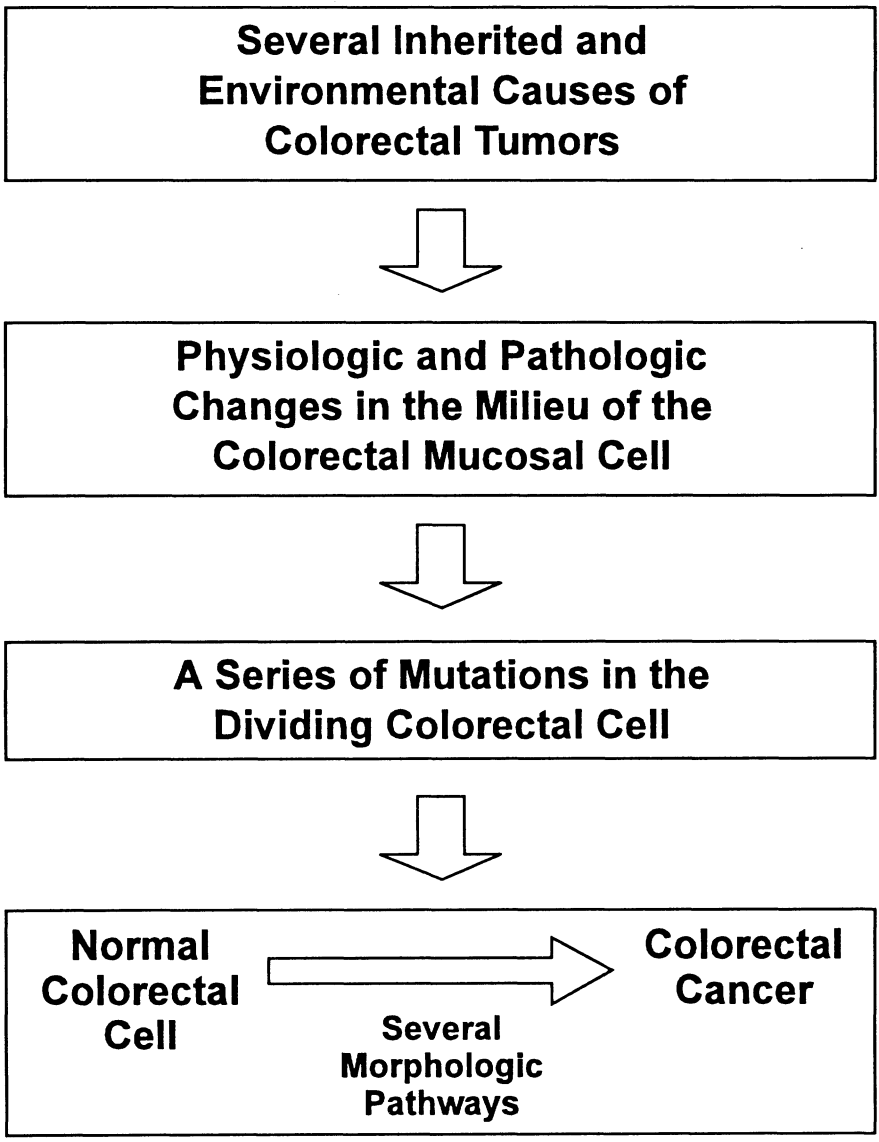

Figure 17.1 A simple model of colorectal tumor development.

The attributable fractions of the various putative causes are shown in Figure 17.2. The figures given are very approximate and merely represent the order of importance that on present evidence may be reasonably attributed to a cause in a so-called developed Western country. Diet factors, beer drinking, and smoking account for about 70% of cases, hereditary factors for about 15% (familial adenomatous polyposis 1%, hereditary non-polyposis colorectal cancer 4% and ordinary colorectal cancer 10%), while uncommon, uncertain and unknown factors account for about 15% of cases.

PUTATIVE CAUSES

Table 17.1, which classifies various factors according to the extent to which evidence suggests they are causal, requires some explanation. The "very likely" causal category, consisting of inherited predisposition, dietary factors, alcohol consumption and smoking, represents a conservative assessment by the writer that would humor epidemiology sceptics who require "rigid or complete proof", which, at least in the biosciences, is not possible. The "very likely" category would provide about as much evidence supporting a causal association, as would smoking and lung cancer, or ultraviolet radiation and skin cancer. The "possible" causal category, which includes physical inactivity, cholecystectomy, number of children, female sex hormones, radiation, stress and stress perception, would have sufficient scientific evidence to be around or above a 50% probability that the exposure is causal.

Table 17.1 Putative causes of colorectal tumors graded according to likelihood of causality

Very likely cause	Possible cause	Unlikely cause
* Inherited predisposition (Ch 5) * Diet (Ch 6) * Alcohol (Ch 7) * Smoking (Ch 8)	* Physical inactivity (Ch 9) * Cholecystectomy and cholelithiasis (Ch 10) * Number of children, female sex hormones (Ch 12) * Radiation (Ch 14) * Stress, perception of stress and personality profile (Ch 15)	* Bowel habit, constipation, diarrhea, laxative use (Ch 11) * Asbestos exposure (Ch 13) * Other occupational exposures (Ch 13)

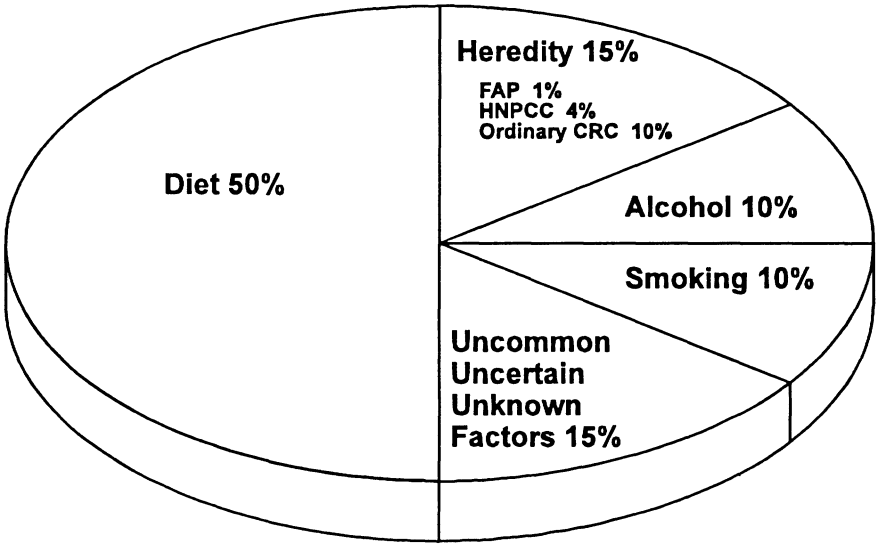

Figure 17.2 Approximate order of risk attributable to proposed etiologic factors in Western populations.
FAP – Familial adenomatous polyposis syndromes.
HNPCC – Hereditary non-polyposis colorectal cancer.
CRC – Colorectal cancer.

COLON VERSUS RECTUM DIFFERENCES

In the past much has been made of differences in the etiology of colon cancer versus rectal cancer; however, a closer examination of the data discloses these differences to be a matter of degree in most instances, that is, a difference which is quantitative rather than qualitative. Moreover, it is important to appreciate that in the interpretation of these differences, particularly in studies which rely on mortality data based on death certificates, a significant number of rectal cancers are misclassified as colon cancer (Percy et al 1981). In prevalence or incidence data or even in etiologic studies, particularly if there is no clinical or surgical input among the investigators (surgeons, for practical reasons are acutely aware of the difference), rectal cancer is sometimes misclassified as colon cancer, although precise data are not available (McMichael and Giles 1994).

There are, however, some quantitative differences in the effect of several exposures, which are not due to site misclassification. An inherited susceptibility is more common in colon cancer than in rectal cancer (Chapter 5). The risk for alcohol consumption is stronger for rectal cancer than for colon cancer (Chapter 7). The physical activity effect is predominantly, if not entirely, for colon cancer, and this differential effect fits in well with the proposed mechanism (Chapter 9).

PROXIMAL COLON VERSUS REST OF LARGE BOWEL DIFFERENCES

As noted for colon versus rectum differences, most proximal colon versus rest of large bowel differences are a matter of degree of the effect, rather than categoric or qualitative differences. Hereditary non-polyposis colorectal cancer occurs more commonly in the proximal than in the distal large bowel (Chapter 5). In ordinary colorectal cancer there is also a statistically higher rate of proximal versus distal colorectal cancer in those with a family history of colorectal cancer, when compared to those who do not have that positive family history (Chapter 5). The cholecystectomy effect is probably entirely on the proximal colon and this fits in well with the likely mechanism which has been proposed (Chapter 10). The pelvic irradiation effect involves rectal and distal colon cancer, since the irradiation is almost always directed to the pelvis (Chapter 14).

GENDER DIFFERENCES

Male–female differences, just like site-specific differences, have largely been shown to be differences in degree of the observed effect, rather than qualitative differences. There are gender differences in the incidence of colorectal cancer, and standardized colorectal cancer incidence rates were shown to be higher in males than in females for both colon and rectal cancer, with the exception of colon cancer between ages 35 and 60 years, where a female excess was shown, especially for right colon cancer in studies performed in the 1970s and 1980s (Kune et al 1986); however, more recent studies show rates to be higher for men for all sites and all ages (Chow et al 1991). Right colon cancer following cholecystectomy may be more common in women, though precise comparative data are not available (Chapter 10). Bowel transit time, which is positively associated with colon cancer, is longer in women than in men and this may have a hormonal basis (Chapters 11 and 12). The alcohol risk appears to be stronger in men than in women in several studies (Chapter 7). This difference in the alcohol risk has been explained by women metabolizing alcohol quantitatively differently to men; however, it may also be due in part to an effect of weak statistical power of some studies caused by the generally low prevalence of alcohol consumption in women. The number of children and age at first birth effect appears to be similar in men and in women, though the effect is slightly stronger in women, suggesting an additional effect, which may be due to female sex hormones (Chapter 12).

MECHANISMS OF ACTION OF CAUSAL FACTORS

Several physiologic and pathologic changes which have been studied mainly in relation to various dietary factors, and to some extent also in relation to alcohol consumption, smoking, physical activity, previous cholecystectomy and pelvic

radiation, have been noted to produce either a cascade of effects or a succession of changes inside the lumen of the large bowel, or in the colorectal mucosa, or affect bowel motility, or produce their effects systemically. These physiologic and pathologic changes are postulated to result in a series of mutations in the dividing colorectal mucosal cell, which transform it stepwise into a colorectal cancer.

Table 17.2 Physiologic and pathologic changes in relation to various putative causal factors

Type of change	Nature of change	Cause (Chapter No.)
Luminal factors	Physical characteristics of feces	Diet (6)
	Chemical compounds present in feces (mutagenic or protective)	Diet (6) Alcohol (7) Smoking (8)
	Bile acid metabolism	Diet (6) Alcohol (7) Cholecystectomy (10) Female hormones (12)
	Fecal bacteria	Diet (6)
Bowel wall function	Bowel motility and transit time	Diet (6) Physical activity (9) Bowel habit (11) Female hormones (12)
Systemic factors	Nitrosamine metabolism	Diet (6) Alcohol (7) Smoking (8)
	Systemic effects of absorbed metabolites (known, suspected or unidentified)	Diet (6) Alcohol (7) Smoking (8)
	Immunologic factors (not yet characterized)	Alcohol (7) Smoking (8) Stress (15)
	Hormones (gastrin and insulin)	Epithelial and tumor growth factors

The several mechanisms of action may be divided further into "luminal" factors which appear to be most important, or factors which influence the "function" of the large bowel, or extraluminal "systemic" factors (Table 17.2). Table 17.2 is obviously an oversimplification of the various mechanisms; however, it serves to underline the complexity of the mechanisms involved in colorectal

tumorigenesis, and in that table the reader is referred to the relevant chapters for a detailed account of the particular mechanism.

GENETIC CHANGES – CELL MUTATIONS

A series of mutations, some of which are inherited but most are acquired somatic changes during life, are the result of the several causes producing physiologic and pathologic changes in the environment of the colorectal mucosal cell, and these mutations are in turn responsible for morphologic changes which transform the normal cell into a cancer cell (Chapters 3 and 5). Collaboration between cancer epidemiologists and molecular biologists in recent years has shown that certain dietary factors, alcohol consumption and smoking can all be associated with mutations, with an overexpression of oncogenes and deletions in tumor suppressor genes (Chapters 3, 5, 6, 7, and 8). It is now becoming clear that there are several pathways of genetic change, which are likely to correspond to several pathways in the evolution of colorectal tumors from a normal epithelial cell to a colorectal cancer (Chapters 3 and 4, Table 3.1, Figure 4.2).

MORPHOLOGIC CHANGES IN ORDINARY COLORECTAL NEOPLASIA

One decade ago, the only two pathways to colorectal cancer were postulated, namely the normal cell – hyperproliferation – adenoma – carcinoma, as the main pathway, and the less common pathway, normal cell – hyperproliferation – dysplasia of increasing severity – carcinoma, the latter also called the "de novo" carcinoma sequence. During the past decade, the recognition of aberrant crypt foci, microadenomas and flat adenomas, as well as molecular genetic changes associated with these morphologic entities suggests that there are likely to be several genetically controlled morphologic pathways to colorectal cancer (Chapters 3 and 4, Table 3.1 and Figure 4.2).

CONCLUSION

This four level scheme of colorectal tumor development, integrating causes, mechanisms of action, genetic changes and morphologic changes is of very recent origin, having been developed only over the past 30 years. It underlines the importance of a multidisciplinary approach to the study of cancer causation, and can serve as an important model for the future study of other common cancers, such as cancer of the breast and prostate, in which the causes are less well understood.

* * * * *

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18

PRIMARY PREVENTION OF COLORECTAL TUMORS

It seems certain that cancer is to a very great extent preventable. Conquest of predisposition is possible. But the degree of justifiable hope will depend on the strength of the will.

The Honourable Rollo Russell
Preventable Cancer. A Statistical Research.
Longmans, Green, London 1912.

BASIC CONCEPTS OF PRIMARY PREVENTION

The essence of prevention of illness, including cancer, is the ability of individuals, groups, and of society in general to make changes in behavior.

OBSTACLES TO CHANGE

Individual or Personal Change

In Western societies, humans tend to resist change. Evidence from secondary prevention programs suggests that knowledge about what needs to be done is much more widespread than the actual practice, and very likely this would also apply for primary prevention. Furthermore, there is less responsiveness to change among certain groups, including the older age groups, those in the lower socio-economic groups, and men.

Industry

There are forces in society coming from industry, such as the tobacco industry, brewers, fast food outlets, the advertising industry, and many others, who for corporate economic reasons, resist changes which may lead to the primary prevention of illness, including cancer. The form of this resistance is usually not visible, and generally it is subtly woven into the fabric of daily life.

The Medical Establishment

In contrast to one of the ideals of medical practice which recognizes prevention as having an important role, the medical establishment until recently has been an important source of frustration for the advocates of primary prevention of cancer. For a long time the medical establishment has not recognized that cancer is of epidemic proportions around the world, principally because of a close focus on the clinical aspects of illness, particularly on diagnosis and treatment. With the development of strategies to control illness, expertise has developed focussing on biotechnology rather than etiology, and efforts at cancer control have been resisted, sometimes obviously but usually in more subtle ways, by clinical and biotechnology medical groups, particularly when it was perceived that primary prevention research will compete for their funding. An eminent biotechnical researcher once told me, "*We must be sure that medical research doesn't get transferred from the laboratory bench to the park bench*". Biotechnologists working in rigidly definable fields have demanded a 99% level of proof from cancer etiology work, not understanding the difficulties of human research, nor the "brick-by-brick" construction of an etiologic hypothesis, in contrast to morphologic, test tube or animal experimental research.

Cancer Epidemiology

Until recently, cancer epidemiologists as a group have been somewhat timid, and have not had a major influence on legislative authorities. Many were not medically trained, especially in the USA, and did not have the influence or respect of either the community at large or of the legislature. Moreover, until recently, they often did not work in conjunction with clinical groups, were not able to make sufficiently clear recommendations, nor were they able to substantiate recommendations with the clarity and facility available to biotechnology and clinical groups. Also, cancer epidemiology has been and remains, significantly under-funded in comparison to biotechnology and clinical groups, which appear more "scientific" by virtue of their research into the mechanisms rather than the prevention of illness. It is only in the last 15 years that major interventional studies in secondary prevention have commenced, and only in the past few years that major studies in the primary prevention of cancer have started.

Legislature and Regulatory Bodies

Legislators are sometimes influenced by lobby groups resisting changes, whether it be in industry, agriculture or medical research. Regulatory bodies are often mainly influenced by the medical establishment, which in the past has been dominated by biotechnologists, a group which for various reasons, often in subtle ways, resisted efforts in primary prevention of illness, including cancer.

STRENGTH OF THE ETIOLOGIC EVIDENCE

An important aspect of primary prevention is the judgement of the strength of the causal evidence which would allow the confidence to recommend measures of primary prevention. Thus with smoking and lung cancer, it became evident by the early 1970s that about 90% of lung cancer can be explained by smoking and there was substantial confidence in recommending cessation of smoking in order to prevent lung cancer, and also to prevent numerous other smoking-related illnesses.

Apart from the strength of the causal association, the time-setting of when to commence primary preventive measures of an exposure is very important. For example, beta-carotene consumption decreases colorectal mucosal cell proliferation, hence dietary primary prevention probably needs to commence early in adult life, assuming a time-scale of decades for an invasive cancer to develop. The importance of a specific exposure in terms of the size of the "attributable risk" for a particular cancer is another important consideration in primary prevention. For example, the attributable risk of dietary factors in colorectal neoplasia outweighs all other causes, and in any considerations of primary prevention, dietary modifications are likely to have the largest effect of all putative causal factors in the primary prevention of colorectal cancer.

MAKING RECOMMENDATIONS

The first important consideration is that recommendations need to be practical and clear, especially for exposures such as diet and alcohol. For example, the quantitative recommendations for diet need to be clear in terms of serve sizes for commonly eaten foods, and in terms of the type and number of alcoholic drinks per day for alcohol. The second important consideration in making recommendations is to consider how the recommendation impacts on practices of overall healthy living, including risk of illness-producing side effects, such as may occur with regular aspirin use as a chemopreventive agent.

DIETARY PREVENTION

Fight Cancer With the Help of Your Greengrocer.

Headline in Australian newspaper,
The Age, July 1994

There is overwhelming epidemiologic evidence that dietary factors are the most important causal determinant of colorectal tumors, both of adenomas and of colorectal cancer (Chapter 6). In Western cultures the risk attributable to diet in colorectal cancer has been estimated to be about 50% (Kune et al 1992).

In principle, the diet that would appear to have a preventive effect in colorectal neoplasia is a diet high in vegetables, fruit and cereals, and therefore high in dietary fiber from all sources, high in calcium-containing foods and low in red meat, animal fat and total energy intake. A high vegetable intake appears to be the single most protective diet factor (Chapter 6). With less certainty, the other preventive aspects of diet are that it is high in fish intake and low in heavily fried and grilled foods, and also low in salt content. This type of diet as a primary prevention for colorectal tumors fits in well with diets advocated for a generally healthy lifestyle, as well as in the prevention of cardiovascular disease and maturity onset diabetes. Furthermore, this type of diet has not been shown to have any risks or undesirable side effects and may be safely recommended. Put simply, an increase of fiber content from a variety of sources to at least 20 g per day, a decrease of saturated fat intake to represent less than 25% of energy, increased calcium intake and perhaps fish intake, and a decrease in heavily fried and grilled meat and of salt, would result in a significant reduction in the incidence and mortality of colorectal cancer in Western-type populations (Shike et al 1990).

It was demonstrated in Chapter 6 that dietary factors in adenoma formation are identical to those for colorectal cancer, and in view of the long time frame of the adenoma-carcinoma sequence (Winawer and Shike 1992; Kune and Vitetta 1995), preventive strategies are best commenced early in adult life, and at a population level are probably best started in primary school education. Primary schools would be an ideal setting to teach the fundamentals of sound human diet in order to establish healthy dietary habits in the prevention of major illnesses in developed countries, particularly cardiovascular disease, maturity onset diabetes and some cancers, in particular colorectal cancer. The dietary patterns of adult brothers living apart has been found to be strikingly similar by Sellers et al 1991, suggesting that dietary habits are often established early in life and persist into adulthood, and therefore diet change or appropriate diet habits need to be learned early in life and need to be incorporated into the education of children.

NATURAL EXPERIMENTS IN COLORECTAL CANCER PREVENTION

Lower than expected rates of colorectal cancer have been recorded among vegetarians, and also among Seventh Day Adventists, who as a group are largely vegetarians (Phillips 1975; Phillips et al 1980; Berkel and DeWaard 1983; Jensen 1983; Frentzel-Beyme et al 1988; Beeson et al 1989; Frentzel-Beyme and Chang-Claude 1994). Other factors are also involved, such as abstinence from alcohol and smoking, and a low energy diet. A generally healthier lifestyle, with physical activity and a low body weight, appears to be also involved in these groups (Frentzel-Beyme and Chang-Claude 1994). These natural experiments in selected populations pose a strong argument for dietary practices being important in the prevention of colorectal tumors.

EXPERIMENTAL PRIMARY PREVENTION USING DIET

In an experimental study, a nutritionally adequate "low-risk" diet was formulated through non-extreme dietary manipulations of low dietary fat, high dietary fiber, high protein, high vitamin A, vitamin E and selenium versus a "high-risk" diet, in order to test the rate of azoxymethane induced colon cancer in rats (Rao et al 1988). In that study, the incidence of colonic adenocarcinomas in the low-risk diet group was 4% compared to 29% in the high-risk diet group, and this difference was statistically significant. There were also more adenomas in the colon of the high-risk diet group compared to the low-risk diet group. This study also succinctly reviewed similar previous experimental interventional studies, indicating that high fat intake and a high protein intake increased colon tumor incidence, whilst a high fiber, high vitamin A, vitamin E and selenium intake decreased the incidence of chemically induced colon cancer in experimental animals. More recent chemically induced colon cancer studies underline the above findings, in which a diet high in wheat bran and/or fiber, psyllium and/or added beta-carotene offered significant protection from colon cancer even in the presence of a high fat and low calcium diet (Alabaster et al 1993, 1995).

STUDIES IN DIETARY PREVENTION OF COLORECTAL TUMORS

Early Dietary Intervention Studies

The first dietary intervention studies were designed to prevent coronary artery disease and not cancer, and usually took the form of advice to reduce either total fat intake or substitute polyunsaturated fat for saturated fat in the diet. The early trials included the Oslo Diet-Heart Study, the Medical Research Council Trial in the United Kingdom of soya bean oil, the Veterans' Administration Trial in the USA, the Sydney Diet-Heart Study, the Oslo Randomised Trial, the Göteborg Trial in Sweden and the Multiple Risk Factor Intervention Trial (MRFIT) in the USA, all studies involving men only. Differences in total cancer deaths between intervention and control groups were examined and no statistically significant

differences emerged in any of these studies (MRC Research Committee 1968; Dayton et al 1969; Leren 1970; Pearce and Dayton 1971; Ederer et al 1971; Woodhill et al 1978; Hjermann et al 1981; MRFIT Research Group 1982; Wilhelmsen 1986).

These trials do not provide evidence that cholesterol-lowering type diets affect cancer risk, either adversely or beneficially. Their limitations need to be remembered, since they were not designed to test dietary intervention in cancer. The largest study of primary prevention of coronary heart disease was the Göteborg trial, in which over 30,000 men were studied, involving almost the entire male population of the city. In this study, individuals were randomized and the intervention consisted of anti-hypertensive treatment if necessary, clinically based dietary advice and intensive advice to stop smoking (Wilhelmsen et al 1986). In this study total cancer mortality after a mean follow-up of almost 12 years was slightly lower in the intervention group than among the controls, but regrettably separate figures were not given for each cancer site. The authors of the study also point out that the period 1970 to 1983 was a time in Sweden in which there was a general decline in smoking, and there were also substantial changes in the dietary habits of the whole population, so that the intervention would have only caused marginal additional effects. Moreover, it is now evident that by far the most important protection would be provided by a high consumption of vegetables and of fruit and fiber, rather than by a marginal lowering of fat consumption. However the Göteborg trial, though not showing a clear difference for overall cancer mortality, did provide evidence that it was possible for a whole population to change their dietary habits in a significant way, over a period of a decade (Rose 1986).

Current Controlled Nutritional Intervention Trials

There are 3 current controlled intervention trials which include nutritional intervention in relation to fat consumption, as well as advice on smoking, and which have reported on cancer rates, including rates for colorectal cancer. These are the World Health Organisation European Collaborative Trial, the trial in North Karelia in Finland, and the MRFIT in USA (World Health Organisation European Collaborative Group 1990; Hakulinen et al 1990; Friedewald 1990). The number of colorectal cancers identified in the intervention and in the control groups was strikingly similar in these studies. These studies are entirely unsatisfactory from the aspect of primary prevention of cancer in general, and of colorectal cancer in particular, for the following reasons:

1. These studies were not designed to examine reduction in cancer incidence and mortality.
2. Modification of fat consumption and weight control are unlikely to be of major importance in the primary prevention of cancer, and of colorectal cancer in particular.

3. Colorectal cancer has a natural history of a decade or longer and current evidence indicates that dietary primary prevention probably needs to commence early in adult life. Moreover, all future cancer interventional studies would need to include a high consumption of vegetables and a reasonably high consumption of fruit and cereals as the main part of the nutritional intervention.

Intervention Studies in Adenomas

Canadian Polyp Study

In a randomized trial of 201 post-polypectomy subjects reported from Canada, a high fiber/low fat diet did not appear to influence adenoma recurrence overall (McKeown-Eysen et al 1991, 1994). In women, there was a statistically non-significant reduction in adenoma recurrence with reduced fecal bile acids of those on a low fat/high fiber diet, whilst in men there was an elevated risk and an increased concentration of fecal bile acids. Although the authors suggest this difference is due to some qualitative gender effect, known gender differences in compliance following dietary counselling could have also been an explanation for the findings.

Australian Polyp Prevention Project

Almost 400 adenoma patients have been randomized in the Australian Polyp Prevention Project to a low fat (fat as 25% of energy), high fiber (25 g unprocessed wheat bran) and 20 mg of beta-carotene supplement (MacLennan et al 1991). A significant suppressive effect on the rectal epithelial cell kinetics was noted in the group randomized to beta-carotene, and a trend was evident with the high fat/low fiber diet (Kilias et al 1993; Macrae et al 1995). Although at 2 years no significant differences emerged, the 4-year analysis showed that low fat diet reduced larger adenoma development greater than 1 cm, and that the combination of low fat and wheat bran was even more effective (MacLennan et al 1995; Macrae et al 1991, 1995). The Australian study is the first interventional trial showing statistically significant effects of diet on colorectal tumor development (MacLennan et al 1995).

Other Polyp and Cancer Prevention Studies

Two other studies are currently underway, one in the United States and another in Europe. The USA Polyp Prevention Trial is examining the effects of a diet low in fat and high in vegetables and fruit (Schatzkin et al 1990b). The European study is a placebo-controlled randomized study, in which several countries are taking part, examining the effects of calcium supplements (2 g per day) and fiber supplementation in the form of psyllium 3.5 g per day (Faivre et al 1993). The results of these interventional studies are eagerly awaited.

In a recently reported Danish study in post-colectomy patients ingesting 20 g/day of the fiber plantago ovate seeds (psyllium seeds/husks), significantly increased fecal butyrate was observed, supporting the hypothesis that colonic fermentation of fiber produces butyrate which is important in colon cancer prophylaxis (Nordgaard et al 1995).

A randomized study in Japan is examining adenoma or carcinoma recurrence 2 and 4 years after endoscopic resection of colorectal tumors (Ishikawa et al 1995). In this study all patients had 2 or more colorectal tumors excised and are randomized to either a dietary advice group or to dietary advice plus wheat bran biscuits group.

Rectal mucosal cell proliferation has been shown to be inhibited in a controlled study of those with a family history of colorectal cancer, using wheat bran (Rooney et al 1994). This study is of special significance because dietary intervention in a high-risk group, which is possibly under genetic control, can reverse early preneoplastic changes. It also adds weight to the contention that dietary intervention needs to commence early.

Metachronous Adenoma Studies

Metachronous adenoma formation following colonoscopic excision of adenomas was positively associated with a high-fat intake in two studies in women, in one of which it was also positively associated with saturated fat consumption and inversely with dietary fiber (Neugut et al 1993; Jacobson et al 1994).

In a double-blind placebo-controlled trial, low-dose fish oil supplementation significantly reduced the rate of rectal mucosal cell proliferation in subjects with previous colonic adenomas (Anti et al 1994). This finding is in keeping with the increasing volume of evidence that fish and fish oil consumption is protective.

Future of Nutrition Intervention Studies in Colorectal Neoplasia

Colorectal Cancer as Endpoint

Nutritional cancer prevention trials are demanding because a large study population with high compliance rates is required, and a follow-up of many years is necessary because of the long natural history from a normal cell to a symptomatic cancer, making the economic burden of the study enormous. These practical difficulties of dietary prevention trials have so far stopped the execution of a satisfactory study which has its endpoint as cancer incidence.

Proliferative Activity as Endpoint

If the endpoint is an intermediate and identifiable biologic marker, such as the known precursor lesion, colorectal adenoma, or even more immediate biomarkers, such as alterations in the rate of mucosal cell turnover and proliferative activity, then less expensive intervention trials of relatively short duration will be the design of future studies (Zelen 1988; Lipkin 1988;

Lippmann et al 1990). For example, a recent study by Steinback in 1994 has shown that caloric restriction reduced the rate of rectal cell proliferation, and throughout this chapter there are other examples of human and experimental intervention studies using proliferative activity as a biomarker of response to the intervention. Validation of the techniques used is an important next step; however, the use of early biomarkers is likely to become the most important single recent advance in intervention studies of colorectal tumorigenesis (Schatzkin 1990, 1994; Macrae et al 1994a).

DIETARY RECOMMENDATIONS

The general recommendations which follow are derived from several sources, namely from epidemiologic evidence as well as from the recommendations of the World Health Organization Collaborating Center for the Prevention of Colorectal Cancer (Shike et al 1990), as well as from the results of recent large well-conducted epidemiologic and intervention studies. The recommendations are:

1. Ensure a particularly high intake of all vegetables, including yellow and green vegetables and cruciferous vegetables, as well as a high intake of various fruits and cereals, so that the total dietary fiber intake is 25 g per day, or more. A high and varied vegetable intake is probably the most important single component of primary nutritional prevention.
2. Reduce total energy intake by reduction of fats, particularly animal fats, but also of other high energy containing foods, such as sugar. Meal frequency should be reduced to 3 per day, and snacks avoided. The energy content of fat should not exceed a quarter of the total energy consumption. Energy intake should be balanced with energy expenditure in relation to physical activity, in order to avoid excessive body weight. Reduction of total energy intake, combined with an increased output through physical activity may prove to be one of the simplest means of reducing colorectal cancer risk.
3. Other recommendations based on current scientific evidence are to increase the intake of fish, of calcium-containing foods, limit the consumption of heavily fried and grilled meat, and decrease salt intake.

CALCIUM SUPPLEMENTATION

There is epidemiologic evidence that calcium in the diet is modestly protective for colorectal cancer (Chapter 6). There are 6 uncontrolled studies and 8 controlled studies in which rectal epithelial cell proliferation was used as an endpoint to measure the effect of supplemental calcium, and in 5 of 6 uncontrolled studies and in 2 of 8 controlled studies, a reduction in the

proliferation rate was recorded (Wargovich et al 1992; Barsoum et al 1992; Kleibeuker et al 1994; Armitage et al 1995; Baron et al 1995; Bostick at al 1995; Cats et al 1995). In a randomized double-blind, placebo-controlled study using 1.5 g of calcium carbonate three times per day over 12 weeks, a statistically non-significant reduction in epithelial cell proliferation of the rectum, and no change in the left colon, was noted in the calcium group, among family members of hereditary non-polyposis colorectal cancer families (Cats et al 1995). However, in 3 recent randomized double-blind placebo-controlled studies of previous adenoma patients, taking calcium supplementation did not affect colorectal mucosal proliferative activity (Armitage et al 1995; Baron et al 1995; Bostick et al 1995). These data can be interpreted in several ways: that calcium supplementation may not have an important effect early in the neoplastic process (Chapter 6), or that its effect is on aspects other than proliferative activity, or that the calcium-containing foods also contain substances other than calcium, which adds to the protection. Two further interventional studies are in progress in which calcium supplementation has been administered as an intervention in relation to metachronous adenoma formation as the endpoint of the study, and the results of these studies are awaited with great interest (Faivre et al 1991; Lubin et al 1991).

At present specific recommendations cannot be made on calcium supplementation in relation to the prevention of colorectal tumors. Adults are advised to bring their dietary calcium intake to 1000–1200 mg daily, in keeping with general diet guidelines. If calcium intake is increased with the use of dairy foods, care needs to be taken not to also increase total fat intake, and this can be done using fat-reduced milk and other dairy products.

ASPIRIN AND NON-STEROIDAL ANTI-INFLAMMATORIES

Although several experimental studies since 1980 have consistently shown that non-steroidal anti-inflammatory drugs (NSAID) reduce the rate of experimentally induced colon cancer in rats, it was first formally proposed by Kune and co-workers in 1988 in the Melbourne Colorectal Cancer Study that regular aspirin use and possibly other NSAID use is protective for colorectal cancer, and is a candidate chemopreventive agent (Kune et al 1988). From experimental studies, it was noted that prostaglandins increase cell proliferation and tumor growth and that aspirin and NSAID use inhibits some pathways of prostaglandin synthesis, and that this may be one of the mechanisms of how these drugs are protective for certain cancers.

ASPIRIN AS A CHEMOPREVENTATIVE AGENT

Colorectal Cancer

Case-control Studies

The first study which examined the relationship between aspirin use and colorectal cancer was the population-based Melbourne Colorectal Cancer Study (Kune et al 1988). The design of this study was such that it was possible to simultaneously examine all putative causal and protective factors in one data set, and examine also the effect of most major illnesses, operations and previous drug use (Kune and Kune 1986, 1987). In that study, a highly statistically significant protective effect for both colon and rectal cancer in both males and females was found for previous users of aspirin and aspirin-containing medications. This effect remained after statistical correction was made for other risk factors, and particularly for all the dietary risks found in the study. Furthermore, the effect remained also when corrections were made for hypertension, heart disease and chronic arthritis, illnesses which were under-represented in the colorectal cancer population. The investigators of the Melbourne study pointed to the potential significance of this finding, and suggested that as aspirin was widely used in the chemoprophylaxis of cardiovascular disease, it may also be useful in the prevention of colorectal cancer, and perhaps also of other cancers (Kune et al 1988).

Following the Melbourne study, 5 other case-control studies also reported a protective effect of aspirin use in colorectal cancer (Rosenberg et al 1991a, 1991b; Suh et al 1993; Peleg et al 1994, 1995; Logan et al 1994).

Cohort Studies

The large American Cancer Society Cancer Prevention Study II cohort of over 620,000 adults who provided information on aspirin use, showed a statistically significant protective effect for aspirin use in their first report of 1991, and also in a later follow-up of 1993 (Thun et al 1991, 1993). In this study the regular use of aspirin, on average every second day for at least one year, reduced mortality from colon cancer by half over a 6 year period. In their 1993 publication, statistically significant protection was also evident for gastric cancer and esophageal cancer, so that for regular aspirin users there was a statistically significant protection for several digestive cancers in both men and women (Thun et al 1991, 1993). In the National Health and Nutrition Examination Survey I cohort (NHANES I), a statistically significant protective effect in men was noted in the incidence of colon cancer for previous aspirin users (Schreinemachers and Everson 1994).

In the US Health Professionals' Cohort, in which 251 incident cases of colorectal cancer were identified in 47,900 respondents, a statistically significant reduction of risk among regular aspirin users was shown, and this protective

effect remained after statistically controlling for age, previous polypectomy, family history of colorectal cancer, physical activity, body mass index, smoking, alcohol consumption and the dietary factors of red meat and vitamin E intake (Giovannucci et al 1994). In the twin study, the Nurses' Health Study, in which 331 incident cases of colorectal cancer were identified, in over 550,000 person-years of follow-up, women who regularly used aspirin for 10 or more years had a substantial reduction of colorectal cancer risk, a protective effect which remained after controlling for age, family history of colorectal cancer, dietary factors of animal fat, fiber, red meat, folate, methionine, vitamin D and calcium, smoking, alcohol, body mass index and physical activity level (Giovannucci et al 1995a).

A Scandinavian population-based cohort of almost 12,000 patients who had previously been hospitalized with rheumatoid arthritis, and presumably had aspirin and/or NSAID treatment, were followed; these patients showed a statistically significant reduction in colon, gastric and liver cancer incidence, when compared to the expected rate in the population (Gridley et al 1993). The only cohort study which did not find a protective effect for aspirin use was from a California retirement community cohort in which 231 incident cases of colon cancer were identified by 1990, with data at entry being obtained in 1981 (Paganini-Hill et al 1989, 1991). Why this study should be different from the others is not clear, and remains unclear even after a recent re-examination of the data (Paganini-Hill 1995). It is possible that protection is in part afforded earlier in life as will be noted from the section below dealing with the effect of aspirin in colorectal adenomas, so that non-users at entry may have been past users. This cohort was considerably older than subjects in other studies, aspirin users differed from non-users in some respects, a number changed their aspirin intake after entry, and about a quarter of daily users took aspirin for preventing heart disease, and this is usually a low aspirin dose (Paganini-Hill 1995). This study is probably not representative of the effect of aspirin use in modifying colorectal cancer risk.

Other Studies

Recent reports indicate a statistically significant risk reduction for colon cancer among groups of patients who would be frequent users of aspirin and other NSAID preparations, namely those with peripheral vascular disease, osteoarthritis and ischemic heart disease, as well as in those with peptic ulcer disease, a proportion of which would have been caused or contributed to by aspirin and NSAID intake (Kune et al 1988; Müller et al 1994; Limburg et al 1994).

Colorectal Adenomas

Several studies between 1993 and 1995 reported a protective effect of previous aspirin use and colorectal adenoma formation. Thus, 3 case-control studies showed risk reductions with aspirin use (Suh et al 1993; Peleg et al 1993, 1995).

In the US Health Professionals' Follow-up Study fewer adenomas were found among aspirin users compared to non-users (Giovannucci et al 1994). In the Nottingham Faecal Occult Blood Study, the metachronous adenoma rate was statistically significantly reduced in aspirin consumers when followed for one year after adenoma resection (Logan et al 1993). In the Australian Polyp Prevention Project a non-significant level of protection was noted among aspirin users, for large adenomas (Macrae et al 1994).

In a randomized trial in the USA in which the effect of vitamin C and vitamin E supplementation was examined, consistent aspirin users were statistically significantly protected against adenoma development (Greenberg et al 1993).

Aspirin Dose and Duration of Use

A randomized trial of low-dose aspirin had no effect on adenoma rates after a 5 year follow-up (Gann et al 1993). This is a disappointing finding; however, the dose of aspirin that may result in protection against colorectal adenoma development may need to be higher than that used in the prevention of cardiovascular disease, and it also appears from later data that aspirin may need to be used for longer than 5 years, so that, in this study, the dose used may have been too low and the duration of use may have been too short to show an effect. A partial explanation of why the California Leisure World Study, described earlier, did not show an aspirin effect is the low-dose aspirin intake in a significant proportion of that population (Paganini-Hill 1995).

The need for a higher dose of aspirin for adenoma prevention was supported by a recent colonoscopic case-control study, which suggested that a minimum daily dose of 325 mg of aspirin is necessary to prevent the development of colorectal adenomas (Johanson and Salisbury, 1995). Important data on the dose and duration of aspirin use for protection in colorectal cancer was recently documented in the US Nurses' Health Study cohort, in which the regular use of aspirin (2 or more tablets per week) was protective, but only after use for 10 years or longer (Giovannucci et al 1995a). In that study optimal risk reduction occurred with a dose of 4–6 tablets per day.

Although a careful dose-response effect has so far not been studied in relation to colorectal tumor protection, there does appear to be a dose-response effect in the degree of protection afforded, both in terms of quantity and duration of aspirin use, as gleaned from those studies in which an attempt was made to measure dose (Logan et al 1993; Suh et al 1993; Giovannucci et al 1995a; Johanson and Salisbury 1995). On currently available evidence, which is limited, it would be reasonable to suggest that one standard aspirin tablet (300–325 mg) on alternate days, used for 10 years or longer, would substantially reduce the risk of colorectal tumor development.

Experimental Evidence

Aspirin has been shown to have an inhibitory effect on chemically induced colon cancer in rats, supporting the human data described above (Craven and DeRubertis 1992; Reddy et al 1992, 1993). In chemically induced colon cancer in rats, aspirin can inhibit colon cancer development up to 80%, and a dose-dependent inhibitory pattern has also been shown to be present (Reddy 1992). Aspirin reduces the rate of aberrant crypt foci, considered to be preneoplastic lesions, in these rat models of colon cancer, suggesting that it has an effect early in the process of colorectal neoplasia (Mareto et al 1994; Wargovich et al 1995a, 1995b). Moreover, aspirin treatment of colon adenocarcinoma cell lines has an antiproliferative effect, and it also induces programmed cell death or apoptosis (Koutsos et al 1995a). Recent experimental evidence in humans suggests that a low dose of aspirin (80 mg/day) reduces the levels of rectal mucosal prostaglandins, but whether this has an effect on rectal neoplasia cannot be concluded from that study (Ruffin et al 1995).

Mechanisms of Action of Aspirin

Aspirin and other NSAID use is protective for colorectal tumors possibly through the inhibition of several pathways in the synthesis of prostaglandins (Kargman et al 1995; Marnett 1992, 1995). In a recent study, however, steroidal anti-inflammatories have not been found to be protective for colorectal tumors (Peleg et al 1995). Prostaglandins in the E series appear to play an important role not only in the growth of colonic mucosal cells, but also in their neoplastic transformation, and may also produce immunosuppression (Marnett 1992, 1995). Aspirin is a protein acetylator, and it may affect the colorectal neoplastic process by changing arachidonic acid metabolism, and possibly also by changing platelet function (Marcus 1995). Aspirin inhibits several enzymes including cyclo-oxygenase and phospholipase, the former important in prostaglandin synthesis and the latter in intracellular signalling (Bomalaski et al 1986; Marnett 1992; Powis and Alberts 1994). However, the precise mechanisms of action of aspirin in the prevention of colorectal tumors remains uncertain.

Primary Prevention with Aspirin

There seems little doubt that consistent aspirin use is a chemopreventive agent in colorectal neoplasia for both colorectal adenomas and colorectal cancers. At present it is not known to what extent this effect occurs during adenoma formation and to what extent it occurs in the late adenoma to carcinoma change, although recent epidemiologic and experimental data suggest aspirin may be important in the early part of the neoplastic process (Giovannucci et al 1995a). Up to the present time the published studies do not give a precise indication of either the minimum or the optimum dose that may be a chemopreventive, although it has been noted in one study that the so-called "low-dose" aspirin

effect used in cardiovascular chemoprevention does not protect against adenoma development (Gann et al 1993), and in another, that the likely minimum daily dose is 325 mg (Johanson and Salisbury 1995), and in another that 4–6 tablets per week used for 10 years or longer are protective (Giovannucci et al 1995a).

The prolonged use of aspirin is known to have side effects, particularly in the upper gastrointestinal tract with the development of peptic ulcer disease, gastroduodenitis and hemorrhage, and this factor needs to be taken into consideration, since an ideal chemopreventive agent should not have any serious side effects (Trujillo et al 1994).

At present a definite recommendation regarding aspirin use in the chemoprevention of colorectal neoplasia cannot be made, partly because of insufficient information on duration of use and on the minimum or optimal dose, and partly because of the gastrointestinal toxicity and other known side effects of prolonged aspirin use. Aspirin may find a place in chemoprevention of those who have had colorectal adenomas removed and in whom the risk of metachronous adenoma development is high. Some have already advocated the alternate day use of 325 mg aspirin in high-risk groups, such as those with familial syndromes, inflammatory bowel disease, past history of colorectal cancer or adenoma, family history of colorectal cancer, and past history of ovarian, breast or uterine cancer (Marcus 1995).

ACETOAMINOPHEN—PARACETAMOL

No statistically significant association or protection between previous acetoaminophen (paracetamol) use and colorectal cancer was found in almost all studies (Thun et al 1991; Logan et al 1994; Muscat et al 1994, 1995; Peleg et al 1994, 1995). In the Nottingham study, recurrent adenoma rate was not reduced with the regular use of acetoaminophen when followed for one year after adenoma resection (Logan et al 1993). However, in another study, women who took aminoacetophen daily had a non-significantly reduced risk of colorectal cancer; however, there were insufficient male patients who took aminoacetophen regularly to be able to evaluate this association adequately (Muscat et al 1994, 1995). This suggests that acetoaminophen cannot be ruled out as having a protective effect in colorectal cancer, and particularly as it has been suggested that this compound is also a prostaglandin inhibitor (Clissold 1986). This association should be examined in a population in which there is a high prevalence of acetoaminophen use, such as in those who suffer with chronic arthritis or myofascial pain such as in the fibromyalgia syndrome. As acetoaminophen has few gastrointestinal side effects, in contrast to aspirin, it would be a safer chemopreventative than aspirin should it be shown in a large controlled study to have efficacy.

OTHER NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

In this section the relationship between colorectal tumors and NSAID use other than aspirin and acetoaminophen will be described.

Familial Adenomatous Polyposis

The use of the NSAID Sulindac was shown to have a chemopreventive effect on patients with familial adenomatous polyposis (FAP) by Waddell and co-workers in 1983 and 1989. Subsequently, French workers in a randomized placebo-controlled trial have shown complete regression of rectal polyps in 6 of 9 patients taking Sulindac and partial regression in the remaining 3 patients, whilst the placebo arm showed increase in polyps in 5, no change in 2, and a decrease in 2, making this a most important contribution to knowledge of chemoprevention in FAP (Labayle et al 1993). Similar results have been reported after 3 months of treatment with Sulindac, in which both the number and size of adenomas was reduced in another placebo-controlled trial (Giardiello et al 1993). In a study from the United Kingdom, 6 months treatment with Sulindac showed polyp regression and also regression of mucosal cell proliferation, not only in the rectum, but also in the duodenum (Nugent et al 1993). This last study is most relevant, since upper gastrointestinal tract cancer is an important cause of death in patients with FAP who have had a prophylactic subtotal colectomy. Finally, the number of rectal polyps, but not of abnormal rectal mucosal proliferation, was noted in one study of FAP patients who had a total colectomy and ileorectal anastomosis, and who were given Sulindac for 60 days (Spagnesi et al 1994). These data are most exciting, not only in the primary prevention of FAP, but also in showing that NSAID use can have an important preventive effect even in the group which has a very strong inherited cause. These studies on FAP also indicate that NSAID use can be effective after polyp formation, and also that actual regression and complete disappearance of polyps can be achieved.

Ordinary Colorectal Cancer

In ordinary colorectal cancer the previous use of NSAID other than aspirin and acetoaminophen was first reported to have a statistically significant protective effect for colon cancer for both women and men in the Melbourne Colorectal Cancer Study, with a relative risk of 0.66 and a p value of 0.001 (Kune et al 1988). There was no protective effect noted for rectal cancer in that study, in contrast with previous aspirin use in which statistically significant protection was present for both colon and rectal cancer, for both males and females.

In the Nottingham study a statistically non-significant protection for colorectal cancer was present for NSAID use (Logan et al 1994). In a hospital-based case-control study, reported recently from the American Health Foundation, a statistically significant protective effect was found for both males and females with the previous regular use of NSAID; however, in that study,

aspirin was grouped with other anti-inflammatory agents (Muscat et al 1994). In a hospital- based case-control study, substantial NSAID use was also associated with protection (Peleg et al 1994). The data on NSAID use other than aspirin is limited, and indicates a less strong and less consistent protective effect for ordinary colorectal cancer than does aspirin use.

Ordinary Colorectal Adenomas

In the Nottingham study, the metachronous adenoma rate was statistically significantly reduced among NSAID users when followed for one year after adenoma removal (Logan et al 1993). In the Australian Polyp Prevention Project, NSAID use was associated with a reduction in metachronous adenomas (Macrae et al 1994). In a recently reported small placebo-controlled study of 4 months use of Sulindac, in histologically documented adenomas less than 1 cm, one adenoma in the 9 patients on Sulindac treatment disappeared, while there was no change in the 12 patients who were in the placebo group (Ladenheim et al 1995).

Experimental Data

Since 1980 there has been ample and consistent experimental evidence that several anti-inflammatory drugs, and in particular Indomethacin, Piroxican, Sulindac and Carprofen, suppress the rate of chemically induced colon cancer in rodents (Thun et al 1991; Reddy et al 1992; Muscat et al 1994; Rao et al 1995a). This extensive experimental data reinforces the human studies showing a protective effect of previous NSAID use other than aspirin. The NSAID Ibuprofen has also been shown recently to suppress aberrant crypt foci, a likely early preneoplastic lesion, in chemically induced rat colon cancer (Wargovich et al 1995a). Moreover, NSAID treatment of colon adenocarcinoma cell lines has an antiproliferative effect, and it also induces programmed cell death, or apoptosis (Koutsos et al 1995a).

Primary Prevention with NSAID Use Other than Aspirin

At present the only recommendation that can be made for the use of NSAID other than aspirin is in patients who have FAP and in whom the colon has been removed. Prolonged NSAID use shares with aspirin the gastrointestinal side effects, in particular bleeding and gastroduodenitis, and these agents are also a contributory component cause of peptic ulcer disease, so that NSAID in therapeutic doses cannot be recommended at present for the prevention of ordinary colorectal tumors (Trujillo et al 1994).

The recent detection of a proliferation-associated gene which is a new form of cyclo-oxygenase (COX-2), which may be the enzyme responsible for prostaglandin synthesis in the colon but which may not cause the serious side effects of inflammation, bleeding and ulcer formation in the upper gastrointestinal tract, is of particular interest for colorectal tumor

chemoprevention (Marnett 1995). A COX-2 selective inhibitor may therefore become an effective chemopreventive agent against colorectal cancer, without the gastrointestinal tract side effects of aspirin and other NSAID (Eberhart et al 1994; Marnett 1995; Sano et al 1995). This is a most exciting prospect for the chemoprevention of colorectal tumors.

VITAMIN SUPPLEMENTS

A high consumption of vitamin C-containing foods is probably protective against colorectal cancer (Chapter 6). The one study which was able to make a quantitative estimation of the protective effect of dietary vitamin C, showed that dietary vitamin C was protective only for intakes greater than 230 mg of vitamin C per day, suggesting that only very high levels of dietary vitamin C are protective (Kune et al 1987a). There is also some epidemiologic support for the protective effect of beta-carotene containing foods, and for reasons that are unclear, a protection also for vitamin B6-containing foods (Chapter 6).

The regular use of vitamin supplements were reported to be a statistically significant independent protective factor for colorectal cancer in one population-based study (Kune et al 1987a). In that study, the regular use of Vitamin A and Vitamin C-containing multivitamin supplements was highly statistically significantly protective for colorectal cancer, and this protection was independent of all other dietary risk and protective factors found in the study (Kune et al 1987a). As it was suggested that multivitamin use reflects "health consciousness", the data were re-analyzed subsequently, and this protection with multivitamin use remained after statistical corrections were also made for physical activity, alcohol consumption and smoking (Kune and Watson 1995, unpublished data). Moreover, in 2 large prospective studies reported recently, there was a statistically non-significant protective effect in women, attributed to the intake of multivitamin supplements (Kampman et al 1994).

Rectal mucosal cell proliferation and other abnormalities of rectal cell kinetics appear to be intermediate biomarkers of colorectal neoplasia, and these abnormalities have been shown to be reduced by the administration of Vitamin A, C and E supplements (Paganelli et al 1992). A later study showed that Vitamin C supplementation reduced colonic crypt cell proliferation in all crypt compartments, beta-carotene at the base of the crypt only, and Vitamin E supplementation had no effect on colonic crypt cell proliferation (Cahill et al 1993). The administration of trans-retinoic acid significantly reduced the number of aberrant crypt foci which developed in chemically induced colon cancer in rats (Stopera and Bird 1993). Vitamin supplements of beta-carotene and vitamin C inhibit chemically induced colon cancer in experimental animals, providing a further basis to undertake controlled human studies (Yamamoto et al 1994). Moreover, vitamin E, and beta-carotene independently inhibit the growth of

aberrant crypt foci in chemically induced colon cancer in rodents, even in the presence of a high-fat and low-fiber diet (Shivapurkar et al 1995).

Controlled Studies of Adenoma Prevention and Vitamin Supplementation

There have been 5 published studies of the use of anti-oxidant vitamins and colorectal adenomas, particularly with the use of vitamin C, and in some, also with the use of vitamin E and vitamin A. There were 2 studies in FAP patients, in the first of which vitamin C supplements were noted to decrease the number of polyps in the rectal stump; however, in a subsequent trial no effect was noted when vitamin C and vitamin E were given to a group of FAP subjects (Bussey et al 1982; DeCosse et al 1989). Both these studies had relatively few subjects, and also the effect of supplemental vitamin C and vitamin E may differ in FAP from that in sporadic colorectal adenomas.

Three controlled studies examined the rate of metachronous adenomas using vitamin supplements. A study reported in 1988 from Canada, in which the rate of metachronous adenomas over 2 years in 143 patients randomly assigned to vitamin C and E treatment showed a 20% reduction in metachronous adenoma formation, compared to the placebo group, a difference which was not statistically significant (McKeown-Eyssen et al 1988).

A study from Italy reported in 1993 of 148 patients randomly given vitamin A, C and E supplements compared to a group receiving no treatment, showed a statistically significant reduction in the incidence of metachronous adenomas (Roncucci et al 1993). A further arm of this study using lactulose, which lowers fecal pH (an effect which may be protective for colorectal cancer), was also included, and showed a protective effect with respect to metachronous colorectal adenomas. The weaknesses of this study were that placebo was not given to the controls, and that dietary assessments were not made.

In a large carefully conducted randomized double-blind placebo-controlled multicenter study in the USA, the Polyp Prevention Study Group, 864 patients who had previously had their colons cleared of adenomas colonoscopically, were included in the study (Greenberg et al 1994). Patients were assigned to placebo, 25 mg per day of beta-carotene, 1 g of vitamin C per day, or 400 mg of vitamin E per day, making 4 treatment groups, namely placebo only, beta-carotene plus placebo, vitamin C and E plus placebo, or beta-carotene plus vitamin C and E. There was excellent compliance with 751 completing the 4–year clinical trial. At the completion of the trial there was no evidence that either beta-carotene or vitamin C or vitamin E reduced the incidence of recurrent adenomas, with relative risks being close to one. There appeared to be no major dietary differences in any of the study groups, either at entry or after 4 years. The major shortcoming of this extremely well-conducted trial is that the length of follow-up is only 4 years, a relatively short period of time in terms of the known natural history of adenoma formation. Indeed, most of the metachronous polyps

were small, less than 5 mm, and unlikely to progress to a cancer. However, the study does underline the epidemiologic and experimental data, outlined in Chapter 6, which suggests that vegetables and fruit contain numerous other substances which may reduce the risk of colorectal tumors, over and above the anti-oxidant effects of vitamin C, E and beta-carotene.

The results of longer term trials are awaited. The current data do not give strong support to the use of vitamin supplements alone for the prevention of colorectal tumors, and suggest that in terms of dietary prevention they are unlikely to be the "quick fix", and more importantly that more benefit will be gained from concentrating on a diet high in vegetables, fruit and cereals as the main basis of primary prevention of colorectal tumors. On current evidence, supplementation with vitamin C, and perhaps beta-carotene, holds the most promise for reversal of early morphologic changes of colorectal hyperproliferation.

HORMONE REPLACEMENT THERAPY

Recent epidemiologic data consistently indicate a significant protective effect for the prolonged use of menopausal hormone replacement therapy, or HRT (Chapter 12). Some have gone as far as to speculate that the current high prevalence of HRT use of 20% among menopausal women in the USA has already contributed to a lowering of colorectal cancer incidence and mortality observed in the USA during the past generation (Potter 1995).

Although a specific trial of HRT in relation to colorectal cancer risk has not been conducted so far, and the effect of important changes in the formulation of HRT in recent years, in particular the addition of progestogens to estrogens, has not been addressed in relation to colorectal cancer risk, HRT, because of its wide use, needs to be placed, almost by accident, on the list of putative chemopreventive agents for colorectal cancer in women.

OTHER POTENTIAL CHEMOPREVENTIVE AGENTS

A variety of other chemical agents have had a limited chemopreventive trial in chemically induced models of colon tumors in rodents.

GREEN TEA EXTRACT

In an interesting publication from Japan, a low dose of green tea extract, which contains polyphenols, had a potent inhibitory effect on chemically induced colon cancer in rats (Narisawa and Fukaura 1993).

MAGNESIUM HYDROXIDE

In chemically induced large bowel neoplasms in rats, the administration of magnesium hydroxide reduced the incidence of tumors and also suppressed preneoplastic epithelial cell changes (Mori et al 1993).

YUGAO-MELON, PROTOCATECHUIC ACID

In 2 separate studies from Japan, yugao-melon in powder form, and protocatechuic acid, an antioxidant found in fruit and vegetables, were each able to significantly suppress the development of chemically induced colon cancers in rodent models (Tanaka et al 1994; Furukawa et al 1995).

CURCUMIN AND TURMERIC

This yellow vegetable pigment is present in turmeric, possesses both anti-inflammatory and anti-oxidant properties, and is used frequently as a food coloring agent and spice, and its administration inhibited the development of chemically induced aberrant crypt foci and tumors in mice and rats (Rao et al 1993, 1995c; Huang et al 1994).

URSODEOXYCHOLIC ACID

Administration of the primary bile acid ursodeoxycholic acid has been found to be highly protective in chemically induced colon cancer rat models, and this protection may be due to the suppression of fecal bacterial formation of secondary bile acids (Earnest et al 1995). Treatment of colon adenocarcinoma cell lines with this bile acid induces programmed cell death, or apoptosis, and this may be a further mechanism whereby ursodeoxycholic acid is a chemopreventive agent in these animal models (Koutsos et al 1995b).

ORGANOSELENIUM COMPOUNDS

In a program aimed to develop organoselenium compounds as chemopreventive agents for colorectal cancer—compounds that are less toxic and more effective than inorganic selenium—several compounds have been found to have chemopreventive action in chemically induced models of colorectal cancer in rodents (Reddy et al 1994).

OTHER CHEMICAL AGENTS

A non-calcemic synthesized analogue of 1 alpha 25-dihydroxyvitamin D3 (RO24-5531) has been shown to be an effective oral chemopreventive agent in experimental colonic carcinogenesis (Wali et al 1995). Similar results were obtained with the use of a synthesized retinoidal butenolide, also in azoxymethane-induced intestinal carcinogenesis experiments (Kawamori et al 1995b).

Caffeic acid esters present in propolis, which is a resin produced by honey bees, have been shown to be potent inhibitors of human colon adenocarcinoma cell growth, and also of chemically induced prenoeplastic lesions in the rat colon. A recent report indicates that a derivative, phenylethyl-3-methylcaffeate given orally, is also a potent inhibitor of azoxymethane induced colonic carcinogenesis (Rao et al 1995b). Subcutaneous depot amiloride injections also inhibit azoxymethane induced colonic tumors (Tatsuta et al 1995).

Other substances which have shown protective effects in chemically induced bowel tumors in rats include ascorbylpalmitate (Rao et al 1995d), the mucosal healing agent carbenoxolone (Rao et al 1995d), a garlic diet (Cheng et al 1995), and an extract from cauliflower of S-methyl methane thiosulfonate (Kawamori et al 1995a).

ALCOHOL CONSUMPTION

Regular alcohol consumption appears to be a component cause of both colorectal adenomas and colorectal cancer (Chapter 7). The risk may be higher for men and higher for rectal tumors. The most important at-risk alcoholic beverage is beer. Although there are several likely mechanisms whereby alcohol promotes colorectal neoplasia, a potentially important mechanism with respect to the possibility of prevention may be by interfering with nitrosamine metabolism in the body. Nitrosamines have been largely eliminated from beer; however, animal experiments have indicated that ethanol administration prevents the clearance of nitrosamines by the liver, and this possibly exposes various organs and tissues of the body to the carcinogenic effects of nitrosamines (Chapter 7).

Data derived from the Melbourne Colorectal Cancer Study showed that a high consumption of vitamin C-containing foods was one of the independent protective factors, and beer consumption was one of the independent risk factors, the latter particularly for rectal cancer (Kune et al 1987b). Of specific interest with respect to primary prevention was that beer consumption did not increase the risk of rectal cancer when the intake of dietary vitamin C was high and exceeded 230 mg per day (Kune et al 1987b). It is known that vitamin C blocks the synthesis of N-nitroso carcinogens by destroying the nitrite molecule; this may be the mechanism of action, since there is evidence that a low consumption of vitamin C-containing foods is a risk for colorectal cancer (Chapter 7). Wines, particularly white wines, often contain vitamin C, used as an anti-oxidant and preservative, and in general adverse effects with wine consumption and colorectal cancer risk have not been detected in numerous studies which have examined wine risk (Chapter 7). Three studies, two of which were restricted to US women, and one Australian study, noted an inverse relationship between wine consumption and colorectal cancer risk, suggesting a protective effect (Kune et al 1987b; Newcomb et al 1993; Gapstur et al 1994). This protective

effect is speculated to be exerted through the vitamin C additive often present in white wine.

In the US Health Professionals' Follow-up Study, particularly high risks were noted for both colorectal cancer and adenomas, among alcohol consumers who also had a low "folate" diet (folate is found mainly in vegetables and fruit) and a low "methionine" diet (methionine is found in red meat, poultry, dairy foods and fish); however, in the presence of a high folate-methionine diet, alcohol consumers did not have elevated risks (Giovannucci et al 1993, 1995b).

The author speculates that, short of cessation of beer drinking and a diet pattern which includes a high vegetable and fruit consumption, the addition to beer of vitamin C which is stable in beer, is relatively inexpensive and causes no serious side effects, may be useful as a preventive in colorectal neoplasia among regular beer consumers, who are known to be at an increased risk for colorectal tumors. Similarly, it is speculated that the addition of folic acid to beer may be a useful measure which might reverse hypomethylation effects among regular beer drinkers.

Intervention studies in relation to alcohol, and particularly beer consumption, have not been conducted so far; however, it would be of great interest to examine post-colonoscopy rates of metachronous colorectal adenomas in a controlled study which includes alcohol abstention. However, in one post-adenoma excision follow-up study, alcohol consumption did not influence adenoma recurrence rates (Jacobson et al 1994). The only natural experiments which have been conducted in relation to alcohol abstention and colorectal cancer risk are those among Seventh Day Adventists and Mormons for whom alcohol is proscribed.

SMOKING CESSATION

Recent epidemiologic evidence indicates that smoking is likely to be an important component cause of colorectal neoplasia, and that it exerts its effect early in the neoplastic sequence, that is, at a time when a colorectal mucosal cell is transformed into an adenoma (Chapter 8). This important finding, which apart from the other well-known ill-effects of tobacco use, adds further weight to the advocacy of abstention from smoking, or its cessation. Cigar and possibly pipe smoking, as well as the smoking of hand-rolled cigarettes or unfiltered cigarettes, may have stronger effects in colorectal neoplasia than smoking of ready-made and particularly filtered cigarettes; however, all types of tobacco consumption increase risk. The most damning evidence regarding mortality in relation to smoking has come from 2 large cohorts with a long follow-up, namely the cohort of British male doctors, in whom it was found after 40 years of observation, that 50% of all regular cigarette smokers will eventually die prematurely because of their smoking habit (Doll et al 1994), and from the US Veterans cohort in whom after a 26-year follow-up, over 50% of cancer deaths were attributable to cigarette smoking (McLaughlin et al 1995).

So far there have been no interventional studies specifically designed to test cessation of smoking in relation to metachronous adenoma formation following colonoscopic excision of adenomas. This would be a most important study to perform, as smoking cessation may allow surveillance intervals to be prolonged in these subjects. However, in an important study from New York, the risk of adenoma recurrence was statistically significantly higher among heavy smokers compared to non-smokers in both men and women (Jacobson et al 1994).

Religious groups in which smoking is proscribed, such as Seventh-Day Adventists and Mormons, show a reduced incidence of colorectal tumors, and particularly with Mormons for whom there are no dietary proscriptions, it can be hypothesized that absence of smoking is one of the reasons for these reduced rates.

PHYSICAL ACTIVITY

There is consistent epidemiologic evidence of an inverse relationship between physical activity and colon cancer risk and adenoma risk for both men and women (Chapter 9). Physical activity appears to have an independent protective effect, and it is probably independent from the dietary effects, obesity, alcohol consumption and smoking. It appears that for physical activity to be protective, it needs to operate over many years. The protective effects of physical activity have been noted in other cancers, as well as for benign large bowel disease, particularly diverticular disease of the colon, and this indicates that both the local and general effects of physical activity play a part in its protective action.

Physical inactivity is often associated with other life-style factors which are risks not only for colorectal cancer but also for other common illnesses such as cardiovascular disease, namely smoking and a high-fat and high-energy diet. Though there are few data, the opposite also seems to apply, that a life-style which includes regular physical activity is also often associated with sound dietary habits, absence of smoking, and low levels of alcohol consumption.

Up to the present time there have been no interventional studies to test the effects of physical activity in colorectal neoplasia; however, the benefits of regular physical activity are known to be numerous, both in the maintenance of good general health and in the prevention of cardiovascular disease, so that providing there are no medical contraindications to exercise, regular physical activity can be recommended simply as an aspect in the maintenance of sound health. The types of physical activity that can be easily accomplished in most environments include walking, cycling, swimming and gymnasium work.

STRESS MANAGEMENT

There is nothing either good or bad, but thinking makes it so.
Hamlet, Act II, Scene II

William Shakespeare 1564-1616

The concept that the management of stressful life changes and the perception that such changes are stressful and can play a role in the primary prevention of illness in general and of cancer in particular, does not sit comfortably with medical scientists who traditionally have a commitment to the ethos of a mechanistic and somatic approach to the causes and prevention of illness. Nevertheless, the evidence presented in Chapter 15 from several controlled studies, including 2 large population-based studies of colorectal cancer, does suggest that stressful life changes and their perception is related to the time of onset of the clinical diagnosis of colorectal cancer (Kune et al 1991; Kune 1992; Courtney et al 1993). Although actual life changes cannot often be prevented, their perception of being stressful and particularly that they remain perceived as stressful for a prolonged period of time can, in principle, be altered by various means such as meditation, relaxation, autogenic training or cognitive restructuring. The value of making such changes in thinking has been pointed out recently to be an untapped resource within the person, which may assist not only in the treatment of an illness but also in the prevention of major illnesses which may be stress-perception related, such as heart disease and cancer, including colorectal cancer (Kune 1993).

As at present biomedical scientists are still struggling with the acceptance of the general concept of stress and its perception having an etiologic relationship to illness, it will be some time yet before any intervention studies will be conducted in the primary prevention of stress perception and illness, including cancer. There would be major logistic difficulties in developing intervention projects; nevertheless, this form of primary prevention may well become an important consideration in the 21st century, for the maintenance of good health and in the prevention of illness including cancer.

CONCLUSIONS

There is an immense potential for the primary prevention of colorectal tumors in view of the advanced knowledge of the several contributory component causes. Public education and the education of health science professionals in the promotion of good health and in the prevention of illness, including that of colorectal cancer, are aims which are achievable, and which work in harmony with a knowledge of the etiology of colorectal neoplasms. Thus, the promotion of dietary habits which reduce total energy intake, encourage a high consumption of vegetables, fruit and cereals, a high consumption of calcium-containing foods,

and a low consumption of animal fat and meat, particularly in a heavily grilled and fried form, the avoidance of smoking, the avoidance of beer consumption or suitable modification of beer, and regular participation in exercise, are all habits which promote good health and prevent illness, without risk.

The development of a potent, non-steroidal anti-inflammatory agent which can be taken orally without causing gastrointestinal side effects, and which will further lower the risk of the development of colorectal tumors, especially among high-risk groups, is also an exciting future prospect in primary prevention of colorectal neoplasms, as is the possibility of the development in the future of other chemopreventive agents. Education in so-called stress management appears to have major potential in the prevention of illness, including cancer, and is an option that may be developed and used with little cost and risk, though this is only likely to take place sometime in the 21st century.

It was noted when discussing the inherited aspects of colorectal cancer that there is a stronger inherited influence in proximal tumors, and a stronger environmental influence in distal tumors, and that recent time-trend analysis in the USA has shown an increasing proportion of proximal tumors (Steele 1994). Moreover, an examination of the time trends in colorectal cancer incidence and mortality from 1950 through 1990 shows declining incidence and mortality rates in successive birth cohorts, which suggests that these reductions in rates are at least in some part due to lifestyle changes which have already occurred on a wide scale among the past generation (Chu et al 1994). These important, though indirect data, give rise to great optimism regarding the primary prevention of colorectal cancer, suggesting that the wider community in some Western societies is already involved in changing lifestyles, with a consequent reduction in both the incidence and mortality of major illnesses, including colorectal cancer.

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19

PRINCIPLES OF CANCER SCREENING AND SURVEILLANCE

Make a habit of two things: Help or at least do no harm.

Hippocrates, about 430 BC

DEFINITIONS

SCREENING FOR CANCER

Screening for cancer may be described as the performance of certain tests in a symptomless person or population, and in which positive tests make a presumptive identification of the cancer or of its precursor lesion. Screening tests for cancer are not diagnostic procedures, and a certain number of false positive and false negative tests will occur. A positive screening test needs to be followed up by further tests which have a high degree of diagnostic accuracy in order to confirm or deny the presence of the suspected cancer or its precursor lesion.

SURVEILLANCE OF CANCER

Surveillance is a follow-up at regular intervals, of those who have had a cancer or its precursor lesion removed, by using further tests to detect at an early stage, the development of new tumors or a recurrence of the cancer. Surveillance for cancer is therefore restricted to a much smaller group than screening. The tests performed for surveillance are usually of a high level of diagnostic accuracy.

SOME TERMS USED IN SCREENING AND SURVEILLANCE

The following terms used in relation to screening and surveillance tests may be useful to those who do not deal with prevention regularly.

Sensitivity of Test – Measures the ability of the test to give a true positive result. Calculated by dividing the number of true positives by the sum of true positives and false negatives.

Specificity of Test – Measures the ability of the test to give a true negative result. Calculated by dividing the number of true negatives by the sum of true negatives and false positives.

Positive Predictive Value of Test – Measures the proportion with a positive test who have the disease under consideration (in this instance, a colorectal tumor). Calculated by dividing the number of true positives by the sum of true positives and false positives.

BASIC TENETS OF SCREENING AND SURVEILLANCE

There are several basic assumptions and principles which are followed when a program of screening and surveillance is being planned for a particular cancer. These assumptions focus on screening and surveillance of large groups or of entire populations; nevertheless, they apply also to screening and surveillance of an individual.

CANCER SCREENING A MAJOR HEALTH PROBLEM

Most cancers are of relatively low incidence, although the lifetime risk of developing a common cancer can be quite high. The relatively low incidence means that most of those being screened will have negative tests, a corollary of which is that screening tests need to be safe. However, a cancer can be regarded as a major health problem even in the presence of a relatively low incidence rate, if the lifetime risk of such a cancer is high and if that cancer has a high mortality and high morbidity, and when the cost of treatment for the community is high.

ETIOLOGY AND NATURAL HISTORY OF THE CANCER IS KNOWN

This assumes that target groups for screening and surveillance are known from an understanding of the etiology, demographic characteristics and pathogenesis of the cancer under investigation. It also means that the major precursor lesion of the cancer is known and identifiable, particularly in terms of its morphologic characteristics with respect to malignant transformation. A knowledge of the natural history of the cancer also implies that the time frame of the change from a normal cell to a precursor lesion and then to an actual cancer is known.

EFFECTIVE SCREENING AND SURVEILLANCE TESTS AVAILABLE

This refers to the availability of tests which are medically effective, cost effective, safe and acceptable to the population and to the health providers who have been educated to understand the significance of the program. The following are the desiderata which need to be met for an effective screening and surveillance program.

Target Groups Identified

This refers to high-risk groups having been identified, or that the entire population above a certain age has been identified as being of sufficient risk to merit screening.

Screening and Surveillance Medically Effective

This refers to screening tests having an acceptable level of sensitivity, specificity, and therefore having an acceptable predictive value. Acceptable levels would vary from one population to another, often depending on availability of resources when screening and surveillance is contemplated on a population basis. Furthermore, medical effectiveness also implies the availability of tests providing a high degree of accuracy in the diagnosis of the positive screenees, as well as the availability of highly accurate surveillance tests.

Cost Effective

On an individual basis and on the basis of screening high-risk groups, cost is uncommonly a barrier in developed countries. Screening on a population basis, however, should only be contemplated for cancers which form a major health hazard and only when screening tests are available with an acceptable degree of sensitivity and specificity, and therefore of an acceptable predictive value, so that the total work-up of the positive screenees, which usually involves expensive radiologic and/or endoscopic procedures, can be accommodated within the economy of the country. In the end, cost effectiveness needs to be decided by each individual community or population.

Safety of Tests

As the majority of those screened and a large proportion of those subsequently under surveillance will be negative, the screening tests need to be shown to be safe, in that they produce more good than harm to both the total population, as well as to those being screened and placed under surveillance.

A consideration of the balance between good and harm produced by screening and surveillance tests needs to include a consideration, not only of the physical aspects of the complications which may arise following screening techniques, but also the emotional problems which may arise in someone who is in a screening and surveillance program (Marteau 1989).

Acceptability

In order to achieve a high compliance rate, acceptability is of enormous importance in a screening and surveillance program. Acceptability is related to the discomfort that may be experienced with screening and surveillance tests, as well as to social and cultural aspects of acceptability of certain procedures, by both the population and health professionals. Since mass screening implies major behavior changes in the population, appropriate education and communication with those to be screened, as well as with health professionals, is very important.

EFFECTIVE TREATMENT OF POSITIVE SCREENS AVAILABLE

Clearly it is of little value to have a screening and surveillance program if there is no effective treatment available for either the cancer or the precursor lesion. Effective screening tests imply that precursor lesions are identifiable and hence can be treated successfully before a cancer develops, and also that a sizeable proportion of the asymptomatic population identified by screening will be found at an early stage in the development of the cancer, with a high chance of cure.

SCREENING AND SURVEILLANCE REDUCES INCIDENCE AND MORTALITY

The fundamental assumption behind all screening and surveillance programs which are population-based, is that such programs will reduce both the incidence and the mortality of the particular cancer in the population. This reduction in incidence and mortality would arise from successful removal of precursor lesions, and from the detection of cancers at an earlier stage and therefore with a better prognosis than when these cancers are detected in the symptomatic stage.

BASIC TENETS IN COLORECTAL CANCER SCREENING AND SURVEILLANCE

In this subsection a broadly based outline will be given of how the basic tenets of screening and surveillance apply to colorectal cancer, in the present state of knowledge.

COLORECTAL CANCER – A MAJOR HEALTH HAZARD

Globally, colorectal cancer is important, with about 700,000 new cases occurring each year (International Agency for Research on Cancer, 1993). This is the third most common cancer in the world after lung cancer and gastric cancer. It has a very high incidence in developed countries, including the USA, United Kingdom, Canada, Australia, New Zealand, France and Italy, which have not "developed" sufficiently to be able to eradicate this cancer so far. For example, about 150,000 new cases of colorectal cancer occur in the USA, about 40,000 in

the United Kingdom and about 9,000 in Australia (Boring et al 1994; Office of Population UK 1987; Giles et al 1993). There is little doubt that colorectal cancer is a major health problem, both globally and in developed countries.

ETIOLOGY AND NATURAL HISTORY OF COLORECTAL CANCER KNOWN

The demographic characteristics of colorectal cancer are well understood and target groups in terms of high risk have been characterized and are constantly being refined, as noted in the previous sections of this book. Inherited or presumed inherited high-risk groups have been taken into consideration for screening; however, these form only about 15% of cases. Uncommon conditions such as familial adenomatous polyposis, and chronic ulcerative colitis, have also had screening programs instituted. Dietary factors, for example, have an attributable risk three times as large as hereditary factors, yet so far have not been taken into consideration for screening programs. Thus, future screening programs will need to include other high-risk groups also, such as heavy beer consumers, smokers, those with poor dietary habits, and perhaps also those who are physically inactive and obese, and possibly those who have had a cholecystectomy in the past.

Colorectal adenomas have been identified as the major precursor lesion, and about 2 in 3 colorectal cancers commence in relation to an adenoma. The time frame for the development of a colorectal cancer from a normal cell has a range of 5–30 years, and a median time of about 10 years (Chapter 4). There is sufficient information to proceed with the screening of individuals in a health care setting, and with the screening of certain high-risk groups, and we appear to be on the verge of population screening for colorectal cancer, at least in developed countries.

The following distinctions can be made at present regarding risk levels for colorectal cancer.

High Risk

1. Inherited factors (Chapter 5)
    * Familial adenomatous polyposis (FAP)
    * Hereditary non-polyposis colorectal cancer (HNPCC)
    * Family history of colorectal cancer or adenoma
2. Past colorectal cancer or adenoma
3. Chronic inflammatory bowel disease
    * Ulcerative colitis
    * Crohn's colitis

4. Past breast, uterine or ovarian cancer
5. Dietary factors (Chapter 6)
6. Alcohol (Chapter 7)
7. Smoking (Chapter 8)
8. Physical inactivity (Chapter 9) – possibly
9. Cholecystectomy/gallstones (Chapter 10) – possibly.

Average Risk

1. Individuals over 50, symptomless, without high-risk factors
2. Possibly some subgroups of high risk
   * Only one close relative with colorectal tumor
   * Only one small tubular adenoma on endoscopy.

EFFECTIVE, ACCEPTABLE SCREENING TEST AVAILABLE FOR COLORECTAL CANCER

Fecal occult blood testing, flexible fiberoptic sigmoidoscopy and fiberoptic colonoscopy are currently the three major forms of effective tests available for screening and surveillance of colorectal cancer.

Significant determinants for participation in screening include a positive attitude towards prevention in general, a recent contact with a health service, family history of colorectal cancer, belief that bowel cancer can be cured if detected early, a perception of personal susceptibility to bowel cancer, and the acceptance of the screening technique (Dent et al 1983; American Cancer Society 1983; Ferrands et al 1984; Macrae et al 1984; Weller et al 1995a). Education campaigns for screening are relatively ineffective for older age groups, especially men, and particularly those with a below average level of education (McCullough and Gilbertson 1969; Macrae et al 1986). Acceptance is better for older women with a family history of colorectal cancer (Macrae et al 1986). Population-based studies of colorectal cancer screening have noted that women accept screening more often than men at all age groups (Faivre et al 1991; Kronborg and Wahrendorf 1994).

The reasons for noncompliance with screening appear to be multifaceted, and relate to noncompliers more often being men, those in younger and older age groups (below 55 and over 80), poor understanding of the concept of asymptomatic disease, fear of screeening tests, fear of cancer, no contact with previously screened individuals, and a generally negative attitude towards screening (Faivre et al 1991; Kronborg and Wahrendorf 1994; Hart et al 1995; Linholm et al 1995; Thomas et al 1995).

The education and cooperation of physicians and allied health professionals in the community is essential for a successful screening and surveillance program, as it has been shown that contact with a health service is an important predictor of compliance with screening. Education of physicians and allied health professionals implies that they understand those at risk, have knowledge about the role and interpretation of the various screening tests, and that there are clear guidelines for screening and surveillance, based on current scientific data (Macrae et al 1982c; St. John 1994; Weller et al 1994). At present, at least in countries such as the USA and Australia, physicians have a variable knowledge of high-risk groups, and a variety of attitudes towards screening for colorectal cancer (American Cancer Society 1985; Weller et al 1994).

There is some evidence that screening for colorectal tumors has a financial advantage (Allison and Felman 1985; Eddy 1990). However, other data indicate that mass screening may not greatly reduce the total cost of care for colorectal cancer (Whynes et al 1993; Hart et al 1995). A recent assessment is that the cost of one cancer detected is about $US14,000, and that about half of this cost relates to colonoscopy of the positive screens (Weller et al 1995b). Accurate cost assessments of screening are not available, and would vary in different countries.

TREATMENT OF COLORECTAL TUMORS IDENTIFIED BY SCREENING IS EFFECTIVE

Effective treatment of colorectal adenomas and colorectal carcinomas identified by screening is certainly available, using either endoscopic excision of adenomas and some very early cancers, or with surgical resection of more advanced cancers. Curative treatment of screen-identified colorectal cancers is more often possible than in the symptomatic group, because screen-identified cases are much more often diagnosed at an early stage of their development, such as at a Dukes A or Dukes B stage, and also because screening identifies a significant number of adenomas, which can be excised before malignant change supervenes.

SCREENING REDUCES INCIDENCE AND MORTALITY OF COLORECTAL CANCER

The data indicate that population screening and surveillance for colorectal tumors will significantly reduce both the incidence and the mortality of colorectal cancer in those populations in which colorectal cancer is a major health problem (Chapters 20, 21 and 22).

* * * * *

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SCREENING FOR COLORECTAL TUMORS

A recent examination of the time trends in colorectal cancer incidence and mortality in the USA from 1950 through 1990 reveals declining mortality rates in the late 1980s (Chu et al 1994). In that survey, as well as in other recent data discussed in Chapter 22, a greater detection rate at earlier stages of colorectal cancer suggests that the increased use of fecal occult blood testing and sigmoidoscopy leading to colonoscopy, has already played a role in reducing mortality from colorectal cancer in the USA.

HISTORICAL ASPECTS OF COLORECTAL CANCER SCREENING

Although the testing of feces for occult blood, and the performance of a rigid sigmoidoscopy as part of a general medical check up has been practised in a nonsystematic way by individual clinicians and institutions for many years, the concept of systematic screening for colorectal cancer with fecal occult blood testing and rigid sigmoidoscopy is only one generation old, with reports first appearing in the 1960s (Hertz et al 1960; Gilbertsen and Wangensteen 1963; Greegor 1967).

The routine use of rigid sigmoidoscopy and of other tests, such as colon cytology and fecal occult blood testing, was first reported by Cameron and Thabet in 1960. Reports from Hertz and co-workers in 1960 from the Strang Cancer Prevention Clinic in New York and from Gilbertsen and Wangensteen in 1963 from the Cancer Detection Center in Minnesota, in programs which

commenced in the 1940s, emphasized the role of rigid sigmoidoscopy for systematic screening of the distal sigmoid colon and rectum.

The first commercially available fecal occult blood test was the guaiac test named Hemoccult, and Greegor in 1967 reported enthusiastically on its value in the detection of 7 colorectal cancers in 2000 physical examinations performed as an office procedure in symptomless patients. Hemoccult II® (SmithKline Diagnostics Inc), which is a guaiac-impregnated card, was then developed as were other similar tests, and in the 1970s and 1980s large scale population-based international trials were commenced to show the feasibility and the advantages of fecal occult blood testing as a means of reducing the incidence and mortality of colorectal cancer.

Fiberoptic colonoscopy first became available clinically in the late 1960s. An instrument which can directly examine the entire colorectal mucosa (Figure 20.3), the flexible fiberoptic sigmoidoscope which is 60 cm long and can examine the descending colon, sigmoid colon and rectum (Figure 20.2), first became available in the 1970s and was first reported used for screening in 1977 (Goldsmith et al 1977). The advent of endoscopic examination of the large bowel represented an important advance in the diagnosis of colorectal tumors, because a direct examination was possible, and also because biopsy, and for certain tumors, immediate endoscopic excision without major surgery could also be performed.

Clinical markers of colorectal tumors have not been well studied. Simple skin tags have been associated with colorectal adenomas in two preliminary studies; however, later and more careful studies failed to identify an association (Leavitt et al 1983; Kune et al 1985; Piette et al 1988; Gould et al 1988; Brendler et al 1989).

Systematic screening and surveillance of colorectal cancer was first reported only in the 1960s, but in spite of its very short history, progress particularly in the last 10 years, has been both rapid and dramatic. The refinement of fecal occult blood testing, the development of fiberoptic endoscopy, and the ability to remove safely and without the need for major surgery the main precursor lesion, colorectal adenomas, have all contributed to this progress.

The future of screening for colorectal tumors is equally exciting with the prospects of a clearer definition of high-risk groups, the development of more sensitive and more specific fecal occult blood tests, the application of molecular biology to genetic testing for an inherited predisposition (Park et al 1994; Kohonen-Corish et al 1995), as well as the use of DNA in stool as genetic markers of mutated genes, such as K-ras mutations or p53 mutations in desquamated colorectal mucosal cells, and other compounds in feces such as the glycoprotein decay–accelerator factor (Sidransky et al 1992; Dugani et al 1995; Gilbert et al 1995; Mizuno et al 1995).

FECAL OCCULT BLOOD TESTING

Fecal occult blood testing (FOBT) for the screening of colorectal tumors has been extensively used in both an uncontrolled manner, as well as in large population-based studies. This type of testing relies on the preparation of a fecal smear on a guaiac impregnated card, which on treatment produces a color change due to the pseudoperoxidase activity of heme. Most of the information relates to the use of Hemoccult II® (SmithKline Diagnostics Inc), which is called Haemoccult® (Rohm Pharma) in the United Kingdom. Immunochemical tests, which detect the presence of fecal human hemoglobin are also available, and these have been less extensively studied than guaiac impregnated cards.

In order to make an assessment of the effectiveness of FOBT, we need to know the *Positivity Rate*, the *Sensitivity* of the test (the ability to give a true positive result), the *Specificity* of the test (the ability to give a true negative result), as well as the *Positive Predictive Value* for cancers and adenomas, which is the proportion with a positive test who have a colorectal tumor.

FOBT TECHNIQUES

Guaiac FOBT

Hemoccult II® type FOBT has been shown to be more sensitive in the proximal large bowel than in the distal large bowel, and least sensitive for rectal lesions, and this has also been noted for other types of FOBT including immunochemical tests (Songster et al 1980; Macrae and St. John 1982a; Schnell et al 1994). The sensitivity of the test is also increased by having several evacuations tested, as well as by "rehydration", which means adding a drop of water to the dry preparation (Macrae and St. John 1982a). Rehydration increases the sensitivity from 50% to up to 90%; however, it greatly decreases the specificity with about a threefold increase in false positives from 2% to 6%. This decrease in specificity leads to a threefold increase in the number requiring a colonoscopic workup, thus adding significantly to the cost of screening. The positivity rate for adenomas also increases with an increase in the size of the adenoma (Macrae and St. John 1982a; Crowley et al 1983). The major difficulty with the non-rehydrated guaiac impregnated card tests is its relatively low sensitivity for colorectal cancer, as well as for adenomas (Macrae and St. John 1982a; Crowley et al 1983). The major problem with the rehydrated tests is the high rate of false positives.

This low sensitivity is revealed by a relatively high rate of "interval" cancers as noted in the large population-based controlled screening studies, to be described in more detail subsequently (Kronborg et al 1987, 1994; Kewenter et al 1988; Hardcastle et al 1989; Jensen et al 1992). Interval cancers are cancers diagnosed in spite of one or more negative screening tests, and in the Danish study constituted half of all cancers diagnosed in the screened population (Jensen et al 1992). This implies that unrehydrated Hemoccult II® FOBT may miss up to

half of all cancers. This rate of interval cancers decreases with rehydration, as the hydrated test is much more sensitive, although with a loss of specificity, resulting in a large number of unnecessary total large bowel workups (Kewenter et al 1988).

False positives may also be produced by a diet rich in peroxidase, such as red meat and uncooked plant food, although in practice dietary restrictions appear to be of relatively minor importance with the unhydrated test (Macrae et al 1982b). If diet restrictions are practised, beef, lamb, turnip, broccoli and cantaloupe must be omitted from the diet during testing. Vitamin C supplements need to be avoided during the test, as vitamin C inhibits the test reaction, giving rise to false negatives (Gnauck et al 1984). The problem is that dietary restrictions decrease compliance rate in population screening programs (Jorgensen et al 1994a). In practice, two samples are taken from each of three consecutive stools in order to check for the presence of blood. When heme is present in a sample, the addition of the developer which contains hydrogen peroxide is followed by the appearance of a blue color on the test card.

In a large study, which was both prospective and retrospective, a positive Hemoccult II® test meant a 10% probability of a colorectal carcinoma and a 33% probability of an adenoma (Allison et al 1990). In that study, a negative test implied a 1% chance that a colorectal tumor is present, and if Hemoccult II® was the only screening method used, about 50% of colorectal tumors will have remained undetected (Allison et al 1990). In a well-planned study of over 200 average risk individuals between the ages of 50 and 75 years with negative FOBT, total colonoscopy revealed adenomas in 25%, cancer in 1%, and significant lesions (cancer or adenoma >1 cm) were present in 7% (Rex et al 1991). In another recent study significant colorectal tumors were missed by FOBT in 4% (Cauffman et al 1994). In a study of over 400 men aged 40 and over who had a negative FOBT, flexible sigmoidoscopy revealed adenomas in over 20% and significant neoplasms in over 5% of the participants (Gupta et al 1989). In a provocative paper Ransohoff and Lang in 1990 suggested that many small adenomas are detected by chance as a result of workup colonoscopy in the presence of a positive FOBT because of their high prevalence, and because of false positive FOBTs, since only 1% of these adenomas bleed at the time of testing.

In the large controlled international trials which will be described in more detail below, positivity rate was about 2%, and depending on slide rehydration sensitivity in the range of 70–92%, specificity in the range of 90–98%, with a range of positive predictive values when colorectal cancer and adenomas were combined between 22% and 58%. In the Minnesota Colon Cancer Control Study, with rehydration, the positivity increased from 2.4% to 9.8%, sensitivity increased from 81% to 92%, while specificity decreased from 98% to 90%, and the positive predictive value for cancer decreased from 5.6% to 2.2% (Mandel et al 1993).

Rehydration of the slides increases the sensitivity of the test and increases the number of colorectal neoplasms which are detected; however, with the decrease in specificity of the test, the need for a full examination of the large bowel by colonoscopy rises three-to-fourfold, hence the total cost of the screening program rises considerably with rehydration (Kewenter et al 1988; Mandel et al 1993). A survey of published articles between 1966 and June 1993, including the 5 large cohort studies on which data are available and using rehydrated Hemoccult II®, revealed a small but significant lowering of the mortality after 10 years of screening, and a false positive rate of almost 10% (Solomon and McLeod 1994).

More Sensitive Guaiac Tests

An example of this is Hemoccult SENSA®. Tests of this type increase the sensitivity of the test; however, it does mean that there needs to be a tighter restriction on the intake of red meat and peroxidase-containing plant foods (Macrae et al 1982b). There is concern that the very high sensitivity of these tests lowers specificity. The performance characteristics of these newer tests are in general better than those for tests such as Hemoccult II® (St. John et al 1993b).

Quantitative FOBT

A quantitative fecal occult blood test has been devised called HemoQuant®, which is based on the fluorescence of hemeporphyrins. This test is not influenced by vitamin C and iron, but it is influenced by dietary meat and aspirin ingestion, as well as by the intake of other drugs which can increase blood loss from the upper gastrointestinal tract (St. John et al 1992). It is also relatively costly. This test is unlikely to be useful for screening of large bowel tumors.

Immunochemical FOBT

Immunochemical tests differ from the guaiac tests because they utilize antibodies against the globin part of human hemoglobin, so that they detect fecal human hemoglobin. There are various techniques available, namely radial immunodiffusion, latex agglutination, enzyme-linked immunosorbent assay (ELISA), as well as hemagglutination. The immunochemical tests have a particularly low sensitivity for upper gastrointestinal tract bleeding, and they are not affected by diet, vitamin C consumption and medication with iron.

Information on the performance of immunochemical FOBT HemeSelect® is now available from a large population-based screening study in the United Kingdom in which HemeSelect® had substantially better performance characteristics than Haemoccult® (Robinson et al 1994). Immunochemical tests have been evaluated against guaiac tests and in general have been found to have better performance characteristics (Kapparis and Frommer 1985; Saito et al 1985; Nakayami et al 1992; St. John et al 1993b; Robinson et al 1994; Bertario

et al 1994). A recently reported comparison of Hemoccult II®, the more sensitive guaiac test Hemoccult SENSA®, HemoQuant®, a heme porphyrin test, and HemeSelect®, an immunochemical test, indicated that the immunochemical test provided the best combination of sensitivity and specificity (St. John et al 1993b).

One of the immunochemical fecal human hemoglobin tests (Detectacol®) has been extensively evaluated in South Australia, first on a group at high risk for colorectal cancer (previous colorectal neoplasia or first-degree relative with colorectal cancer), and more recently on over 6000 self-recruited participants (Williams et al 1982; Williams et al 1987; Hunter et al 1988; Weller et al 1994). The sensitivity was 83%, the specificity 96%, with an estimated positive predictive value for colorectal cancer in that population of 7.5% (Weller et al 1994b). However, further analysis of this self-recruited population showed that they were probably at a higher than average risk for colorectal cancer so that the predictive value of the test in that study is probably not generalizable. Nevertheless, both the sensitivity and specificity of the test appears to be high and as good if not better than the more commonly used test Hemoccult II®. This immunochemical test is more expensive than Hemoccult II®, however it is not affected by diet, vitamin C or iron medication, as is the case with all immunochemical tests. A controlled study using immunochemical FOBT is desirable.

A recently reported case-control study from Japan has found a statistically significant reduction in mortality from colorectal cancer in those screened with an immunochemical hemagglutination FOBT (Saito et al 1995). This study, however, did not compare guaiac FOBT with immunochemical FOBT. In a large uncontrolled immunochemical FOBT study in Japan of over 122,000 subjects, a positive test was obtained in 9%, over 50% of these agreed to diagnostic tests, and among these 108 patients with colorectal cancer (prevalence 1 per 1000) and 1131 patients with colorectal adenomas (prevalence 12 per 1000) were found, suggesting to the authors that immunologic FOBT is effective for colorectal tumor screening (Takayama et al 1995).

FOBT STUDIES IN AVERAGE RISK

There have been 2 large retrospective case-control studies and 6 large controlled prospective cohort studies which reported on the influence of fecal occult blood testing in the secondary prevention of colorectal tumors.

Case Control Studies

The research group from Kaiser Permanente in Oakland, California, found that exposure to at least one screening FOBT statistically significantly protects those screened from colorectal cancer, and is associated with a 31% reduction in

mortality from that cancer (Selby et al 1993). A case-control study from Saarland in Germany reported similarly to the Californian study (Wahrendorf et al 1993).

Cohort Studies

There are 6 major prospective controlled cohort studies of screening FOBT with a total of over 450,000 participants, conducted in Funen, Denmark (Kronborg et al 1987, 1989), Göteborg, Sweden (Kewenter 1988, 1989, 1994), Nottingham, United Kingdom (Hardcastle et al 1989), New York, USA (Winawer et al 1993c), Minnesota, USA (Mandel et al 1993) and Burgundy, France (Faivre et al 1991). The USA studies were on volunteers, while the European studies are population-based. Participation rates in these large studies has been in the vicinity of 50%. Longitudinal compliance for repeat tests is highest in the age group 55–80 and lower at younger and older ages, as well as among those who had a negative colonoscopy workup previously (Thomas et al 1995). The several reasons for screening non-compliance have been discussed in Chapter 19. These studies have all used guaiac impregnated cards using Hemoccult II® and in the English study its equivalent, Haemoccult® (Rohm Pharma) was used. The Minnesota and the New York studies have been completed and published, whilst in the other 4 studies the interim results have been published and the final results are awaited. A recently published meta-analysis of the mortality data from these studies suggests a 19% reduction in colorectal cancer mortality with Hemoccult® screening (Towler et al 1995). There is also a large population-based study from Saarland in Germany, which was commenced in 1988, to examine mortality rates of those previously exposed to FOBT compared to those not so exposed. The preliminary report from this case-control study nested in a cohort of the Saarland region of Germany, points to a protective effect of FOBT screening (Robra and Wahrendorf 1990). Other uncontrolled data from Germany also point to the effectiveness of systematic annual FOBT screening in that country (Gnauck 1995).

Funen, Denmark Study (Kronborg et al 1987, 1989, 1994)

In a cohort of 62,000, the first screening was performed in 1985-1986, and the second screening in 1987–1988, half being screened with FOBT and half were controls (Table 20.1). The FOBT slides were not rehydrated. During screen #1, 37 cancers and 86 adenomas were identified in the screened group and during screen #2, 13 cancers and 76 adenomas were identified. In 40 of the screened population an interval cancer developed, while cancer developed in 39 among the non-responders of the screened group. During the same period of time, cancer was diagnosed in 115, and adenomas in 100 of the control population.

More colorectal cancers identified in the screened group were in an earlier stage than in the control group (Table 20.1). There were 37 colorectal cancer related deaths in the screened group, and this included the interval cancers and cancers in non-responders, versus 51 cancers in the control group, indicating a

27% reduction in mortality of the screened group. The difference in mortality was not statistically significant; however, it is very likely that at the next evaluation of the study there will be a statistically significant reduction in colorectal cancer related mortality in the screened group.

In the latest, though still interim report in 1994, there were 157 deaths in the screened group and 194 in the control group. A significant reduction in mortality from colorectal cancer is expected, in spite of a non-responder rate of 33% and in spite of a relatively high rate of interval cancers being identified (Kronborg and Fenger 1994).

Göteborg, Sweden Study (Kewenter et al 1988, 1989, 1994a, 1994b).

In this cohort of over 68,300 inhabitants of Göteborg, half were controls and half were invited to participate in an FOBT screening test. At the first screen 63% responded, and at the second screen 60% responded. This study is of particular importance because half of the screened group had a non-hydrated FOBT and half had a hydrated FOBT in the initial screen. The positivity rate for the non-hydrated group was 1.9%, and in the hydrated group 5.8%, with statistically significantly more neoplasms detected in the hydrated group ($p < 0.01$). There were 61 cancers detected in the screened group versus 20 in the control group ($p < 0.001$). In the test group 162 adenomas were detected compared to 24 adenomas in the control group ($p < 0.01$).

In the initial screening half of the cancers were detected with the use of Hemoccult II®; there were 34% Dukes A cancers in the screened group compared to 21% Dukes A cancer in the total of the screen invitee population, compared to 15% Dukes A cancers in the control group. A complete workup for the Hemoccult II® positive group included a clinical examination in which a rectal examination was also performed, as well as flexible sigmoidoscopy using the 60 cm instrument, and a double contrast barium enema. This complete workup was done 3 times more often in the hydrated group than in the non-hydrated group; however, twice as many neoplasms were detected in the hydrated group relative to the non-hydrated group. The positive predictive value in the non-hydrated group was 32%, whereas in the hydrated group it was 22%. The rate of false positive tests defined as the absence of neoplasms was 71% in the non-hydrated group and 83% in the rehydrated group. Rehydration thus considerably increased workload, and therefore cost, with respect to a complete workup for colorectal neoplasms; however, it doubled the yield of tumors. Rescreening showed similar results to the initial screen, although the sensitivity of the test was higher at rescreening, as was the proportion of Dukes A cancers (Table 20.1). The distribution of the cancers by Dukes staging was statistically significantly better among participants than among those who refused ($p < 0.02$). The number of significant adenomas (≥ 1.0 cm), in those screened was 7 times that among the controls during the screening period (Kewenter et al 1994b). The

group attributes the reduced number of cancers in the screened group compared to the controls in the seventh year of follow-up to excision of the large number of adenomas found at screening (Kewenter et al 1994b). Rescreening data suggest to this group that the optimum screening interval is about 2 years and that a screening interval of 3 years is too long (Kewenter et al 1994a, 1994b). This group strongly believes in rehydration of the FOBT slide.

A further aspect of interest from this study is that a risk questionnaire showed the possibility of diagnosing a colorectal neoplasm was twofold with a previous history of rectal bleeding in the past 6 months, fourfold with a history of a previous colorectal neoplasm, and 19-fold in a subject who had a positive FOBT (Kewenter et al 1989).

The Swedish group believes that a high compliance rate is essential and can be achieved, making mass screening feasible. Mortality data so far are not available, and the Swedish group does not recommend mass screening until a decrease in mortality has been demonstrated by a longer period of follow-up (Kewenter et al 1994b).

Nottingham, United Kingdom Study (Hardcastle et al 1989)

In this large cohort of 156,000 subjects, half were invited to have FOBT screening, of whom 53% responded. Among the positive tests, colorectal cancer was identified in 63 subjects and adenomas in 266 subjects. An interval cancer in the negative group was noted in 20 subjects, with 83 cancers detected in non-responders. Of the cancers identified at screening 52% were Dukes A, in contrast to 11% Dukes A of the 123 subjects with colorectal cancer identified in the control group (Table 20.1). This group so far has not released data on mortality.

New York, USA Study (Winawer et al 1993c)

In this study of almost 22,000 patients aged 40 and over, who presented at the Preventive Medicine Institute – Strang Clinic, for routine medical examination, were enrolled by selected calendar periods either into a study group in which they were offered annual rigid sigmoidoscopy and FOBT, or into a control group who were offered only annual rigid sigmoidoscopy. Most of the FOBT cards were not rehydrated. Those with positive FOBT had double contrast barium enemas and colonoscopy. Compliance with the initial screen was high, but was substantially lower at rescreening. The rate of positive FOBT was age-related, with few positive tests under 50 years of age. Positive FOBT was highest in the first screen and highest in those without prior screening. Many more adenomas than cancers were detected. A significant number of early stage cancers were detected by FOBT (Table 20.1). The survival probability shown in Figure 20.1 was significantly greater in the FOBT group than in the control group ($p < 0.001$), and colorectal cancer mortality was reduced with a borderline statistical significance ($p = 0.053$). This mortality difference was observed in all age groups. This group concluded that the addition of FOBT to rigid sigmoidoscopy

will increase the detection rate of colorectal cancer at an early stage, and will result in increased survival.

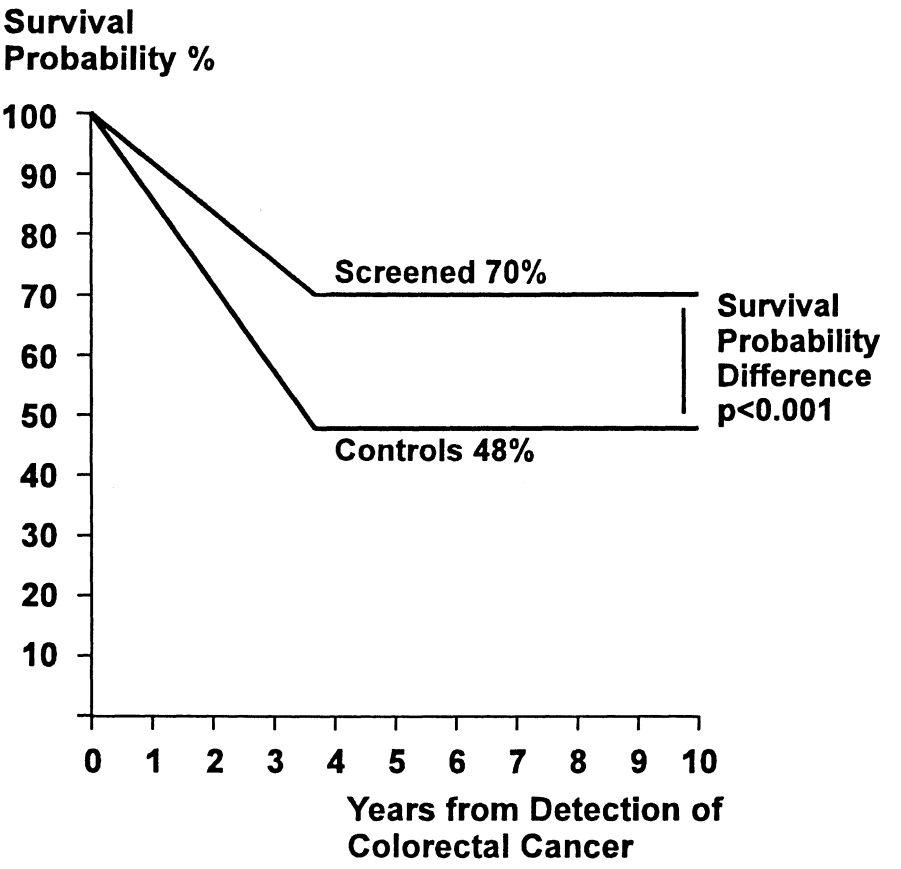

Figure 20.1 Survival probability estimate in the Strang Clinic New York Fecal Occult Blood Study described in the text (Modified from Winawer et al, J Natl Cancer Inst 85:1311-1318, 1993a).

Minnesota, USA Study (Mandel et al 1993)

This important randomized controlled study of over 46,500 participants 50 years or older from Minnesota USA has concluded, and the final results of the study were published in 1993 (Table 20.1). Participants were randomly assigned to FOBT screening once a year, or once every two years, or to a control group. The study was commenced in 1975, with some slides rehydrated from 1977 and all slides rehydrated from 1982 until the end of screening in 1992. The 13-year

cumulative mortality per 1000 from colorectal cancer was 5.88 in the annually screened, 8.33 in the biannually screened, and 8.83 in the control group. The rate in the annually screened group was statistically significantly lower than that in the biannually screened and in the control group. In the annually screened there was an increased rate of detection of colorectal cancer, cancers were detected at an earlier stage and there was a statistically significant reduction in mortality. In the group screened two-yearly, there was a 6% statistically non-significant reduction in mortality. This group concluded that annual FOBT with rehydration of the slides decreased the 13-year cumulative mortality from colorectal cancer by one-third, compared to the control group.

Burgundy, France Study (Faivre et al 1991)

This large study involves 94,000 participants, of whom half were offered FOBT. Half in the test group elected to have FOBT with a high participation rate in the 55–69 years group, higher among women, and lower in the younger and older age groups. More took FOBT when it was free than when it had to be paid for. The positivity rate was 2%, the positive predictive value for a colorectal tumor was 44% (for an adenoma over 10 mm 19%, for cancer 8%), there were 1.6 cancers detected per 1000 screened, and of these 52% were Dukes A stage (Table 20.1).

Summary Data of 6 Controlled FOBT Studies

The principal data of the 6 large controlled studies of FOBT screening is from several sources and shown in Table 20.1, indicating number in cohort, positivity rate, number of cancers detected, the positive predictive value and the number of early cancers compared to the number in the control group. These data were collected from the published papers, personal communications, and from tables constructed by Winawer et al 1990a and by Kronborg and Wahrendorf 1994.

CONCLUSIONS

FOBT as a Screening Test

1. The guaiac-impregnated type of FOBT, such as Hemoccult II®, may be considered as an established screening test with well-defined parameters for sensitivity and specificity to detect colorectal tumors. Used alone and without rehydration, it will miss about half of all colorectal tumors; however, only a small proportion of these will be significant lesions.
2. Rehydration will increase sensitivity, decrease specificity and therefore decrease the positive predictive value of the test, requiring more colonoscopies.
3. Immunochemical FOBT have better performance characteristics than guaiac FOBT, however are more costly.

Table 20.1 Results of FOBT screening for colorectal cancer and adenomas in 6 large controlled studies.

Study	Number in cohort	Positivity rate %	Cancers detected per 1000 screened		Positive predictive value % (adenomas+cancer)	Dukes A cancers detected %		Dukes A & B cancers	
			First screen	Second screen		Screened	Controls	Screened	Controls
Funen, Denmark	62,000	1.0	1.8	0.7	58 (NH)	51	9	81	55
Göteborg, Sweden	68,300	1.9	1.9(NH) 5.8 (H)	6.4	32 (NH) 22 (H)	26	9	54	44
Nottingham, UK	156,000	2.1	2.3	1.5	53 (H)	52	11	90	40
New York, USA	22,000	1.7	–	–	30	–	–	65	33
Minnesota, USA	46,500	2.4(NH) 9.8(H)	–	–	31	–	–	78	35
Burgundy, France	94,000	2.0	1.6	–	44	52	–	–	–

NH = non-hydrated tests

H = hydrated tests

Data Sources

This table was compiled from the following studies:
Winawer et al 1990a, 1993a; Mandel et al 1993; Kronborg and Wahrendorf 1994; Kewenter et al 1988, 1994; and other sources quoted in the text.

FOBT for Mass Screening

Based on the results of large controlled screening studies using guaiac FOBT, the following generalizations can be made:

1. FOBT mass screening is feasible. In a well-conducted project, participation rate is likely to be about 50%.
2. Positivity rate will be about 2%, suggesting that one screened person in 50 will need colonoscopic workup if slides are not rehydrated. There will be few positives under the age of 50 years, suggesting that for average risk screening, ages 50 and over are appropriate to screen. Positivity is highest in the first screen.
3. Slide rehydration increases sensitivity, detects more tumors, decreases sensitivity and the positive predictive value, and trebles colonoscopy rate, thereby significantly increasing the total cost of screening.
4. FOBT will detect many more adenomas than cancers. However, it will detect a much higher proportion of early and therefore eminently curable cancers than would be detected in the non-screened population.
5. Annual mass screening with FOBT of individuals over 50 years of age would significantly lower the incidence of colorectal cancer in developed Western countries, and more importantly, would lower premature death from colorectal cancer by about 15–20%.

RIGID SIGMOIDOSCOPY

The rigid sigmoidoscope, which is usually a 25 cm (10 inch) instrument, has been used for decades for the diagnosis of abnormal conditions of the distal sigmoid colon, rectosigmoid junction and rectum. The regular use of rigid sigmoidoscopy as a means of diagnosing and removing early rectal and sigmoid tumors has been described since the 1950s (Christiansen and Tenner 1951; Portes and Majarakis 1957). However, the systematic use of this instrument for the screening of asymptomatic rectal neoplasms was first suggested by Hertz and co-workers in 1960, and by Gilbertsen and Wangensteen in 1963 based on their large experience since the 1940s. Subsequently Gilbertsen reported enthusiastically on the use of this instrument in screening for rectal cancer in several publications, emphasizing this technique as a method of lowering rectal cancer mortality.

Although skilled operators can usually pass a sigmoidoscope to the full 25 cm in 75% of cases, the average distance the rigid sigmoidoscope is passed by most operators is 15–20 cm (Hughes 1957; Marks et al 1979; Nivatvongs and Fryd 1980; Winnan et al 1980). Furthermore, a high false negative rate has been noted above 16 cm from the anal verge, when rigid sigmoidoscopy was followed

by fiberoptic flexible sigmoidoscopy (Bohlman et al 1977). This means that for practical purposes about 50% of cancers can be detected by rigid sigmoidoscopy, limiting this instrument's value to the rectum and rectosigmoid junction. The diagnostic accuracy of rigid sigmoidoscopy for adenoma and carcinoma of the part reached by the sigmoidoscope is high, although a careful study of its accuracy in a screened population has not been made. The accuracy of this procedure is enhanced by the ability to perform a biopsy or even cytology and by the performance of repeat examination if the initial procedure is unsatisfactory or equivocal (Kune et al 1984).

Complications are rare, and the rate of perforation is 1 in 10,000 examinations (Portes and Majarakis 1957; Nelson et al 1982). An important problem with rigid sigmoidoscopy is that it is uncomfortable and not acceptable to a proportion of asymptomatic subjects, particularly when it comes to re-examination (Winawer et al 1987). For a complete workup of the large bowel, rigid sigmoidoscopy needs to be combined with either double contrast barium enema, or preferably by total colonoscopy.

RIGID SIGMOIDOSCOPY SCREENING STUDIES IN AVERAGE RISK

Uncontrolled Descriptive Studies

Gilbertsen and co-workers from Minneapolis, Minnesota, have advocated the use of rigid sigmoidscopy since 1963 as a screening procedure for rectal cancer, based on their experience which started in 1948. They published several papers, the last of which in 1978 describes the results in over 21,000 men and women who had an initial rigid sigmoidoscopy followed by annual rigid sigmoidoscopy with over 92,000 patient years of follow-up performed at the Cancer Detection Center in Minneapolis, USA (Gilbertsen and Nelms 1978). The screened individuals were over 45 years of age and when adenomas were found, they were always removed. At the initial screening sigmoidoscopy, 25 cancers were found and at subsequent sigmoidoscopy 13 cancers were found instead of the expected number of over 80 rectal cancers. Furthermore, the rate of "localized" rectal cancer was 78% at the initial sigmoidoscopy and 100% at subsequent sigmoidoscopy, compared to the 45% rate of localized rectal cancers, as gauged from the end results data in USA of about that time (Gilbertsen and Nelms 1978). The absolute 5 year survival rate was significantly higher for the rectal cancers found in the screened group, both at initial sigmoidoscopy and at subsequent sigmoidoscopy than the end results data were in the USA around that time. Although it is not clear from this report that all incident cases of colorectal cancer were ascertained in the cohort, nor is it clear what happened to those who did not return to follow-up, the survival data are most impressive.

Other early reports also showed a survival advantage with the use of screening rigid sigmoidoscopy, and emanated from the Strang Clinic – Preventive Medicine Institute in New York, and the Kaiser Permanente

Foundation in California (Hertz et al 1960; Dales et al 1973). Several other uncontrolled studies have also found that the sigmoidoscopic removal of rectal and rectosigmoid adenomas substantially decreased the risk of rectal carcinomas when compared to levels expected in the general population (Colvert et al 1948; Spencer et al 1984; Atkin et al 1992).

Although rigid sigmoidoscopy is regarded as being diagnostically accurate, there have been no prospective randomized controlled clinical trials to support its efficacy in screening (Neugut and Pita 1988; Selby et al 1988). However, in an important case-control study nested in a cohort of members of a pre-paid health scheme from California, previous rigid screening sigmoidoscopy was statistically significantly protective against death from cancer of the sigmoid colon and rectum (Selby et al 1992). In this well-planned study, 261 cases of fatal colorectal cancer at sites within the reach of the sigmoidoscope were compared to 868 age/sex matched controls, with respect to screening rigid sigmoidoscopy in the 10 years prior to diagnosis. Having had at least one previous screening sigmoidoscopy conferred a highly statistically significant level of protection against fatal colorectal cancer. This level of protection remained after statistical corrections were made for several confounding factors, namely a past history of colorectal cancer, a family history of colorectal cancer, and the number of previous health check ups. Another arm of this study indicated that mortality from colorectal cancer above the reach of the sigmoidoscope was not influenced by previous screening sigmoidoscopy. In a detailed examination of the most recent screening sigmoidoscopy, significant protection against fatal colorectal cancer remained even if the last sigmoidoscopy occurred 10 years previously. The persistent protective effect for 10 years is entirely consistent with what is known about the time-frame of the adenoma–carcinoma change (Chapter 4). The authors conclude that screening rigid sigmoidoscopy reduces cancer mortality, at sites within the reach of the sigmoidoscope, by about 60%. The results of this study can certainly be translated to results that would be achieved by flexible sigmoidoscopy screening also.

CONCLUSION

Rigid sigmoidoscopy used as a screening procedure in asymptomatic individuals can result in about a 60% reduction in mortality from cancer at sites within its reach, and this would mean about a 25% reduction in mortality from colorectal cancer as a whole. However, the use of rigid sigmoidoscopy for screening purposes has been almost entirely replaced by the use of flexible fiberoptic sigmoidoscopy, particularly in those countries in which resources for the use of this instrument are available, because it is more acceptable to patients, and because it can examine three times the length of the distal large bowel compared to the rigid instrument.

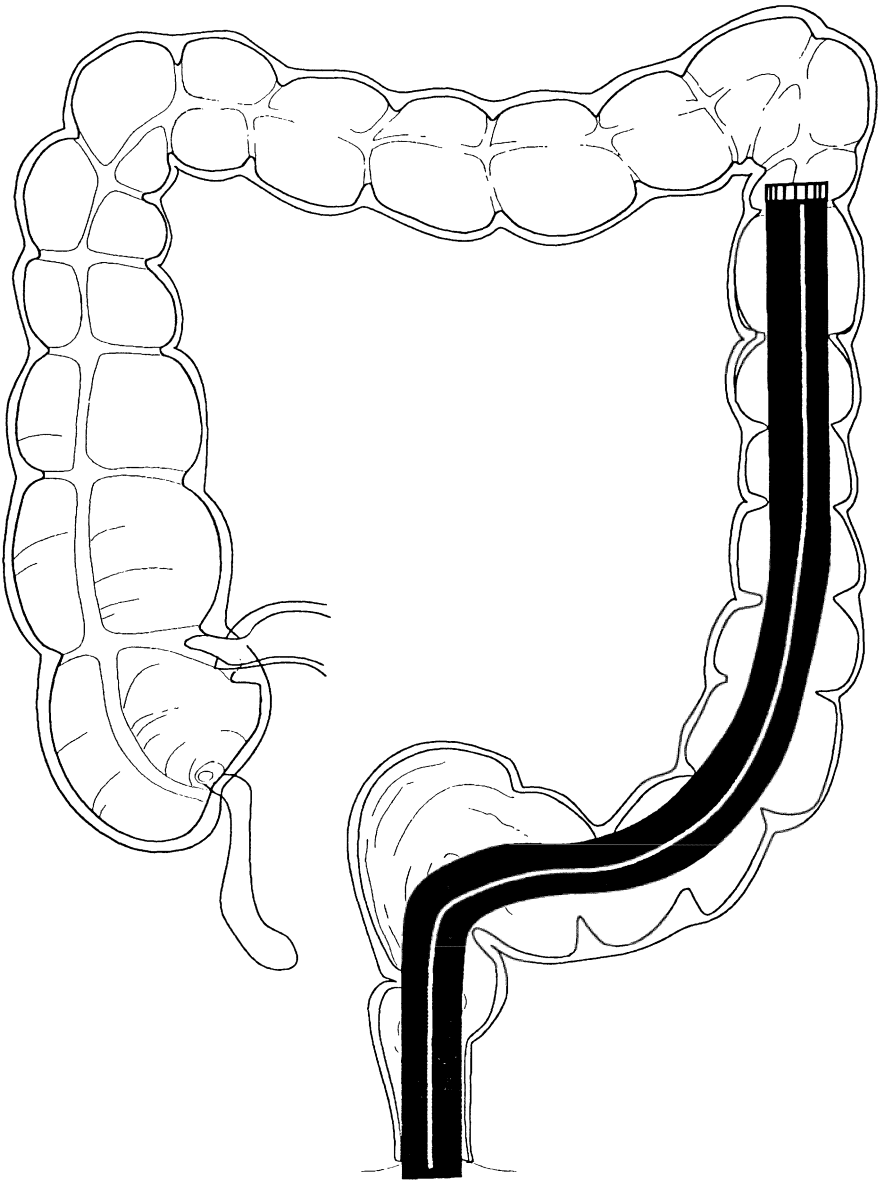

Figure 20.2 Flexible fiberoptic sigmoidoscope fully inserted (Modified from Gastrointestinal Endoscopy for Surgeons, Pearl RK. Boston: Little Brown, 1984, with permission).

FLEXIBLE FIBEROPTIC SIGMOIDOSCOPY

The flexible fiberoptic sigmoidoscope was introduced clinically in the 1970s and was first reported as a screening procedure in 1977 (Goldsmith et al 1977). It is 60 cm long or 24 inches, and will allow an examination of the rectum, sigmoid colon and descending colon (Figure 20.2). Approximately two-thirds of all colorectal cancers are located within reach of the flexible fiberoptic sigmoidoscope, as can be gauged from the frequency of tumors found in various segments of the large bowel in recent population-based studies of incident colorectal cancer (Kune et al 1986). There is also a 35 cm (14 inches) instrument, which if fully inserted would identify over half of all colorectal cancers. Most of the data, however, relate to the 60 cm instrument.

SAFETY, AND RISKS OF FLEXIBLE SIGMOIDOSCOPY

Flexible sigmoidoscopy is a very safe procedure. When performed for screening the perforation rate is less than 1 in 5000 examinations (Rodney and Albers 1986). A simple bowel preparation using a phosphate enema can be used, it can be performed as an office or outpatient procedure, and the procedure is usually well accepted (Leicester et al 1983; Winawer et al 1987). Several studies have shown that flexible sigmoidoscopy is much better tolerated than rigid sigmoidoscopy, and in most instances is an acceptable screening and surveillance procedure (Bohlman et al 1977; Winnan et al 1980; Rodney and Frame 1987). This is a very accurate investigation and identifies significantly more neoplasms than the rigid sigmoidoscope; however, precise diagnostic accuracy in a screening context has so far not been determined (Marks et al 1979; Lipshutz et al 1979; Winnan et al 1980).

The disadvantages of the procedure include a relatively high total cost of each sigmoidoscopic examination, the need for capital equipment costs, and the need for a well-organized rapid turnover efficient setting. At present the procedure is generally performed by specialist gastrointestinal tract endoscopists, be they gastroenterologists or gastrointestinal surgeons. However, nurse endoscopists have been well accepted by those screened, and in fact returned more often for further examinations when the test was done by a nurse endoscopist than when the investigation was performed by a gastroenterologist or a gastrointestinal surgeon (Schapiro 1984; Rosevelt and Frankl 1984; Maule 1994). The role of the primary care physician in screening with flexible fiberoptic sigmoidoscopy has not been clearly established, nor has the training required to be able to effectively perform such screening procedures (Winawer et al 1982; Bowman and Wherry 1985). It seems that screening costs could be significantly reduced if procedures were performed in a centralized high turnover efficiently run setting, and performed by suitably trained, non-physicians, such as nurse endoscopists.

ACCURACY OF FLEXIBLE SIGMOIDOSCOPY AS SCREENING TOOL

Using flexible sigmoidoscopy as the initial screening examination in average-risk individuals over 50 years of age, there are three main possibilities, namely no lesions are found, hyperplastic polyps are found, or colorectal tumors are discovered. This subsection discusses the implications of these findings with respect to screening and subsequent surveillance for colorectal tumors.

No Lesions Found

How many proximal colorectal tumors will be missed using flexible sigmoidoscopy as the only screening test? A study which attempted to answer this question, found that in 114 flexible sigmoidoscopy-negative asymptomatic men over 50 years of age, 20% had proximal adenomas on subsequent colonoscopy, of which 12%, or 2% of the total negatives, had significant lesions (Foutch et al 1991). In 1000 FOBT-negative asymptomatic subjects over 45 years of age, significant lesions were noted in 36 (3.6%), and total colonoscopy discovered significant lesions proximally in a further 5 subjects or 0.5% of the total group screened (Cauffman et al 1994).

On current evidence, screening flexible sigmoidoscopy performed in average risk individuals over 50 years will not detect about 1–2% of significant colorectal tumors, because they are beyond its reach.

Hyperplastic Polyps Found

Although the early data on hyperplastic polyps indicated that they were "markers" for proximal colorectal tumors, more recent large prospective controlled studies, including the US National Polyp Study, have found that the number of proximal adenomas was similar when only hyperplastic polyps were found, compared to no lesions being found on flexible sigmoidoscopy (Winawer et al 1988; Provenzale et al 1990). Although some still believe that finding hyperplastic polyps is an indication for total colonoscopy, the consensus view at present is that in these individuals, total colonoscopy is not indicated (Pennazio et al 1993; Winawer 1995).

Adenoma or Cancer Found

If an adenoma or cancer is found by flexible sigmoidoscopy, there is a 50% chance of finding synchronous lesions in the proximal colon (Winawer et al 1990). If a significant lesion is found, that is, an adenoma larger than 1 cm or one with marked dysplasia, or villous structure, or if a carcinoma is found, a total colonoscopy is indicated. If only a small tubular adenoma is found, the chances of finding a significant proximal lesion are not much greater than when no lesion is found, that is, about a 2–3% probability (Tripp et al 1987; Grossman et al 1989). In this situation, some argue that a total colonoscopy is not indicated as a

further screening procedure. Others argue that a colonoscopy is indicated because the distal adenoma is a "marker" of diffuse abnormal proliferative activity of the entire colorectal mucosa (Winawer 1995). Only a prospective randomized study can resolve this important question.

FLEXIBLE SIGMOIDOSCOPY SCREENING STUDIES IN AVERAGE RISK

So far, a controlled cohort study of flexible fiberoptic sigmoidoscopy used for screening has not been reported. A controlled study, sponsored by the National Cancer Institute in the USA, was commenced at the end of 1993 and this study is expected to report final results in the year 2008.

Uncontrolled Studies

Since 1977 there have been several reported series of screening flexible sigmoidoscopy in asymptomatic populations. These studies, which were drawn from a variety of populations of variable age and gender, indicate that the procedure is extremely safe, has no mortality and almost no morbidity, and that it will identify a variable proportion of adenomas depending on the age of the population screened, and that about two-thirds to three-quarters of the adenomas are less than 1 cm in size. Among these uncontrolled descriptive flexible sigmoidoscopy screening studies, two were identified which equate to what is the likely future scenario in screening average risk individuals, that is, screening will commence in those 50 years or older, and involve both men and women, and therefore these studies indicate the order of colorectal tumors which may be reasonably expected from screening (Wherry 1981; Yarborough and Waisbren 1985). These two studies involved 900 patients, men and women, 50 years and older, yielding one localized cancer, or one or more adenomas in 16%, and significant adenomas of 1 cm or larger in 7% of the sample.

Industry has also expressed an interest in collaborating with health researchers regarding colorectal cancer screening (Hart et al 1994). It is of interest that two uncontrolled flexible screening sigmoidoscopy studies have been reported recently in an industrial setting (Krevsky et al 1992; Lewis et al 1994). In these studies between 20% and 30% of the screened individuals were found to have adenomas.

Controlled Studies

A statistically significant reduction in mortality from colorectal cancer was recorded with a history of previous sigmoidoscopy in one relatively small case-control study nested in a cohort of a pre-paid health plan (Newcomb et al 1992). In a further population-based case-control study of women conducted by this group in Wisconsin USA, a previous history of screening sigmoidoscopy showed a statistically significant reduction in the incidence of distal colon and rectal

cancer (Newcomb et al 1992). The use of rigid and flexible sigmoidoscopies were grouped together in these 2 studies, so that the protective effect of the flexible instrument alone could not be assessed. With the exception of the extent of the distal large bowel which can be examined by these two instruments, their sensitivity and specificity to detect colorectal tumors is likely to be similar, so that the above 2 controlled studies can be added to the controlled rigid sigmoidoscopic study of Selby and co-workers reported in 1992, and support the conclusion that screening flexible sigmoidoscopy will result in a significant reduction in the incidence and mortality from distal colorectal cancer.

Previous flexible sigmoidoscopy in a large cohort recently reported by the Kaiser Permanente Foundation strongly suggests a reduction in both the incidence and mortality from colorectal cancer, particularly for rectal and sigmoid colon cancer, and to a lesser extent also for more proximal colon cancer (Selby and Allison 1994). In that study, previous FOBT was not significantly protective. In another study it was found that if one flexible sigmoidoscopy is negative, it is very unlikely that a significant neoplasm will be detected if the second examination is within 3 or 4 years (Rex et al 1994).

In an important large case-control study of US Veterans involving over 8700 colon cancer and over 7600 rectal cancer patients who were age, sex and race matched with controls without colorectal cancer, a previous flexible sigmoidoscopy was associated with a statistically significant 44% reduction in colon cancer and a 39% reduction in rectal cancer incidence, and the protective effect was apparent for 6 years (Müller and Sonnenberg 1995).

In view of the data from studies there are several advocates of screening flexible fiberoptic sigmoidoscopy for the average risk individual over the age of 50, such as the Kaiser Permanente Group and the Wisconsin Comprehensive Cancer Center. The results from the National Cancer Institute prospective randomized study are eagerly awaited.

CONCLUSIONS

FOBT followed by flexible fiberoptic sigmoidoscopy is likely to become the screening procedure of the future in average risk individuals, in populations with the resources for these techniques (Jorgensen et al 1994b; Church 1994; Armbrecht et al 1995).

Preliminary data from a large randomized European study have shown a statistically significantly greater yield of adenomas larger than 1 cm, and of cancers, when FOBT was combined with flexible sigmoidoscopy, even though compliance for flexible sigmoidoscopy was poor (Bennett et al 1995).

Flexible fiberoptic sigmoidoscopy used as a screening procedure in asymptomatic individuals over age 50 can result in about a 60% reduction in mortality of cancer within its reach, which would mean about a 35% reduction in colorectal cancer mortality as a whole.

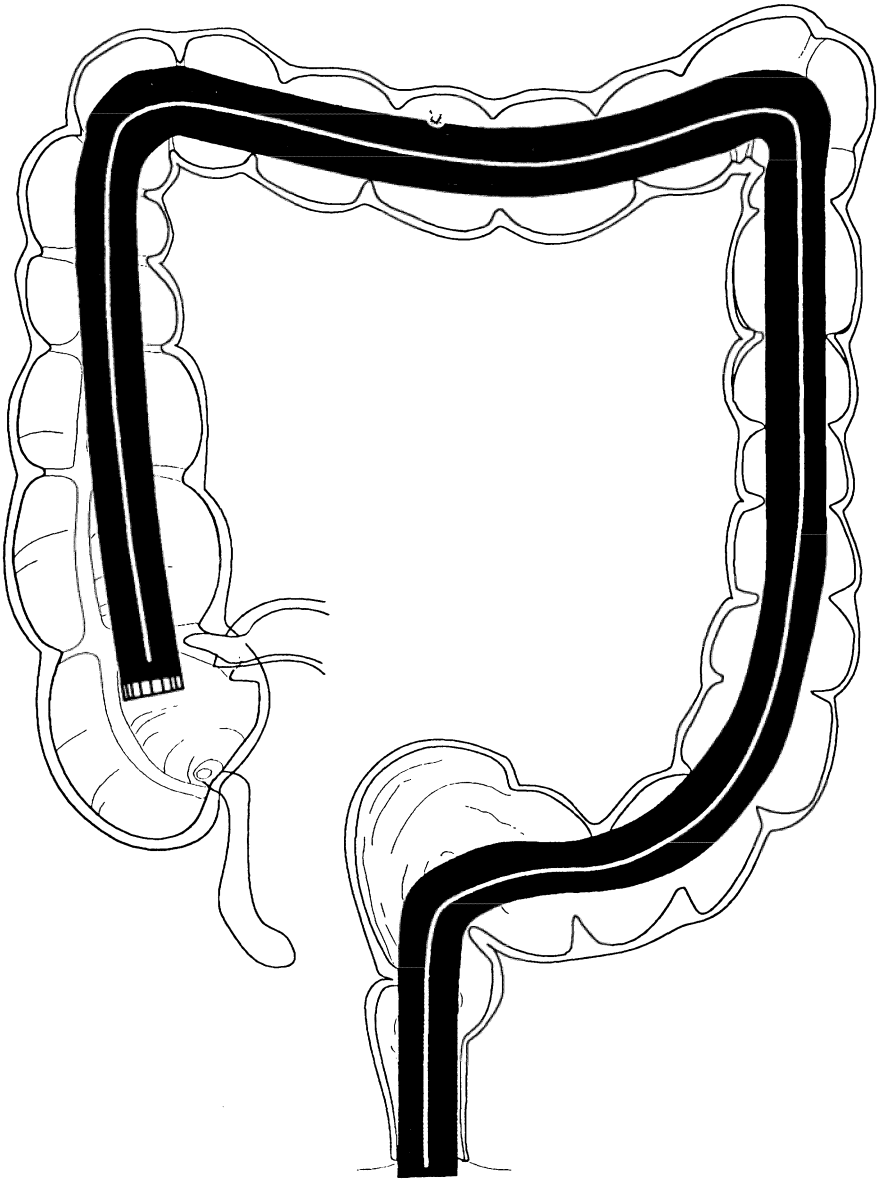

Figure 20.3 Total colonoscopy with end of instrument in the cecum (Modified from Gastrointestinal Endoscopy for Surgeons, Pearl RK. Boston: Little Brown, 1984, with permission).

DOUBLE CONTRAST BARIUM ENEMA

Double contrast (or air-contrast) barium enema was first described almost 30 years ago as a more sensitive means of diagnosis of colonic tumors, especially polyps, than the single contrast investigation (Welin 1967). In expert hands it is an extremely safe investigation. The procedure has the disadvantage that lesions cannot be biopsied or excised. About one-sixth of adenomas less than 1 cm are missed, but only 5% of adenomas larger than 1 cm are overlooked (Williams et al 1974; Ott et al 1980, 1986).

Overall, this investigation is less sensitive for colorectal tumors, particularly small adenomas, than colonoscopy; however, it is more available and much less expensive than colonoscopy (Thoeni and Menuck 1977; Unger and Wanebo 1983; Macrae and Williams 1985).

Colonoscopy rather than double contrast barium enema is used increasingly in more affluent communities for the screening of those individuals in whom a complete evaluation of the large bowel is required, because colonoscopy is more sensitive and specific for colorectal tumors and because biopsy and excision of any lesions found can also be performed during the same procedure.

COLONOSCOPY

The colonoscope was introduced in the 1960s, and electrocautery and biopsy of polyps was first done in 1969 (Wolff and Shinya 1973). This is an investigation with a very high sensitivity of over 90% (Macrae and Williams 1985). However, adenomas, even of a large size, can be overlooked for various technical reasons (Glick et al 1989; Hixson et al 1991).

As shown in Figure 20.3 the entire colon and rectum can usually be examined, and experienced endoscopists will be able to do a total colonoscopy in about 20 minutes in 90% of cases (Winawer et al 1990; Isbister 1995). Colonoscopy places a bigger demand on the person being screened than sigmoidoscopy, as bowel preparation, sedation and analgesia are necessary. Mortality is low, and in an early series of 7000 polyps removed colonoscopically, the mortality was zero (Shinya and Wolff 1979). There was however, a risk of complications, particularly perforation of the bowel and hemorrhage. In the St. Mark's Hospital series of 5000 colonoscopies reported by Macrae and co-workers in 1983, the incidence of bowel perforation was 0.1%, hemorrhage 1%, with a mortality of 0.06%. In a more recent series of almost 1500 colonoscopies, the perforation rate was 0.2%, the bleeding rate was 0.6%, with transfusions required in 0.1% (Isbister 1995). There is also a high cost for each screening colonoscopy, as well as a high capital equipment cost. In a simulated model, colonoscopic surveillance for those at relatively low risk, such as a person having had a small tubular adenoma removed, was not regarded to be cost effective (Ransohoff et al 1991).

Experienced colonoscopists will miss about one in 6 (15%) polyps under 1 cm, but only uncommonly miss significant adenomas larger than 1 cm in size (Hixson et al 1990; Winawer 1995).

COLONOSCOPY IN AVERAGE RISK

Up to the present time there have been no controlled studies of total colonoscopy as the first screening test for average risk individuals. The need for substantial resources, the demands on the patient in terms of bowel preparation, sedation and analgesia, as well as the small but well defined risk of complications, makes colonoscopy acceptable as the first screening procedure for certain high-risk groups only.

In a large case-control study of US Veterans involving over 8700 colon cancer and over 7600 rectal cancer patients, matched for age, sex and race with controls without colorectal cancer, a previous colonoscopy was associated with a statistically highly significant 53% reduction in colon cancer, and a 39% reduction in rectal cancer incidence, and the protective effect was apparent for 6 years (Müller and Sonnenberg 1995). In that study, previous endoscopic polypectomy was associated with a statistically highly significant 41% reduction in colon cancer and a 52% reduction in rectal cancer incidence, and this protection also lasted for 6 years (Müller and Sonnenberg 1995).

CONCLUSION

Screening colonoscopy would undoubtedly have the most marked effect in reduction of the incidence and mortality from colorectal cancer; however, for reasons of resources and some risk which is associated with the procedure, at present colonoscopy is restricted to certain high-risk groups, to be discussed in more detail below.

SCREENING STUDIES FOR HIGH RISK GROUPS

DEFINITION OF HIGH RISK GROUPS

The differentiation between average risk and high risk in colorectal neoplasia has never been firmly or formally established. Quite clearly, the risk for colorectal tumors is very high in familial adenomatous polyposis syndromes (FAP) and also high in families belonging to the hereditary non-polyposis colorectal cancer syndrome (HNPCC). However, those who have a positive family history of colorectal cancer have been shown to be only at a twofold risk compared to those without such a family history, especially if only one close relative is involved (Kune et al 1989; St. John et al 1993a; Fuchs et al 1994).

Comparing the twofold risk in the presence of a family history of colorectal cancer, two-to-threefold levels of risk for colorectal cancer have been found for

alcohol consumption and much higher levels of risk have been found in relation to certain dietary patterns, as discussed in Chapters 6 and 7. Furthermore, in Western societies the attributable risk for dietary factors has been estimated to be of the order of 50%, and for inherited factors, only of the order of 10%, when FAP and HNPCC are excluded (Kune et al 1992). This means that in developed Western societies in which poor dietary habits, alcohol consumption and smoking is widespread, there is unlikely to be much difference in risk between those that are labelled as high risk due to a positive family history of colorectal tumors (especially if only one close relative is involved), and the so-called average risk person. This has been borne out by only a slight increase in the recovery of adenomas on screening of relatives with a colorectal tumor, when compared with expected rates or with controls, as noted later in this chapter. This consideration naturally excludes those with FAP and HNPCC.

PREVIOUS COLORECTAL TUMORS

Those with a history of colorectal adenoma or cancer are known to be at a high risk for metachronous colorectal tumors, and this will be discussed in more detail below. Of interest is the observation that apart from metachronous colorectal tumors, these individuals are also at a 30% increased risk for developing cancer at other sites, and especially in the bladder, kidney, prostate, breast, endometrium and ovary (Enblad et al 1990).

There is sound evidence that those who develop colorectal adenomas or colorectal cancer have an abnormal proliferative activity which may be patchy, although it probably involves the colorectal mucosa diffusely (Terpstra et al 1987; Pandey et al 1995). Evidence for this diffuse and abnormal proliferative activity is the high frequency of synchronous colorectal tumors, as well as the high risk of metachronous tumors. However, the additional role of persistent causal factors such as poor diet, beer consumption and smoking, operating in the development of metachronous tumors, is not known.

Previous Colorectal Cancer

While it is difficult to be certain on follow-up studies that a colorectal cancer is truly a "new" (metachronous) tumor, or a cancer "missed" at the previous examination, nevertheless the risk of a metachronous colorectal adenoma and colorectal cancer in an individual is considerably elevated (Cali et al 1993). The calculation of cumulative risk of metachronous colorectal cancer is difficult because of missed synchronous cancers and because of incomplete follow-up; however, the evidence suggests that the rate rises by about 1% every 3 years (Bussey et al 1967; Weber and Deveney 1986; Luchtefeld et al 1987; Juhl et al 1990; Kune et al 1990; Cali et al 1993). Post-surgical surveillance to detect metachronous tumors is therefore an important part of the management (Chapter 21).

Previous Colorectal Adenomas

Metachronous colorectal adenomas develop frequently, especially if the initial lesion had certain characteristics such as large size, dysplasia, a villous element or multiplicity, with recurrence rates of 30–50% having been reported between 3 and 5 years after initial excision (Juhl et al 1990; Cali et al 1993; Winawer et al 1993b; Axon et al 1994). The surveillance of this important group is discussed in Chapter 21.

INHERITED SUSCEPTIBILITY

Familial Adenomatous Polyposis (FAP)

The screening of families with FAP is well established. It is exciting that the accurate presymptomatic diagnosis of FAP, using linkage studies close to the APC gene and mutational assays, is now a practical possibility (Park et al 1994; Walpole et al 1995). Current recommendations regarding this group will be described subsequently.

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Who to Screen for HNPCC?

Until genetic testing for HNPCC is a realistic possibility, the decision to advise screening of family members will depend on clinical criteria. The International Collaborative Group for HNPCC established three cardinal criteria for inclusion as an HNPCC family, namely three or more relatives with histologically confirmed colorectal cancer, cancer involves at least two successive generations, and at least one of the cases is diagnosed before 50 years of age (Vasen et al 1991). Whilst these criteria are useful for international comparison, they may be too stringent if used as criteria for screening (Jass and Stewart 1992; Jass et al 1992; Percepese et al 1994). At present it may be reasonable to advise screening if 2 of the 3 criteria are met.

In some centers, genetic testing using mutational analysis has commenced with very promising early results (van-de Water et al 1994; Kohonen-Corish et al 1995). This is undoubtedly the way of the future for members of HNPCC families, because if the testing is reliable, endoscopic surveillance of those who do not carry the mutation is unnecessary, whilst for those who do carry the mutation there is an absolute need for surveillance. The difficulty with genetic testing of HNPCC families, in contrast to FAP families which have a uniform gene defect on chromosome 5, is that each HNPCC family is likely to have its own mutation pattern, making the task of reliable genetic testing much more complex and much more costly than that for FAP, although most large HNPCC families will have mutations in hMSH2 or hMLH1 (Froggatt et al 1995).

How and How Often to Screen for HNPCC?

Screening must be colonoscopic, in view of the preponderance of HNPCC in the proximal colon. If a subtotal colectomy has been performed, subsequent surveillance is with flexible sigmoidoscopy. Age of commencement and frequency of screening is at present empiric. Most suggest screening to commence at 25 years of age, with 2-yearly colonoscopy until 35 years, then yearly, while some suggest yearly colonoscopy throughout (Jass et al 1992; Lynch and Lynch 1995; Burt 1995).

Results of Screening in HNPCC

The screening and subsequent surveillance of HNPCC families is now also being standardized, and an international cooperative study of 165 HNPCC families has recently been reported with encouraging results, in which only 6 interval cancers were detected among 682 relatives (Vasen et al 1993). This is the largest study reported so far focussing on HNPCC screening. In a Finnish study of 22 HNPCC families 3-yearly screening was found to more than halve the colorectal cancer rates, and reduce mortality over a 10 year period (Jarvinen et al 1995). Other screening studies are also noting similar results (Cameron et al 1989; Lanspa et al 1990; Jass et al 1992).

Ordinary Colorectal Tumors – Screening Relatives

Those with a positive family history of a colorectal neoplasm represent the commonest group for an inherited susceptibility, and the results of several such studies will be described.

Uncontrolled Screening Studies

Since 1984 several uncontrolled studies have evaluated the prevalence of colorectal neoplasms in asymptomatic individuals in whom a family member has had colorectal cancer (Love and Morrissey 1984; Gillin et al 1984; Gryska and Cohen 1987; Guillem et al 1988; Fisher and Armstrong 1989; McConnell et al 1990; Orrom et al 1990; Houlston et al 1990; Baker et al 1990; Stevenson and Hernandez 1991; Stephenson et al 1993). These uncontrolled studies established that relatives of those with a history of colorectal cancer had a high prevalence of colonic tumors, particularly adenomas, compared to that expected in the population. Gillin and co-workers in 1984 also noted that those with two or more members of the family having colorectal cancer have a higher risk of colonic adenomas than those with one family member only, and further, that in those with one family member only, adenomas developed at a rate similar to that expected in the general population. This was also found in some, but not all other studies (Grossman and Milos 1988; McConnell et al 1990). These studies are of limited usefulness as risk levels cannot be calculated in the absence of controls;

however, they establish that such studies are feasible with a reasonably high overall compliance (Brewer et al 1994).

Controlled Screening Studies

There have been two retrospective controlled studies of colonoscopic screening of relatives with colorectal cancer, and both found an increased rate of tumors detected in those with a positive family history (Sardella et al 1990; Luchtefeld et al 1991). The study of Sardella et al compared symptomatic patients with those who had a family history of colorectal tumors in first-degree relatives.

Five prospective controlled studies have been performed in asymptomatic relatives of colorectal cancer patients. Armitage et al 1987 used FOBT, Rozen et al 1986 FOBT and flexible sigmoidoscopy, Cannon-Albright et al 1988 flexible sigmoidoscopy, Guillem et al 1992 and Bazzoli et al 1995 used colonoscopy. These prospective controlled studies found a significant elevation of risk in relatives of colorectal cancer patients compared to controls. Controlled screening studies found that the risk was higher if two or more family members had a history of colorectal cancer compared to only one family member, a finding also of case-control and cohort studies referred to in Chapter 5 (Rozen et al 1987; Guillam et al 1992; St. John et al 1993a; Fuchs et al 1994). One study which examined first-degree relatives when only one family member had a history of colorectal cancer, found a statistically significant risk level of 1.9 (Bazzoli et al 1995).

Conclusions

The data indicate that first-degree relatives of those with colorectal tumors have a higher incidence of such tumors than the rest of the population. This increased incidence is significant if two or more members of a family have colorectal tumors. The risk is about twofold if only one first-degree relative is involved.

In an important analysis of 20 studies reported in 1994 by Brewer and co-workers from Australia, no cancers and few adenomas were found in family members who were under the age of 40 years when screened, and that the risk rises with age, suggesting that screening may commence at age 40. It was further found in that analysis that colonoscopy yielded most tumors, suggesting that FOBT and/or flexible sigmoidoscopy may be insufficient for the screening of this group, although controlled data are awaited. The need for total colonoscopy as the first screening measure in this group is also underlined by the high rate of proximal tumors, which would be missed by flexible sigmoidoscopy (Bazzoli et al 1995).

DIET, ALCOHOL, SMOKING

Dietary factors appear to be the single most important cause of both colorectal adenomas and colorectal cancer (Chapter 6), yet up to the present time there have

been no screening studies of groups which are at high risk to develop these tumors because of their dietary habits.

Alcohol consumption, and particularly but not exclusively beer consumption, appears to pose a risk of a similar magnitude to that noted for inherited susceptibility of ordinary colorectal neoplasms (Chapter 7). So far there have been no controlled screening studies performed focussing on this high-risk group. Of special interest is that in an uncontrolled study of alcoholics who also had a positive FOBT, a colorectal tumor was present in 38% (Weinstein et al 1987). Smoking is emerging as an important cause in the development of colorectal adenomas (Chapter 8), and up to the present time, this group has not been the subject of any screening studies.

ULCERATIVE COLITIS AND CROHN'S DISEASE

Patients with chronic ulcerative colitis, when compared to the general population, have a substantially increased risk of colorectal cancer 8 to 10 years after onset, and the cumulative incidence in patients with proctocolitis is in the vicinity of 12% at 25 years and 20% at 35 years (Katzka et al 1983; Lennard-Jones et al 1983; Broström et al, 1987; Gyde et al 1988; Ekbom et al 1990a). In two population-based cohorts from England and Sweden totalling over 800 patients followed for between 17 and 38 years, colorectal cancer developed at 8 times the expected rate; however, the risk was twenty-fold with extensive colitis, and only fourfold with left sided colitis (Gyde et al 1988).

The studies quoted indicate that about 12% of those with extensive colitis develop colorectal cancer in the period 10–25 years from the onset of symptoms, and this is the premise on which both prophylactic proctocolectomy as well as screening and surveillance for carcinoma is based. Screening followed by regular surveillance, or proctocolectomy, are at present the only two options for those with extensive disease of 8 or more years duration (Levin et al 1991). In the absence of controlled data, screening colonoscopy and multiple biopsies for evidence of dysplasia or carcinoma, seems reasonable in those with 8–10 years or longer of extensive disease. In this group, the presence of severe dysplasia or carcinoma found on screening would indicate the need for surgery, a policy which will lower mortality from colorectal cancer, partly because surgery removes the target organ in this high-risk group, and partly because it identifies a number of early cancers (Lennard-Jones and Connell 1995; Biasco et al 1995a; Rozen et al 1995). Unfortunately, dysplasia is not a highly sensitive or specific marker of colorectal cancer, since in a proportion cancer can develop without dysplasia, and per contra, cancer may not be present when low-grade dysplasia is noted (Taylor et al 1992). Finally, low-grade dysplasia may be a transient change in some, while in others may progress to high-grade dysplasia or cancer (Lennard-Jones et al 1990; Lynch et al 1992; Woolrich et al 1992).

In those with extensive disease of more than 8 years duration who have not had surgery, colonoscopic screening followed by yearly colonoscopy and multiple biopsies, searching for dysplasia or carcinoma, is the most appropriate course of action, and particularly if initial biopsies indicate dysplasia (Connell et al 1994; Lennard-Jones and Connell 1995). Up to now there are no controlled series which show a reduction in mortality from cancer as a result of screening and surveillance. A prospective randomized study has not been conducted, and indeed would be most difficult to mount, so that all recommendations for screening are at present based on empiric evidence (Polon 1994).

In an interesting recent study from Seattle, USA, abnormalities in the DNA mismatch repair gene MSH2, mutations of which are associated with some HNPCC families, were present in 26% of patients with ulcerative colitis associated with high grade dysplasia or carcinoma, but only in 11% of patients with ulcerative colitis without dysplasia, and in only 9% of healthy blood donors (Brentnall et al 1995). If these findings are confirmed, testing for MSH2 once such assays are established, may become a further screening tool for cancer risk in ulcerative colitis.

In Crohn's ileocolitis and colitis, long-term studies identified a high risk of large bowel cancer in those with previous Crohn's disease, and especially in those who develop Crohn's disease before the age of 30 years (Fielding et al 1972; Gyde et al 1980; Ekbom et al 1990b; Gillen et al 1994a). For those who develop Crohn's colitis before the age of 30 years, the risk of colorectal cancer is similar to those developing ulcerative colitis at that age (Ekbom et al 1990a, 1990b). Dysplasia, similar to that in ulcerative colitis, has also been described (Riddell et al 1983). The actual number of those who develop colorectal cancer is small, because many patients with extensive Crohn's colitis undergo colectomy early, as their disease often does not respond to conservative treatment (Gillen et al 1994b). In contrast to ulcerative colitis, a plan for screening and surveillance has not been developed in unresected Crohn's colitis.

BREAST, UTERINE AND OVARIAN CANCER

Women who in the past have had breast, uterine or ovarian cancer appear to be at an increased risk of developing colorectal tumors subsequently. The level of this elevated risk is discussed in more detail below, but risk levels are not high. The causes of this increased rate of colorectal tumors are thought to be shared etiologic factors, in particular inherited genetic factors, dietary factors and possibly reproductive and hormonal factors. The inherited component has been strongly espoused by data from the Utah Population Database; however, environmental effects cannot be separated in these studies because of absence of data on diet, alcohol, smoking and hormonal factors (Goldgar et al 1994; Slattery and Kerber 1994). In relation to previous ovarian and uterine cancer, a further cause of increased risk is pelvic irradiation, used as part of the treatment of these

cancers, and this results in irradiation-induced preneoplastic changes in the distal colonic and rectal mucosa.

Breast Cancer

Several studies have found elevated risks of the order of 1.5–2 for colorectal cancer in women who have a past history of breast cancer (Howell 1976; Adami et al 1984; Harvey and Brinton 1985; Teppo et al 1985; Toma et al 1987; Kune et al 1988; Eisen and Sandler 1994). The risk elevation applies for colon rather than for rectal cancer. Although one study has found no association, two other studies have noted elevated risks for colorectal adenomas in women with a past history of breast cancer (Bremond et al 1984; Rozen et al 1986; Murray et al 1992).

Of particular interest is the study of Teppo and co-workers in Finland, which showed that colorectal cancer risk was higher in those women who had breast cancer diagnosed before the age of 45 years, and also that the level of this risk rose with increasing duration of follow-up.

Uterine Cancer

The data for uterine cancer are similar to those for breast cancer, and several studies have found risk elevations of the order of 1.5–2, more pronounced for colon cancer than for rectal cancer, and the level of the risk increases with the duration of follow-up (Schoenberg et al 1969; Schottenfeld and Berg 1971; Teppo et al 1985; Curtis et al 1985; Storm and Ewertz 1985; Kune et al 1988). Pelvic irradiation, sometimes used as part of the primary treatment of uterine cancer, also leads to an elevation of risk. Some women who develop uterine cancer are members of HNPCC families (Sumoi et al 1995; Watson et al 1995).

Ovarian Cancer

Early studies have indicated an elevation of risk for colon cancer in women who in the past have had a cancer of the ovary treated (Schoenberg et al 1969; Schottenfeld and Berg 1971). More recent studies have confirmed that this risk elevation is about twofold, and mainly for colon cancer, with the exception of the Finnish study of Teppo et al 1985, in which the risk elevation was for rectal cancer (Curtis et al 1985; Storm and Ewertz 1985; Teppo et al 1985). Pelvic irradiation also increases risk levels for large bowel cancer, especially for those followed for 10 years or longer after the treatment of the ovarian cancer.

Results of Screening Studies

In a controlled screening study from Israel, in which 183 women with a past history of breast, uterine or ovarian cancer were put into a screening program and compared with 252 women of similar age and ethnic background, without a past history of cancers, colorectal neoplasms were identified 2.5 times more

frequently among the cases than the controls, and the relative risk adjusted for a family history of gastrointestinal cancer in those with a past history of breast cancer was 3.0, and statistically significant (Rozen et al 1986). The authors wisely concluded that this type of colorectal screening is best integrated into a combined colorectal, breast and gynecologic tumor follow-up.

In a retrospective case-control study of flexible fiberoptic sigmoidoscopy, Bremond and co-workers from Lyon found an odds ratio of 2.5 for detecting colorectal adenomas with a past history of breast cancer, compared to those who did not report breast cancer in the past (Bremond et al 1984).

PREVIOUS PELVIC IRRADIATION

Irradiation does not appear to be an important or common contributory component cause of colorectal cancer. Apart from the survivors of the atomic bomb in Japan, there are only case series pointing to an association between pelvic irradiation, usually given for the treatment of gynecologic malignancies, and the subsequent development of colorectal cancer (Castro et al 1973; Jao et al 1987). The problem of risk estimation is that a careful epidemiologic study has not been made so far, and also that gynecologic malignancies and particularly cancers of the ovary and uterus, are known to be followed by an increased risk of colorectal cancer. Radiation therapy as a likely factor in the development of colorectal cancer is also pointed to by colorectal cancer developing in the pelvis after pelvic irradiation given for benign conditions (Palmer and Spratt 1956). Post-irradiation proctitis appears to occur in most instances, serving as a marker of subsequent risk, although a history of proctitis may not be present in all cases (Castro et al 1973; Jao et al 1987). A careful assessment of risk levels has not been made, although the case reports indicate that the risk of colorectal cancer rises in a cumulative manner some 5 years after pelvic irradiation.

OTHER PUTATIVE HIGH RISK GROUPS

There is clinical and immunohistochemical evidence of an elevated risk for colorectal tumors in the presence of hypergastrinemia (Smith et al 1989; Wong et al 1991; Biasco et al 1995b; Ciccotosto et al 1995). It has been hypothesized that high levels of the hormones insulin, a growth factor for cells (Giovannucci 1995), and gastrin, a growth promoter of gastrointestinal cells including colorectal epithelial cells (Ciccotosto et al 1995), may be risks for colorectal cancer. Further research into these areas is awaited with interest.

Case series have suggested an association between Barrett's esophagus and colorectal tumors, and more recently also between esophageal adenocarcinoma, which usually arises in a patch of Barrett's esophagus and subsequent colorectal cancer, especially in men (Vaughan et al 1995).

LIMITATIONS AND CONTROVERSIES OF SCREENING

LIMITATIONS OF SCREENING

Individuals who have bowel symptoms are **not** to be considered for screening. Symptomatic individuals, if seeking medical attention, need to have the established forms of highly sensitive and specific diagnostic tests undertaken. It is also important to understand that screening of asymptomatic individuals with the use of FOBT will miss a substantial number of colorectal cancers and adenomas, and there will also be a significant number of false positives, who will be subjected to the inconvenience and risks of an unnecessary colonoscopy or sigmoidoscopy. Screening tests, such as double contrast barium enema, flexible sigmoidoscopy and colonoscopy all have risks, albeit small, and all are associated with false positive and false negative results.

The considerations for screening of "high-risk" individuals in a medical care environment, such as that performed by an individual physician, clinic or hospital, are different to considerations of mass screening of an entire population. Population screening, because of a massive involvement of resources, of necessity needs to have a greater weight of evidence to show benefit to the whole community than screening in the health care setting of a physician or clinic where other considerations are also taken into account, such as the availability of resources, clinical judgement in an individual situation, and a system of already organized health care checks.

SCREENING CONTROVERSIES IN A HEALTH CARE SETTING

There is important discussion among researchers and practitioners working in the field of colorectal tumor prevention regarding the most appropriate screening measures, and this has been already described in several parts of this chapter. The author's perceptions of these controversies will be summarized, focussing on screening for colorectal tumors as it applies in the health care setting of a developed country in which there is a high incidence of colorectal tumors. It is probably too early to make definite recommendations regarding mass screening in developed countries, although this time is fast approaching.

Average Risk Individuals

Controversies exist regarding the age at which to start screening, which screening tests to use and how frequent the screening intervals should be.

What Age to Commence Screening?

Most data now indicate that screening below the age of 50 years has a very low yield of positives, so the age controversy of commencing screening has been largely resolved to those 50 years or older.

Which Screening Test to Use?

The major controversy is whether to use FOBT alone, flexible sigmoidoscopy alone, or FOBT followed by flexible sigmoidoscopy, irrespective of FOBT result. Emerging data indicate that the most appropriate choice may be FOBT followed by flexible sigmoidoscopy. If FOBT is used, there is some controversy whether to use the guaiac impregnated card or immunochemical FOBT, with the latter being more costly but with better performance characteristics. One suspects that immunochemical FOBT will be increasingly used for screening in the future.

Screening Intervals

Whilst annual FOBT is recommended by most, in the absence of conclusive data, controversy remains over the ideal interval following a negative flexible sigmoidoscopy. Emerging data indicate that 3-year intervals may be too frequent and it is likely that 5 or more years will become the recommendation in the future, if flexible sigmoidoscopy was negative.

High Risk Groups

Who is "High Risk"?

Emerging data indicate that certain groups labelled as "high risk" may not be greatly different in risk levels to so-called "average-risk" individuals. For example, where only one member of a family has a colorectal tumor other family members may not be at a substantially higher risk than the rest of the population. Also, risk levels in those with a past history of breast, uterine or ovarian cancer may not be at substantially higher risk levels than so-called "average-risk" individuals, because Western societies are at an elevated risk due to widespread at-risk diet habits, alcohol consumption and smoking. While the choice of the most appropriate screening technique for these subgroups who are only at a slightly increased risk is uncertain, the emerging view is that screening should be similar to so-called "average-risk" individuals, namely using FOBT and flexible sigmoidoscopy, repeating this 3–5 yearly, but commencing screening a decade earlier than for "average-risk" individuals.

Which Screening Test to Use?

For those truly at high risk for colorectal tumors, namely individuals who belong to HNPCC families, those who have two or more relatives with colorectal cancer, and those with longstanding extensive ulcerative colitis, most would agree that FOBT and flexible sigmoidoscopy is insufficient and total colonoscopy is the initial screening test of choice.

RECOMMENDATIONS FOR SCREENING COLORECTAL TUMORS

The recommendations which follow are based on best current scientific data, on current knowledge of the acceptance of the various screening tests in developed countries, as well as on the recommendations of major health surveillance organizations, such as the American Cancer Society, the National Cancer Institute, the American Gastroenterological Association and the International Work Group on Colorectal Cancer (Winawer et al 1990; Levin and Murphy 1992). These recommendations are proposed in the health care setting, they need to be regarded as guides only, and viewed with the likelihood that the recommendations will change as new data are published.

SCREENING AVERAGE RISK INDIVIDUALS

Average risk individuals who make an informed request for screening within a medical health care setting, should be over 50 years of age, have annual FOBT using an approved technique and a test card such as Hemoccult II®, and have the slides rehydrated. Fiberoptic sigmoidoscopy should also be performed irrespective of FOBT findings. Repeat fiberoptic sigmoidoscopy every 5 years is recommended. If the FOBT is positive, it should be followed by a full examination of the large bowel, preferably by total colonoscopy. All lesions should be biopsied and subjected to histologic examination.

Population screening of average-risk individuals at present should be undertaken only in relation to a controlled and approved scientific study, or as part of the evaluation of a screening test. Recommendations for mass screening are very dependent on both the risk levels of the population, and the resources available in the country concerned.

SCREENING INDIVIDUALS WITH INHERITED RISK

There are three categories, of which the first and commonest is the individual who has a near relative or relatives with a history of colorectal cancer or colorectal adenomas, the second are families with likely hereditary non-polyposis colon cancer (HNPCC), and the third are the families with familial adenomatous polyposis syndromes (FAP).

Family History of Ordinary Colorectal Cancer or Adenoma

If only a single first-degree relative is affected, such an individual requires screening similar to that for the so-called average risk person; however, screening should be started earlier. As the risk increases when two or more first-degree relatives are affected, the screening recommendations are more stringent because of the higher risk.

One First Degree Family Member With Ordinary Colorectal Cancer
Screening is recommended to begin at 40 years of age with annual FOBT and flexible sigmoidoscopy every 5 years. If the FOBT is positive and/or an adenoma is found on flexible sigmoidoscopy, total colonoscopy is indicated, and then repeated every 5 years. If a family member was diagnosed with colorectal cancer under the age of 50 years, it may be reasonable to advise 5-yearly colonoscopy instead of flexible sigmoidoscopy.

Two First Degree Relatives Involved
Annual FOBT and colonoscopy every 3 years, beginning at age 40, or at an age 5 years earlier than the age the youngest relative was diagnosed with colorectal cancer.

Three or More First Degree Relatives Involved
This should be considered in the context of HNPCC, to be discussed below.

First Degree Relative with Cancer Under the Age of 30
HNPCC, or FAP, should be suspected, and appropriate screening methods, as described below, instituted.

Second Degree Relatives Affected
Average risk screening advised, that is, FOBT annually and flexible sigmoidoscopy 5-yearly.

First and Second Degree Relatives Affected
FOBT annually and colonoscopy 3-yearly commencing at age 40.

First or Second Degree Relatives with Adenomas
Average risk screening is advised, that is, FOBT annually and flexible sigmoidoscopy 5-yearly.

Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

Individuals in HNPCC families should have annual FOBT and total colonoscopy every 2 years beginning at age 25, or at an age 5 years younger than the age of the youngest colorectal cancer member in the family. Annual colonoscopy is suggested after age 35. Genetic testing is now possible in some specialized centers, and it is clearly the way for the future; however, each HNPCC family is likely to have its own mutation pattern, so that unlike FAP, in which there is a uniform abnormal gene, genetic testing in HNPCC is more complex, time-consuming and costly (van-de-Water et al 1994; Kohonen-Corish et al 1995).

If a potentially curable colorectal cancer is diagnosed in a member of an HNPCC family, a subtotal colectomy with an ileosigmoid or preferably ileorectal anastomosis is advocated, followed by annual flexible sigmoidoscopic surveillance (Lynch et al 1993; Mecklin and Jarvinen 1993; Mecklin et al 1994). Clearly, follow-up after subtotal colectomy will be by flexible sigmoidoscopy.

As endometrial carcinoma is the second most common malignancy in HNPCC, and one-third of female gene carriers will develop it, vacuum endometrial curettage at age 25 is recommended. Hysterectomy and bilateral oophorectomy following subtotal colectomy has been recommended in women over 40 years who have completed their families (Hakala et al 1991; Lynch et al 1993; Mecklin et al 1994; Lynch and Lynch 1995; Watson et al 1995). Cancer patients (or gene carriers) with HNPCC need lifelong surveillance, not only of the large bowel, but also of the urinary tract, stomach, pancreatico-biliary system and the endometrium, if a hysterectomy is not performed (Mecklin et al 1994).

Familial Adenomatous Polyposis Syndromes (FAP)

The accurate presymptomatic diagnosis of FAP using linkage studies close to the APC gene and mutational assay is now possible, and should be performed as the first step in all family members (Powell et al 1993; Park et al 1994; van der Luijt et al 1994; Walpole et al 1995). This form of genetic testing for FAP is a major breakthrough in screening family members, partly because those who are negative will not be burdened by lifelong invasive screening procedures, and partly because those who are positive will need to recognize that there is an absolute need for surveillance based on certainty rather than on a 50% probability that they will develop colorectal cancer in time.

Flexible fiberoptic sigmoidoscopy is advised for all first-degree relatives of individuals diagnosed with FAP and Gardner's syndrome, beginning at the age of 10 or 15, performed yearly until age 30 or 35, and continued every 3 years subsequently. As each family of adenoma bearers begins to develop adenomas at a particular age within the pedigree, the age of beginning and ceasing screening can usually be individualized for the pedigree. The diagnosis and surveillance of the extra-colorectal manifestations of FAP are not considered here. For those who had a total colectomy, flexible sigmoidoscopic surveillance of the rectum yearly is advised, while for those who had a total proctocolectomy, further colorectal surveillance is obviously not relevant.

CHRONIC ULCERATIVE COLITIS AND CROHN'S DISEASE

In the absence of controlled prospective surveillance studies, screening recommendations for individuals who have chronic ulcerative colitis or Crohn's disease, groups known to be at a high risk for colorectal cancer, are based on empiric observational data (Polon 1994). For chronic diffuse ulcerative colitis of longer than 8 years duration, annual colonoscopy is advised, particularly if initial biopsies indicate dysplasia. If dysplasia is not present at the initial biopsy, 2-yearly surveillance colonoscopy seems appropriate. The risk of cancer in chronic ulcerative colitis restricted to the left colon or rectum is not high, and 3-yearly colonoscopy appears to be reasonable.

The risk of cancer in Crohn's colitis is lower than in ulcerative colitis, especially if it develops after age 30. While regular medical supervision is advisable, precise screening and surveillance programs have not been developed for this condition, therefore specific recommendations cannot be made at present. A rational approach would be to recommend screening similar to that for chronic ulcerative colitis in those who have not had a previous total proctocolectomy.

BREAST, UTERINE AND OVARIAN CANCER

Women with a past history of breast, uterine or ovarian cancer are at a somewhat higher risk of developing colorectal cancer than is the general population. In the absence of controlled data, annual FOBT and fiberoptic sigmoidoscopy every 3 years is advisable, and this is probably best done in the context of their systematic check-up for the previous malignant tumor (Rozen et al 1986).

The age of commencing screening is uncertain, and with the exception of two subgroups described below, it would be reasonable to commence screening at age 45–50 years. Women who have had breast cancer diagnosed under 45 years of age should commence screening at 45 years, or no later than 10 years after diagnosis, if diagnosed before age 35. Women with ovarian, uterine or cervical cancer who received pelvic irradiation should commence screening at 45 years, or 5 years after irradiation, whichever comes first.

PREVIOUS PELVIC IRRADIATION

Since therapeutic levels of pelvic irradiation, given for whatever reason, appear to increase the subsequent risk of colorectal cancer about 5 years after treatment, annual FOBT and 3-yearly fiberoptic sigmoidoscopy is advised, commencing 5 years after irradiation.

PREVIOUS COLORECTAL ADENOMA AND COLORECTALCANCER

The surveillance of these two important groups of patients with resected colorectal tumors is discussed in detail in Chapter 21.

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21

SURVEILLANCE AFTER COLORECTAL TUMOR EXCISION

The role of regular surveillance of individuals who have had adenomas excised or have had potentially curative surgical resections of a colorectal cancer will be discussed in this chapter. It is known that these two groups are at an increased risk of developing metachronous tumors.

SURVEILLANCE AFTER ADENOMA EXCISION

Current data strongly suggest that adenoma excision is an important factor in reducing the risk of subsequent colorectal cancer. All adenoma screening and surveillance programs are based on this premise, and on the knowledge that metachronous adenomas frequently develop, since an adenoma is probably a marker of abnormal proliferative activity of the colorectal mucosa diffusely.

ADENOMA RISK

It is known from several studies that those with a colorectal adenoma are at a significantly elevated risk for the subsequent development of colorectal cancer (Prager et al 1974; Brahme et al 1974; Stryker et al 1987; Kune et al 1987b; Atkin et al 1992). The elevated relative risks were between 2 and 6, mostly of the order of 2–3 in the various studies. In Chapter 4, dealing with the adenoma–carcinoma sequence, it was shown that most, though not all carcinomas in Western populations arise in a pre-existing adenoma, that about 5% of adenomas develop into a carcinoma and that the normal cell–adenoma–carcinoma sequence is variable, between 5 and 30 years, with a mean of about 10 years.

Metachronous colorectal adenomas develop often, and recurrence rates of 42% after 3 years and up to 50% 5 years after initial excision have been reported (Juhl et al 1990; Winawer et al 1993b; Axon et al 1994; Neugut et al 1995). Recurrence rates are difficult to assess accurately as a significant proportion may be adenomas missed at the initial endoscopy (Hixson et al 1990; Winawer et al 1993b). The nature of the adenoma found initially has an important bearing on the subsequent development of both metachronous adenoma and colorectal cancer. Colorectal cancer risk and metachronous adenoma rate is significantly elevated if the initial adenoma was 1 cm or larger, if it contained villous elements and if it showed moderate dysplasia, and particularly so if multiple adenomas with these characteristics were present (O'Brien et al 1990; Atkin et al 1992; Zarchy and Ershoff 1994; Neugut et al 1995). A recent preliminary investigation of DNA content abnormalities by flow cytometry suggests that an additional risk factor for metachronous adenomas is DNA aneuploidy (Kristal et al 1995).

By contrast, currently emerging data indicate that small tubular adenomas, less than 1 cm and without dysplasia, if found in the distal colorectum, probably do not indicate a significantly increased risk of subsequent colorectal cancer (Spencer et al 1984; Grossman et al 1989; Atkin et al 1992; Zarchy and Ershoff 1994). The colonoscopic surveillance of this last group is unlikely to be cost effective (Ransohoff et al 1991). This view is challenged by some endoscopic series which conclude that distal small colorectal polyps, whether adenomatous or hyperplastic, are markers of proximal neoplasms, and in these a total colonoscopy is justified (Pennazio et al 1993). Although there is discussion regarding colonoscopy and subsequent surveillance of those with a distal small adenomatous polyp, based on the findings of prospective controlled studies, a consensus view is that finding a distal hyperplastic polyp is not an indication for total colonoscopy (Provenzale et al 1990; Winawer 1995). At present some argue that in those with small distal tubular adenomas there is a 50% probability of proximal synchronous adenomas, as well as these distal adenomas being markers of a diffuse abnormal proliferative activity of the entire colorectal mucosa, and therefore represent an increased risk for colorectal cancer, sufficiently high to be entered for colonoscopy and a future surveillance program (Winawer et al 1990, Winawer 1995). Only a randomized controlled study can resolve these conflicting views.

Adenoma surveillance studies have so far not taken into consideration changes in risk for metachronous adenoma with changes in life habits after adenoma resection, particularly changes in diet, alcohol consumption and smoking, factors which are likely to have an important influence on the etiology of colorectal adenomas, and therefore on rates of metachronous adenomas also.

RESULTS OF ADENOMA SURVEILLANCE STUDIES

The Funen Adenoma Follow-Up Study

A large population-based study on the island of Funen in Denmark commenced in 1978 with several significant publications of interim results (Kronborg et al 1983a,b; Jorgensen et al 1993a,b, 1995). Although there are several aspects of this study which are worthy of note, of particular significance are the results which indicate the benefits of different surveillance intervals after adenomas have been removed, as well as a description of the frequency of complications resulting from the screening procedures.

Between 1978 and 1992 over 1000 patients who had colorectal adenomas removed were allocated to different follow-up intervals ranging from 6 months to 48 months. The last report from this study indicates that only 10 patients developed colorectal carcinoma in the surveillance group. Using estimates of conversion rates of adenoma to carcinoma, based on the number of adenomas over 10 mm and those with severe dysplasia, 110 carcinomas would have been expected, indicating a statistically significant reduction in the incidence of new colorectal cancers. In the surveyed group of almost 4000 colonoscopies, one patient died of colorectal carcinoma and 2 died from complications, a total of 3 deaths compared to the expected number of 7.6, which is a statistically significantly lower than expected mortality. Although the investigators are cautious about generalizing their conclusions because of the relatively small size of the study, and because of the short median time of follow-up, these are the first data from a controlled study showing statistically significant reduction in incidence and mortality of colorectal cancer in this surveillance population.

In relation to the interval between follow-up, the Funen study suggests that it is reasonable for the surveillance interval to be 2 years in large adenomas over 1 cm and in those with high degrees of dysplasia, and for small sessile, tubular, and tubulo-villous adenomas, a surveillance interval of 4 years is appropriate (Kronborg et al 1983a,b; Jorgensen et al 1995).

National Polyp Study USA

This large multicenter study was commenced in 1980, completed in 1990, and consists of a cohort of over 1400 individuals who were followed after adenomas of the colon and rectum were removed colonoscopically (Winawer et al 1992, 1993a,b; O'Brien et al 1990). Excluded from this cohort were those with familial polyposis, inflammatory bowel disease or a previous history of polypectomy or of colorectal cancer. Also excluded were those who had a sessile adenoma with a base larger than 3 cm, and requiring surgical excision. It needs to be noted that these adenomas were not excluded from the Funen study. A 97% clinical follow-up was possible with 80% returning for one or more scheduled colonoscopies, with a total of over 8400 person years of observation, and an average follow-up

period of 5.9 years. The cohort was randomized into two groups, in both of which annual FOBT was performed, and in one colonoscopy was advised at 1, 3 and 6 years after initial adenoma removal, and in the other colonoscopy was performed at 3 and 6 years after initial adenoma removal.

There was no difference noted in the frequency of adenomas with advanced pathology at 3 years, irrespective of whether surveillance included colonoscopy at 1 and 3 years, or at 3 years only. Furthermore, there was no difference in the cumulative risk for adenomas with advanced pathology in the group who had colonoscopies at 1, 3 and 6 years, compared to the group which had it at 3 and 6 years only. Thus, 3-yearly follow-up colonoscopies appeared to be appropriate in this study.

Two asymptomatic colorectal cancers were detected in the group which had colonoscopies 1, 3 and 6 years after initial adenoma removal, one at 3 years and one at 6 years. In the group having colonoscopy 3 and 6 years after initial adenoma removal, 2 asymptomatic colorectal cancers were found 3 years after adenoma removal, and a further one at 7 years after initial adenoma removal.

In order to compare the results of this study with expected numbers of colorectal cancers, the research group used three reference populations, namely a retrospective cohort study of the Mayo Clinic in Rochester, Minnesota between 1965 and 1970 (Stryker et al 1987), a retrospective cohort of over 1600 patients who had rectal and rectosigmoid adenomas excised between 1957 and 1990 at St. Mark's Hospital, London (Atkin et al 1992), and the Surveillance Epidemiology and End Results (SEER Program) of the National Cancer Institute, which monitors the incidence and mortality rate of colorectal cancer from 10 USA registries (Gloeckler-Ries et al 1990). Five asymptomatic colorectal cancers were identified by colonoscopy in the National Polyp Study, when over 48 were expected in the Mayo Clinic Study, over 43 expected in the St. Mark's Hospital Study and over 20 expected from the SEER data, and whichever reference group was used, the reduction in the incidence of colorectal cancer in the surveillance group was highly statistically significant ($p < 0.001$).

The 2 cancers diagnosed at 6 and 7 years in this study are likely to have been new cancers, and it is not known whether the 3 cancers diagnosed at 3 years were new cancers, or cancers missed at the initial colonoscopy.

Other Adenoma Studies

The St. Mark's Hospital follow-up study of neoplastic polyps represents a selected group of patients and the results of this follow-up are awaited (Williams and Macrae 1992). In another uncontrolled post-colonoscopic polypectomy study from Australia in which 65% of over 1000 patients returned for a follow-up colonoscopy, with a mean period of follow-up of 4.4 years and a total of over 2800 person years of follow-up, 3 asymptomatic colorectal cancers were detected instead of the expected 9.4 cases (Meagher and Stuart 1994). In this post-adenoma resection population, the increased risk of developing colorectal

cancer was about 2.5 times that of the general population, and this difference was statistically significant, ($p = 0.02$). In an uncontrolled study of 500 patients followed for a mean of 4 years post-adenoma removal, recurrent adenomas were noted in one-quarter (Olsen et al 1988). In this series, a dramatic reduction of new colorectal cancers was present at a later follow-up among those who complied with follow-up guidelines, versus those who did not (Olsen and Lawrence 1995).

In a large case-control study of US Veterans in which over 8700 colon cancer and over 7600 rectal cancer patients were age-, sex- and race-matched with controls, previous endoscopic polypectomy was associated with a statistically highly significant 41% reduction in colon cancer and a 52% reduction in rectal cancer incidence, and this protection remained for 6 years (Müller and Sonnenberg 1995). This is by far the largest study, and it shows a marked reduction in the incidence of colorectal tumors following endoscopic polypectomy.

POST-ADENOMA EXCISION SURVEILLANCE RECOMMENDATIONS

If an adenoma is found, by whatever means, it needs to be removed and the entire large bowel examined by total colonoscopy, and all adenomas found removed, in order to obtain a "clear colorectum". A surveillance program for these individuals is recommended. Recommendations for follow-up after a "clear colorectum" has been achieved in "average risk" individuals will now be considered. The method and intervals of follow-up in this group is subject to discussion; however, all agree that the nature of the follow-up may differ according to the nature of the adenoma found initially.

Those in whom only a small (less than 1 cm) tubular adenoma was found probably need less frequent follow-up than those in whom a large adenoma (greater than 1 cm), or an adenoma in which there are villous elements and/or moderate or marked dysplasia, has been found at the initial examination. For those from whom an adenoma had been incompletely removed, or removed piecemeal, or in whom numerous adenomas are present, a further total colonoscopy within 3 months is recommended, followed by another colonoscopy in one year, then 3-yearly colonoscopies.

For those in whom a large adenoma or an adenoma with villous and/or dysplastic elements has been found, repeat colonoscopy at 3-yearly intervals is advised. However, with more data emerging, it is possible that this interval may be lengthened to 4 or 5 years in the future.

If only a small tubular adenoma was removed at the initial examination, some advocate total colonoscopy 3 yearly, whilst others suggest that this interval can be increased and that only 5-yearly flexible fiberoptic sigmoidoscopy is needed. However, until further data are available, 3-yearly total colonoscopy is recommended for all types of adenomas removed at the initial colonoscopy.

SURVEILLANCE AFTER COLORECTAL CANCER RESECTION

Some type of follow-up and surveillance following resection of colorectal cancers is necessary for a variety of reasons. Firstly, surveillance is necessary to diagnose and remedy any mechanical complications following surgery, such as benign anastomotic strictures, colostomy or ileostomy retraction, prolapse, or stricture. Secondly, surveillance may also be necessary for the evaluation of any prospective studies of adjuvant cancer therapy. The follow-up for these indications is determined by established surgical principles in relation to mechanical complications, or it is determined by the protocol of the research study of adjuvant therapy, and these aspects will not be considered further.

The third indication for surveillance is to detect early recurrent colorectal cancer, with the aim of further treatment which may improve survival. The fourth, and what appears to be the most important and most effective indication for surveillance, is to detect metachronous colorectal tumors, since a previous colorectal cancer is probably an indicator of abnormal proliferative activity of the entire colorectal mucosa, and metachronous tumors can be expected to develop.

Follow-up of any kind is best reserved for those who have had a potentially curative resection, who are younger than 80 years of age, and who do not have other severe disease.

SURVEILLANCE FOR EARLY DETECTION OF RECURRENCE

Historically, periodic follow-up of patients who have had a colorectal cancer removed has been recommended for many years because of the hope that the early diagnosis of recurrence will lead to excisional surgery, which will improve the salvage rate and the long-term survival of these patients. There have been few prospective controlled studies, and the studies which have been published unfortunately demonstrate very little benefit from such planned surveillance programs.

Surveillance programs for the early diagnosis of recurrences, apart from not showing much survival benefit, also have additional negative aspects, which include the need to inform an asymptomatic patient about the presence of recurrent disease which is incurable, that the investigations for surveillance, such as liver biopsy, colonoscopy and "second-look" surgery have their own complications, with a definite risk of morbidity and occasional mortality, and finally, that such surveillance is very costly.

Although recurrences can be detected earlier with the use of special investigations such as carcinoembryonic antigen (CEA) and other tumor associated antigens, imaging techniques such as ultrasonograpy, computed tomography and magnetic resonance imaging, endoscopy and second-look surgery, significant survival benefit from these methods of surveillance for

recurrence is likely to be small, and recorded in only about 5% of those who develop colorectal cancer (Ballantyne and Modlin 1988; McLeish et al 1992; Patchett et al 1993; Kronborg 1994; Averbach and Sugarbaker 1995).

CEA Directed Second-Look Laparotomy

The so-called second-look surgery for recurrent cancer has been enthusiastically reported on by Wangensteen and co-workers since the 1950s, and since then a large literature has developed in relation to an "aggressive" diagnostic and therapeutic approach to recurrent cancer (Averbach and Sugarbaker 1995). With the development of CEA, which initially held a promise of being a useful marker for recurrent colorectal cancer, when combined with second-look surgery, a substantial improvement in the salvage of patients with recurrent colorectal cancer was expected. Unfortunately, studies which pursued CEA-directed second-look surgery, or the use of other similar aggressive diagnostic programs, have not fulfilled their promise, and at best, with meticulous follow-up, the 5-year survival can be expected to be prolonged in only about 5% of patients (Minton et al 1985; Martin et al 1985; Northover 1985; Ballantyne and Modlin 1988; Wanebo et al 1989; McLeish et al 1992; Minton and martin 1993; Averbach and Sugarbaker 1995).

Resection of Hepatic Metastases

An extensive literature has developed regarding the early diagnosis of hepatic metastases, of the type which may be localized to the liver and surgically resectable with the hope of prolonged survival (Ballantyne and Modlin 1988; Kronborg 1994). A critical analysis of the available data indicates that the benefit obtained from surgical resection of suitable hepatic metastases would benefit, in terms of 5-year survival, at best 3% of patients with advanced colorectal cancer (Ballantyne and Modlin 1988).

Resection of Anastomotic Recurrences

Most local recurrences are not within the lumen of the large bowel. Intraluminal recurrences, though usually well identified by endoscopy, are uncommon, and when they do occur they rarely represent localized disease. They can only be resected uncommonly, and such resection adds little to the 5-year survival of patients with colorectal cancer as a whole (Welch and Donaldson 1978; Malcolm et al 1981; Vassilopoulos 1981; Kronborg 1994).

Conclusion

There is unfortunately little evidence to indicate that in patients who have had a curative resection for colorectal cancer extensive surveillance for early detection of localized and resectable recurrence has a substantial survival advantage, although an occasional patient may benefit.

SURVEILLANCE FOR METACHRONOUS TUMORS FOLLOWING CURATIVE RESECTION

Obtaining a Clean Post Resection Colorectum

If a preoperative total colonoscopy had not been performed, a post-resection colonoscopy within a few months of curative surgery is recommended, in order to deal with any synchronous tumors, and have a "clean colorectum" for future surveillance (Unger and Wanebo 1983; Kronborg 1994).

Risk of Post Resection Metachronous Tumors

Those who have had a curative resection for colorectal cancer were noted to be at an increased risk of both metachronous colorectal adenomas and colorectal cancers, when compared to those without a previous history of colorectal tumors (Chapter 20). As indicated earlier, both the incidence and the mortality of colorectal cancer has been shown to be reduced by adenoma screening and surveillance, and further reductions in incidence and mortality may be possible with repeated endoscopies after curative surgery for colorectal cancer also.

FOBT in Post Resection Surveillance

It appears that FOBT, such as Hemoccult II® or immunochemical tests are too insensitive to identify the majority of metachronous tumors following colorectal cancer resection, so that for surveillance of metachronous tumors, colonoscopy, or if a subtotal colectomy had been performed, flexible sigmoidoscopy needs to be used to identify these metachronous tumors (Jahn et al 1992; Hall et al 1993).

Post Resection Endoscopic Surveillance Studies

In a small study from Paris in which 94 patients were followed endoscopically about 12 months after surgical resection of colorectal cancer, and then annually for 3 years, adenomatous polyps were found in 27, of which 7 were larger than 10 mm (Girodet et al 1985). Three malignant adenomatous polyps were noted, all 3 larger than 10 mm in diameter. The authors concluded that patients who have had colorectal cancers removed are at a high risk of subsequent adenoma or colorectal cancers developing, and should be followed up by repeated colonoscopy.

In a larger study with a 6-year follow-up of annual colonoscopy after resection for colorectal cancer, Juhl and co-workers in Kentucky, USA, noted 9 anastomotic recurrences, in none of which was it possible to reoperate for a curative resection; however, 4 metachronous colon cancers were found and a curative resection performed. Moreover, 30 adenomas larger than 1 cm in size and 7 villous adenomas were also removed in 30 patients in this series, with a yield of significant neoplasm of 5% per year. These authors conclude that colonoscopy annually, at least for the first 6 years post-resection is useful in

order to detect significant new neoplasms, and that this role of secondary prevention is more important than the detection and attempts at cure of recurrent intraluminal colorectal cancers (Juhl et al 1990).

The post-resection colonoscopic surveillance studies indicate that most metachronous cancers found were resectable and potentially curable (Ovaska et al 1989; Juhl et al 1990; Kronborg et al 1991; Kelly and Daly 1992). What is not known is how often colonoscopy should be repeated. There is only one randomized controlled study for the detection of metachronous tumors following curative resection of colorectal cancer; it is being conducted in Denmark and is examining the optimal frequency of colonoscopy (Kronborg et al 1988). The final results of this trial are eagerly awaited. The interim data from this study indicate that colonoscopy should not be performed more often than every 3 years (Kronborg 1994).

POST-CANCER RESECTION SURVEILLANCE RECOMMENDATIONS

Pre-operative or early post-operative total colonoscopy is advisable in those who have had a potentially curative resection, in order to obtain a "clean colorectum" for further surveillance. The current data indicate that post-resection colonoscopic surveillance is of little or no survival benefit with respect to early diagnosis of resectable intraluminal recurrences. However, the early diagnosis of metachronous adenomas and carcinomas is likely to result in a survival benefit.

Current data suggest that endoscopic surveillance performed every 3 years is optimal.

* * * * *

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22

CONTROL OF COLORECTAL CANCER FUTURE DIRECTIONS

To discuss the future directions of colorectal cancer control, the current status of survival which can be achieved by established forms of treatment is first described. It is also important to examine the time-trends in incidence, mortality and survival for colorectal cancer, as well as trends in changing life habits and diagnostic and screening procedures during the past 30 years, and how these trends may be predictive of colorectal cancer control in the future.

CURRENT STATUS OF COLORECTAL CANCER SURVIVAL

Surgical resection of the cancer is the cornerstone of primary treatment, with adjuvant chemotherapy playing an increasing but still relatively minor role. Recurrent or metastatic colorectal cancer is occasionally also treated surgically, but more often it is treated with chemotherapy or radiotherapy. Those with advanced and terminal stages of colorectal cancer receive palliative care. For further reading on the current approaches to the treatment of colorectal cancer, the reader is referred to recent texts on this subject (Cohen et al 1995).

Population-based studies which have detailed clinicopathologic data on the nature of the primary colorectal cancer with a complete follow-up concerning survival, provide the most accurate information on what can be expected with current treatment (Stewart et al 1979; Clarke et al 1980; Mettlin et al 1982; Bear et al 1984; Isbister and Fraser 1985; Kune et al 1990). Survival data can be misleading in studies which are not population-based and can be unduly optimistic if derived from clinics or hospitals in which there is special surgical

expertise, since subtle forms of prognostically favorable selection bias can occur, or they can be unduly pessimistic when the series emanates from major public hospitals whose clientele does not reflect the socioeconomic or health cross-section of the community.

A review of 16 large studies of colorectal cancer survival suggests that the surgical resection rate of the cancer at the initial operation is about 90%, and that the early postoperative mortality is about 5% (Kune et al 1990). When colorectal cancer-specific survival is measured in population-based studies, about 40% survive 5 years after diagnosis, and this figure is lower by a few points 10 years after diagnosis, at which time the mean age of those who had colorectal cancer is 75 years (Kune et al 1990; Sant et al 1995).

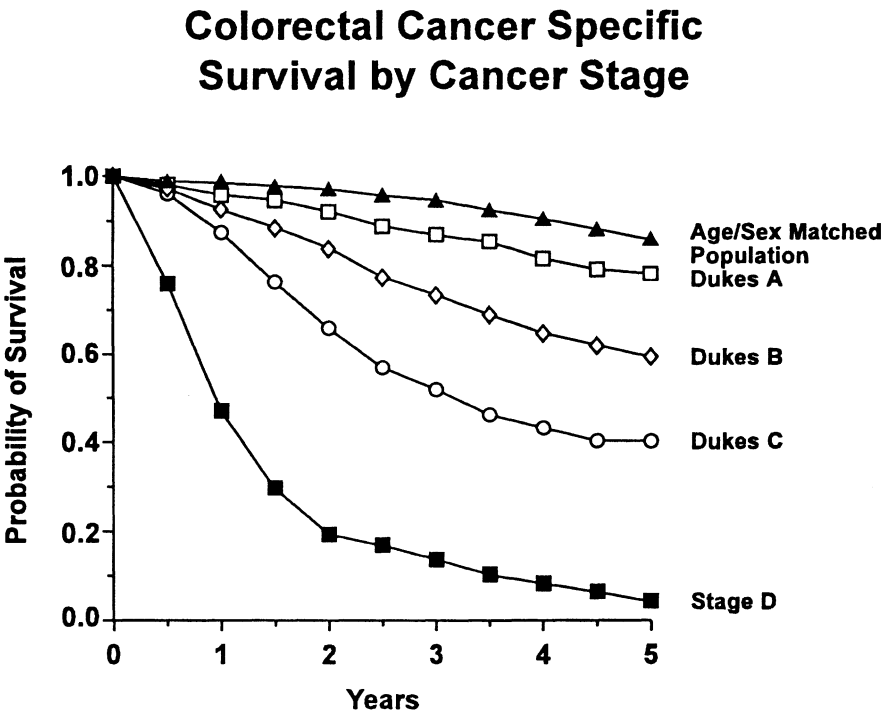

Figure 22.1 Five year colorectal cancer-specific survival by cancer stage, compared to age/sex matched population controls. Data from the Melbourne Colorectal Cancer Study.

The most important and highly statistically significant discriminant of survival for both colon and rectal cancer is the stage of the cancer at diagnosis (McDermott et al 1981; Mettlin et al 1982; Bear et al 1984; Stower and Hardcastle 1985; Kune et al 1990; Slattery and Kerber 1995). Colorectal cancer

stage is usually assessed by a method first devised for rectal cancer by Dr. Cuthbert Dukes of St. Mark's Hospital, London (Dukes Stages A, B and C), to which in recent years a Stage D has been added representing incurable cases, and converting the pathologic classification of Dr. Dukes into a clinicopathologic classification measuring survival (Dukes 1932; Dukes and Bussey 1958; Kune et al 1990). Survival graphs from a large population-based study for the four stages are shown in Figure 22.1 in which colorectal cancer-specific mortality is also shown in an age/sex matched group of the population. Dukes A is colorectal cancer limited to the bowel wall (5 year colorectal cancer-specific survival 85%), Dukes B in which the cancer has spread by direct continuity outside the bowel wall but not into lymph nodes (5 year survival in 65%), Dukes C in which the cancer has spread into the regional lymph nodes (5 year survival in 40%) and Stage D, incurable cases, such as those with distant metastases, peritoneal seedlings or very extensive local disease (5 year survival in 5%). Colorectal cancer-specific 5 year survival was only just statistically significantly worse ($p = 0.05$) in Dukes A patients when compared to colorectal cancer-specific survival among the population group who were matched for age and sex with the cases (Figure 22.1).

Colorectal cancer-specific survival matched for stage is better for women than for men, better for colon cancer than for rectal cancer, and better in those diagnosed at a younger age (Clarke et al 1980; McDermott et al 1981; Mettlin et al 1982; Isbister and Fraser 1985; Kune et al 1990; Sant et al 1995). The gender difference in survival is of particular interest, and will be discussed further in relation to time-trends in colorectal cancer incidence, mortality and survival.

Survival when corrected for stage does not appear to be influenced by other pathologic features, such as the tumor being a synchronous or a metachronous cancer, with the exception of cancer cell differentiation, in which survival decreases with poor cell differentiation (Mettlin et al 1982; Kune et al 1990). DNA contents in terms of ploidy and proliferative index can also be of some value in predicting survival, especially for Dukes B tumors, in that those with diploid tumors and a low proliferative index have a more favorable survival than those with aneuploid tumors and an increased proliferative activity (Conlon and Enker 1995). The presence of mucus or mucus-producing colorectal cancer cells was suggested as an indicator of poor survival (Pihl et al 1980), however this was not confirmed in two population-based studies when this pathologic feature was analyzed by Dukes' staging (Bear et al 1984; Kune et al 1990). Moreover, survival does not appear to be influenced by a family history of colorectal cancer in near relatives (Kune et al 1992; Slattery and Kerber 1995), except possibly in younger men (Slattery and Kerber 1995), nor by the number of children effect (Kock et al 1982; Kune et al 1992; Jacobsen et al 1995), factors which are known to be associated with the risk of colorectal cancer, as indicated in Chapters 5 and 12.

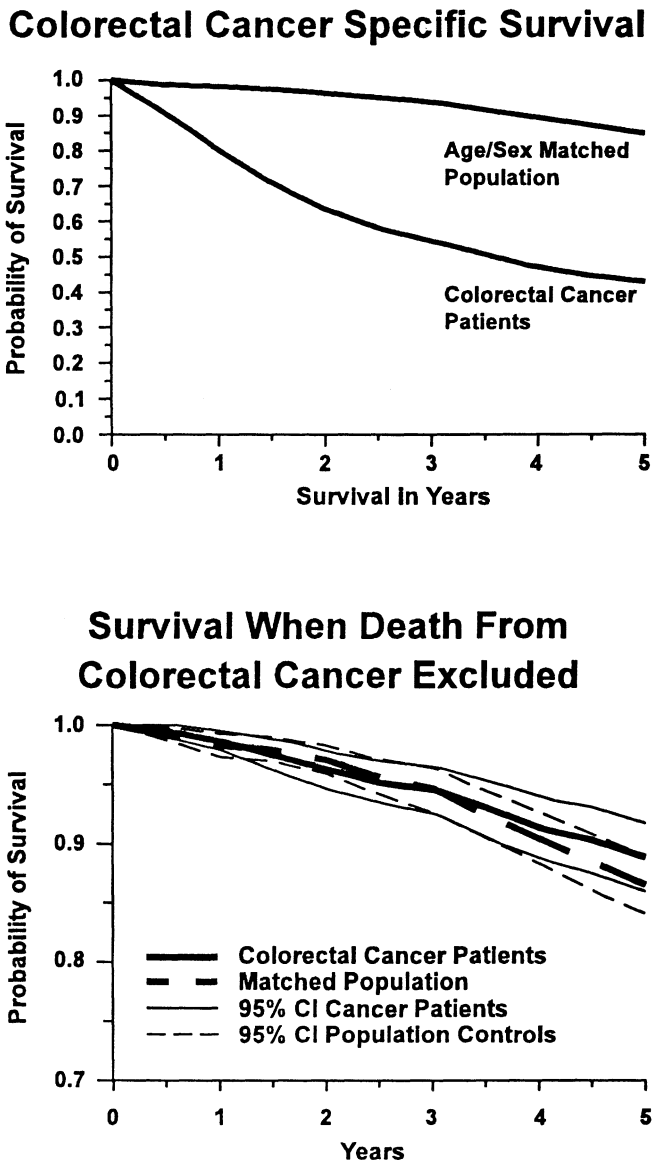

Figure 22.2 Top – Colorectal cancer-specific survival in a large population-based study showing a highly statistically significant ($p < 0.001$) probability of survival between cases and age/sex matched controls.
Bottom – Survival when death from colorectal cancer was excluded (CI – confidence interval).
Data Source: The Melbourne Colorectal Cancer Study.

As expected, colorectal cancer patients die prematurely because of their cancer (Figure 22.2 top), and the death rate from causes other than colorectal cancer is similar in colorectal cancer patients and in the general population which has been matched for age and sex with the cancer patients (Figure 22.2 bottom). As the survival of Dukes A patients is only slightly worse than that of the general population (Figure 22.1), and as systematic screening results in the discovery of a high rate of Dukes A cases compared to the rate when diagnosis is made in the symptomatic stage (Chapter 20 and Table 20.1), survival with colorectal cancer using conventional treatment should improve dramatically following the introduction of mass screening.

PREDICTIONS USING TIME TREND ANALYSIS

Descriptions of colorectal cancer incidence, mortality and survival changes over time in specific populations can be partly explained from a knowledge of changing patterns in diagnostic and screening techniques and changing lifestyle patterns, and therefore have some predictive value regarding the future of colorectal cancer control (Chu et al 1994; McMichael and Giles 1994). Incidence, mortality and survival statistics need to be interpreted cautiously, particularly when making international comparisons because of coding and misclassification differences, differences in diagnostic and screening practices and differences in lifestyle changes which may occur within different populations in one country and also internationally (Piantadosi et al 1988; McMichael and Giles 1994). For example, the frequent misclassification of rectal cancer for colon cancer in mortality statistics, and to a lesser extent in incidence statistics, requires cautious interpretation of site-specific data (Percy et al 1981). Thus time-trend analyses have a definite, though limited predictive value.

TRENDS IN COLORECTAL CANCER INCIDENCE

There is a tenfold variation in age standardized incidence rates of colorectal cancer between high incidence countries such as USA, UK, New Zealand and Australia and low incidence countries such as Colombia and India (IARC 1992). Age standardized incidence rates in developed Western countries such as the USA and Australia have in general been rising gradually for both colon and rectal cancer, more markedly for men than for women up to the mid and late 1980s (Chow et al 1991; Bonett et al 1992; McCredie et al 1992; Chu et al 1994). However, in some parts of the USA, such as Rochester, Minnesota where complete ascertainment of colorectal cancer has existed since 1940, there has been no change in incidence rates over 50 years (Beard et al 1995). In the USA a small incidence peak in 1985 was in part attributed to an increased diagnostic endeavor after diagnosis and treatment of President Reagan's large bowel cancer (Brown and Potosky 1990; Greenwald 1992). However, since about 1985 there has been a consistent decrease in colorectal cancer incidence in the USA for both

men and women as may be seen in Figure 22.3 (Chu et al 1994). This decrease in incidence since 1985 was more marked in women.

Studies in the 1970s and 1980s showed standardized incidence rates to be higher in women for colon cancer (and especially in the right colon) between ages 35 and 60, however more recent studies show rates to be higher for men for all sites and all ages (Correa and Haenszel 1978; Kune et al 1986; Chow et al 1991). Although in general, incidence rates have been rising, those for younger birth cohorts born since 1930, have decreased (McMichael and Giles 1994).

The decreasing incidence rates in the USA since about 1985 and the decreasing incidence of colorectal cancer in younger birth cohorts can be interpreted as being in part due to lifestyle changes in some sections of the population over the past 20 years, particularly in dietary habits, but possibly also in smoking habits and physical activity level (Chu et al 1994; McMichael and Giles 1994). The greater incidence decline in women compared to men may be explained by more widespread lifestyle changes in women, and possibly also by the increasing prevalence of hormone replacement therapy by menopausal women, particularly in the USA (Chu et al 1994; Potter 1995). Incidence rates in low-risk countries such as Japan and Poland, have generally risen for both colon and rectal cancer in both men and women (IARC 1992).

TRENDS IN COLORECTAL CANCER MORTALITY

Site-specific mortality data require cautious interpretation because of the frequent misclassification of rectal cancer for colon cancer in death certificates. In the 40 years 1950–1990, colorectal cancer mortality has in general declined in countries with high rates, such as USA, Canada, Western Europe, remained stable in countries with moderate rates, and increased in countries with low rates, such as Eastern Europe and Japan (Boyle et al 1985; Miller 1991; Aoki et al 1992; Hoel et al 1992; La Vecchia et al 1992; Chu et al 1994; McMicheal and Giles 1994).

One interpretation of these data is, that as low rate countries become more affluent and/or increasingly adopt Western lifestyles, incidence and mortality rates rise, whereas affluent countries with high rates of colorectal cancer increasingly practice early detection with screening and also increasingly change their lifestyle, resulting in a decreased incidence and mortality from colorectal cancer.

In the USA, colorectal cancer mortality had decreased only marginally in men up to 1985 and then there was a more marked decline, whereas in women there has been a consistent decrease in mortality since 1950 and particularly marked since 1985 as seen in Figure 22.3 (Chu et al 1994; American Cancer Society 1995). This gender differential of declining mortality rates mirrors the USA trends in incidence rates, and further suggests that women are more receptive to both lifestyle changes and screening than men (Chapter 19). Colon

cancer mortality rates have been steady or slightly decreasing in men in most Western populations, and decreasing consistently in women, while rectal cancer mortality has been decreasing in both men and women in most countries with a high rate of colorectal cancer (McMichael and Giles 1994).

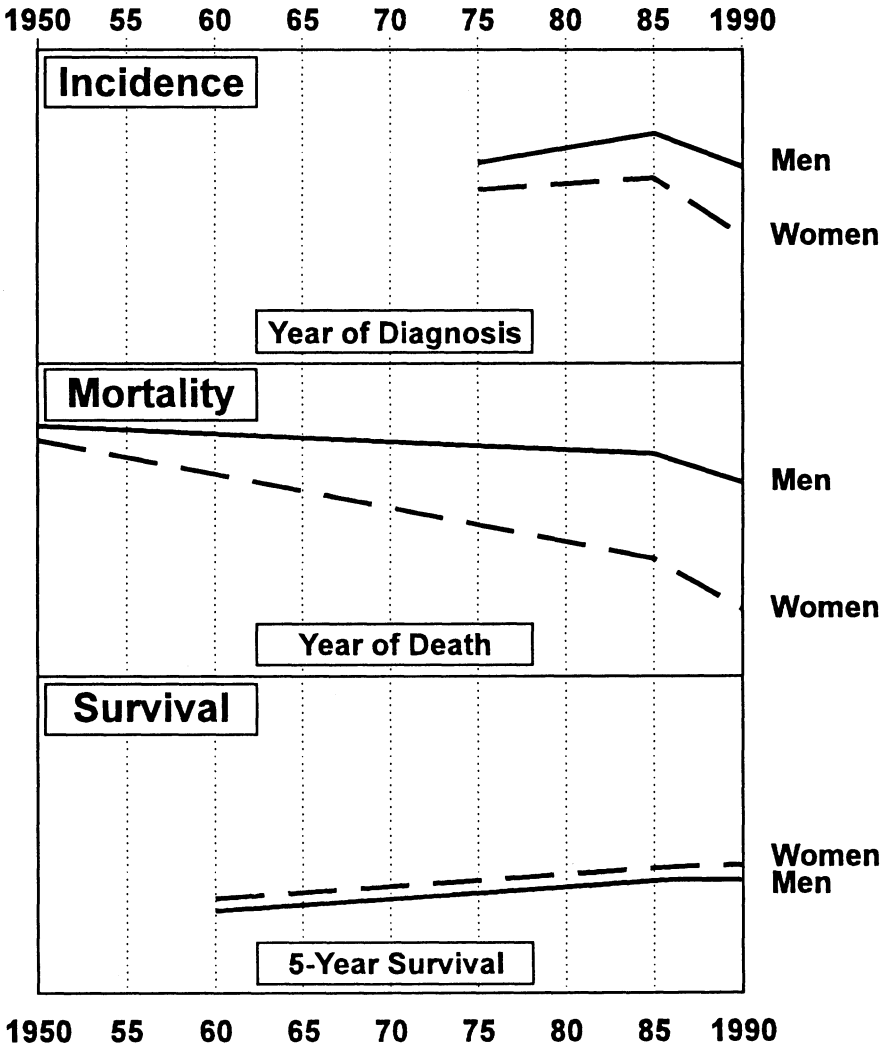

Figure 22.3 Time-trends in colorectal cancer incidence, mortality and survival in men and women in the USA (derived and modified from several sources attributed in the text).

TRENDS IN COLORECTAL CANCER SURVIVAL

In the USA the Surveillance Epidemiology and End Results Program (SEER) has published cancer survival statistics since the 1960s, and this has shown significant positive trends in survival up to the late 1980s (Figure 22.3), for both colon and rectal cancer (Miller et al 1992; Chu et al 1994). In general, survival has been better in women than in men over this time, and this difference is not explained by gender differences in the proportion of cancers at different stages of the disease (Miller et al 1992). Survival improved over this time for both men and women for all stages of the disease, that is, there was a positive trend for localized disease, regional disease and also for those with metastatic or distant disease (Miller et al 1992; Chu et al 1994). Similar positive trends in survival over this time were reported by other Western countries, such as Australia (Bonett et al 1992a) and Denmark (Carstersen et al 1993) and all European countries also (Sant et al 1995).

These consistent improvements in survival over the past 30 years probably reflect improvements in treatment of all stages of the disease, and very likely also reflect a trend for earlier diagnosis of symptomatic patients since the availability of colonscopy, as well as an increasingly greater use of screening in asymptomatic cases with fecal occult blood testing and fiberoptic endoscopy, which detects a large proportion of early stage, so-called "curable" cancers.

TRENDS IN LIFESTYLE FACTORS

Changes over time in the prevalence of lifestyle factors which are likely to be related to colorectal cancer risk would be expected to have an influence on colorectal cancer incidence rates. As noted in earlier chapters, dietary factors are most important in colorectal cancer etiology, and alcohol consumption, physical activity and more recently smoking have also been identified as likely component causes of colorectal cancer. Unfortunately, the prevalence of various lifestyle exposures in the population is at best measured rather crudely (such as "national food disappearance" data for dietary factors), and often data are not available. Moreover, as discussed in the relevant chapters, lifestyle factors such as diet, alcohol consumption and physical inactivity probably need to operate over many years, usually decades, and the smoking effect has a latency period of 2–3 decades, so that changes in these putative causes would be expected to show an effect only 20 or 30 years later. For these reasons, the influence of changing lifestyle factors on colorectal cancer incidence need cautious interpretation.

In a masterful analysis of dietary data derived from the Food and Agriculture Organization of the United Nations, correlated to colorectal cancer incidence rates, McMichael and Giles 1994, found that in most high incidence countries animal fat consumption has decreased, animal protein has stabilized or increased since the 1960s, whilst in low incidence countries animal fat and protein consumption has increased. These changes may be a partial explanation of the

convergence trend for the incidence and mortality rates noted earlier between high- and low-risk countries. Beta-carotene consumption, a good marker for vegetable intake, has increased over the years in most countries (McMichael and Giles 1994).

In the USA, dietary risks such as energy intake and overweight, increased in the 1970s and 1980s (Raper et al 1992; Kuczmarski et al 1993), however animal fat consumption has decreased (McMichael and Giles 1994). Importantly, the consumption of protective factors in the diet, particularly the intake of vegetables, fruit, dietary fiber, calcium, beta-carotene and vitamin C containing foods has increased in the USA (Raper et al 1992; US Department of Agriculture Reports 1992). In the USA also, physical activity levels have probably increased (Stephens 1987), although accurate data on this likely protective factor for colorectal cancer are not available.

PREDICTIONS FOR HIGH AND LOW RISK POPULATIONS

Predicting the future of colorectal cancer incidence, mortality and survival in different populations needs to be made cautiously. For high-risk countries, such as the USA, UK, Western Europe, Australia and New Zealand, it is likely that incidence and mortality rates will continue to fall, and survival from colorectal cancer will continue to improve over the next 20–30 years, as a result of increasing use of screening and continuing changes in lifestyle.

Low-risk countries, such as Japan and Eastern Europe, are likely to experience a continuing rise in incidence and mortality rates over the next 20 years, with increasing affluence and/or increasing adoption of Western life habits.

CONTROL BY POPULATION SCREENING AND SURVEILLANCE

POPULATION SCREENING

Screening for colorectal cancer has been discussed in detail in Chapter 20. Screening at present is practised in Western populations only in a health care setting. Mass screening using fecal occult blood testing (FOBT) with guaiac impregnated cards, such as Hemoccult II®, of individuals over 50 years of age is likely to have a participation rate of about 50%, and without slide rehydration it will miss about 50% of tumors present, although few significant tumors are missed. With rehydration of the slide, FOBT will miss much fewer tumors, however will treble the colonoscopy rate due to the number of false positives, and will therefore add greatly to the total cost of screening.

In Western populations, FOBT mass screening is likely to lower the rate of premature death from colorectal cancer by about 15%. Mass screening using

FOBT has been offered in Germany, however it has not been started in any other Western populations so far, and the cost benefit has not been accurately evaluated. For the future, the development of a highly sensitive and highly specific FOBT with better performance characteristics than the currently used tests, would greatly reduce the total cost of screening because of significant reductions in the rate of workup endoscopies. If major cost reductions can be achieved, governments may be persuaded to fund FOBT screening.

Screening with FOBT followed by flexible fiberoptic sigmoidoscopy or by flexible sigmoidoscopy alone, would have an enormous impact on lowering colorectal cancer incidence and mortality (Chapter 20), however at a very high cost, which at present few countries can afford. For the future, significant cost saving would be possible with the development of efficient high throughput screening centers staffed by paramedical personnel performing flexible fiberoptic sigmoidoscopies (Chapter 20).

GENETIC TESTING

Screening by genetic testing for the very small but important group of individuals who belong to a family, some of whose members carry the familial adenomatous polyposis (FAP) gene is now a reality, and is discussed in detail in Chapter 20 together with all others aspects of screening FAP families.

For the future, further advances in molecular biology are awaited which will allow similar testing of family members belonging to the hereditary non-polyposis colorectal cancer syndromes (HNPCC), which probably accounts for up to 4% of all colorectal cancer cases in Western populations (Chapter 5). Although early results of genetic testing of members of HNPCC families is encouraging, the problem is that each HNPCC family is likely to have its own mutation pattern, which makes genetic testing more complex, much more time-consuming and therefore more costly than for FAP families.

The possibility of being able to perform reliable genetic testing in these individuals (in most of whom the tests will be negative), will have two major advantages. The first is that those who are negative will not be burdened by invasive screening procedures, and there will also be a cost reduction to the community. The second advantage is that those who are positive, will need to recognize that there is an absolute need (rather than a 50% probability) for future surveillance, that is, future surveillance will be essential in order to protect themselves from mortality as a consequence of colorectal cancer.

SURVEILLANCE FOLLOWING TUMOR EXCISION

Extensive surveillance for the early detection of localized and resectable recurrence or metastasis, of those who have had a curative resection of colorectal cancer, appears to have little survival advantage, although it can benefit the occasional individual (Chapter 21). However, regular endoscopic surveillance for

the detection of metachronous tumors after colorectal adenoma excision, or after colorectal cancer excision, has been shown to contribute further to the lowering of mortality from colorectal cancer, if practised uniformly within a population (Chapter 21).

Surveillance intervals are now being redefined, and in general these intervals are being lengthened, especially for some groups, such as those in whom only a small tubular adenoma was found at the initial screening procedure. Also, with large-scale behavior changes in the community with respect to the main preventable likely causes of colorectal tumors, namely diet, alcohol, smoking and physical inactivity, the recurrence rate of colorectal tumors is likely to decrease, and this is likely to be a further reason for decreasing the frequency of surveillance. The future direction of surveillance post-colorectal tumor excision is that endoscopy be performed less frequently, thereby decreasing the overall costs of surveillance.

CONTROL BY PRIMARY PREVENTION

The potential for primary prevention of colorectal tumors is likely to be enormous, given that the attributable fraction in Western populations of preventable factors, namely diet, beer consumption, smoking and physical inactivity, is probably of the order of 70% of the total risk. The important likely causes of colorectal tumors which are capable of modification without risk or harm to the individual are certain dietary factors (Chapter 6), beer consumption (Chapter 7), smoking (Chapter 8), and physical inactivity (Chapter 9). Although none of these causes have been proven beyond the 99% level that would satisfy scientists working in rigidly definable disciplines, there is sufficient evidence to take action now, especially as such advice is known to be harmless (Chapter 18).

As discussed earlier in this chapter, recent examinations of time-trends of incidence and mortality of colorectal cancer in general, as well as in successive cohorts from 1950 through 1990 in the USA, shows declining rates of colorectal cancer incidence and mortality, suggesting that these reductions in rates are at least in part due to lifestyle changes. A particularly notable drop in incidence and mortality for colon cancer, and to a lesser extent for rectal cancer, over this period was reported in women. Moreover, this gender difference may also be due to women as a group being more health conscious, more compliant with screening, and more inclined to adjust their lifestyle than men (Chapter 19). Thus certain sections of the community already appear to have taken positive action towards primary prevention, well before strong endorsement by scientists and governments. It has been speculated that the likely protective effect of prolonged menopausal hormone replacement therapy (HRT), which is now quite prevalent in the USA, has also contributed to this mortality reduction in women (Chapter 12).

For the future, the task for the primary prevention of colorectal tumors is education of the population in terms of sound advice on diet, smoking, beer consumption and physical activity, and this is best commenced at school level. This advice is harmless, poses no risk to individuals, is economically sound and is in keeping with current views on the maintenance of general good health. Given various obstacles to broad behavior changes in the population, such as human resistance to change, the influence of sections of industry, communication media and others, the full potential of primary prevention will probably not be achievable in the future (Chapter 18). However, well-organized prevention programs will, among other major health benefits, result in a substantial decrease in the incidence, and therefore in mortality from colorectal cancer, the extent of which would clearly depend on the extent the particular population is able to change their life habits. The use of chemopreventive agents, such as aspirin, other non-steroidal anti-inflammatories, HRT, calcium and certain vitamins, could lead to further lowering of the incidence of colorectal cancer, particularly if used in certain high-risk groups, as described in Chapter 18.

COLORECTAL CANCER CONTROL INTO THE 21ST CENTURY

Trials never end, of course. Unhappiness and misfortune are bound to occur as long as people live, but there is a feeling now, that was not here before, and is not just on the surface of things, but penetrates all the way through: We've won it. It's going to get better now.

Zen and the Art of Motorcycle Maintenance
by Robert M Pirsig (Corgi Books)

As a result of the amazing explosion of knowledge during the past 30 years on the causes of colorectal tumors, on their mechanisms of action, on the morphologic and molecular changes which occur during the process of colorectal neoplasia, and on technologic advances in the early diagnosis and surveillance of colorectal tumors, described in the preceding chapters of this book, one can feel optimistic that colorectal cancer will be largely controlled within the next generation.

With the introduction of mass screening and surveillance programs, there will be a large reduction in the incidence and therefore in the mortality of colorectal cancer, as a result of the systematic excision of the major precursor lesion, colorectal adenomas, both when done in primary tumors identified through screening, as well as for metachronous tumors picked up in surveillance programs. Moreover, both screening and surveillance will identify a large

proportion of early colorectal cancers which, with appropriate surgical resection, have an excellent outlook for long-term survival. Genetic testing in the relatively small group to whom this applies, namely FAP and HNPCC families, will have their tumors identified early and dealt with in the appropriate manner, and with a good prognosis. Finally, large-scale modifications of dietary habits, beer consumption, smoking and physical activity in the community, as well as the use of some chemopreventive agents, especially for certain high-risk groups, is likely to result in a further and substantial reduction in colorectal cancer incidence, and therefore colorectal cancer mortality.

The major problem at present with secondary prevention, using mass screening and surveillance, is the cost and resources involved, and for the future, costs need to be substantially reduced to allow such screening to be achieved at a population level. The major problem with primary prevention is the difficulty in achieving large-scale change in the life habits of a large proportion of the population. These major difficulties are being recognized by the various groups of scientists involved, and are being overcome gradually by an approach which reaches across many disciplines.

Making predictions about the future is always difficult, however, based on progress which has been achieved in the past 30 years, one can anticipate that the mortality of colorectal cancer in developed Western communities will be reduced to one-tenth of its present rate within the next generation. This prediction gives one a great sense of optimism for the future, not only in relation to colorectal cancer, but also in suggesting that the multidisciplinary approach which will need to be used in the future control of colorectal cancer, will serve as an important model also for the study of the prevention and control of other common malignancies, and particularly cancers of the breast and prostate, in which cancer control is less well developed at present.

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